



*Anniversary Edition • 2020*



# DIMENSIONS

**35 Years of Innovation and Excellence  
in Alzheimer's Disease and Related Dementias Research at the UW**



# 35th ANNIVERSARY EDITION

Hello readers!

The UW ADRC and its associated clinical and educational programs at the UW Memory and Brain Wellness Center are pleased to bring you the 35th Anniversary Edition of *Dimensions!* Through interviews, profiles, historical research, archival documents and photos, this special issue explores the foundation built by the early researchers and team members of our Center and the fruitful avenues of current research that grow from it. We hope you will notice how recurring themes of collaboration, creativity, community outreach, and leadership still define us today. For this project, our current day team spoke with the people who shaped the ADRC as well as those who work today on such efforts, such as answering longstanding research questions, creating innovative programs for caregivers, and better addressing disparities in dementia care, resources, and education for American Indians and Alaska Natives. We listened to the life stories of research participants who share their reasons for giving gifts of time and effort to our research projects and trials.

While it is impossible to represent every valuable team member and project in depth, we urge to you to follow the clues in these stories and timeline to learn more about what interests you. In the future, the impact of the SARS-CoV-2 pandemic will certainly be a part of our Center's history. To rise to these challenges, we adapted many resources and programs, enhanced our virtual offerings of educational programs, conferences, and activities, such as nature walks, and continue to brainstorm about ways we can improve the lives of people living with memory loss.

We want to take this opportunity to thank our generous philanthropic donors for supporting numerous Alzheimer's disease research projects, community initiatives, and faculty positions that help our Center flourish. We recognize the Ellison Foundation, Richard M. and Maude Ferry Charitable Foundation, Paul V. Martinis Estate, Anderson Foundation, Steven G. and Dixie Y. Wilson, Ms. Charlotte Merritt, Sky Valley Whirlwinds, Skyline First Hill, Friends of Alzheimer's Disease Research, Arthur J. and Marcella McCaffray endowment, Arthur Krause endowment, and Nancy and Buster Alvord endowment, and many members of the public. Your interest also makes a difference and helps us advance the day when threats to memory and brain health will be detected and prevented as the standard of care. Happy reading!



### Special Anniversary Edition Credits

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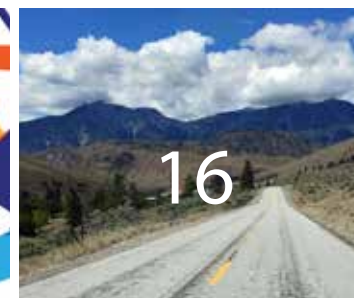
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**DIMENSIONS** Since 1986, *Dimensions* has served as our regular link to the public, including families, people living with memory loss, research participants, scientists, medical professionals, and interested individuals. *Dimensions* is one of the core outreach activities of the ADRC, in partnership with the UW Memory and Brain Wellness Center. Each issue seeks to update people who are interested in ADRC research about the latest dementia findings and news stories, as well as relevant local events and other aspects of healthy aging, caregiving, and living well with memory loss. Contact [gwanucha@uw.edu](mailto:gwanucha@uw.edu) with any questions.

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## Questions About Alzheimer's Disease

Dr. Burton Reifler

In the inaugural issue of ADRC's Dimensions newsletter in 1986, this reader's question was the very first to be answered by Associate Director Burton Reifler, MD, MPH, who was also Founding Director of the (former) UW Geriatrics and Family Services Clinic. This early reader asks: "I am confused about the difference between Alzheimer's disease and senility. How can you tell them apart?" Looking back, with over three decades of clinical research under our belt, this question still gets to the heart of tricky issues about brain health and aging, but also reveals substantial progress. View the answer from 1986 and join us as we reflect on how clinical researchers at the ADRC-affiliated UW Memory and Brain Wellness Center would update that answer with the most recent knowledge and a prescription for action and hope!

A:

*"You can't tell Alzheimer's disease and senility apart, because in most cases, they are one and the same. At one time, it was thought that 'senility' was simply a normal part of getting older. At that time also, we thought that Alzheimer's disease applied only to an individual under age 60 who had the slow, progressive loss of mental ability so characteristic of the illness. If the person had the same symptoms and was over 60, we called it 'senility'. We now know that mild forgetfulness, such as not remembering names, can be quite normal. Significant, sustained forgetfulness is a disease. Alzheimer's disease now refers to all individuals, regardless of age, who are subject to the slow, progressive deterioration of their mental functioning." –Dr. Burton Reifler, 1986*



*Thirty-Four Years Later....*

A:

Indeed, as Reifler notes, the word 'senility' was commonly used in past decades to label elderly individuals who showed signs of severe cognitive impairment. Today, the medical community defines that condition as 'dementia'. Through massive improvements from decades past, the field has better diagnostic tools to clarify whether Alzheimer's disease is playing a role in a person's symptoms. It is also now possible to make early diagnoses to help families adapt and plan for the future while they are still able.

But, that readers' inquiry in 1986 is still relevant today—It's just asked with different language: 'What's the difference between "dementia" and "Alzheimer's disease?" remains a baffling question to this day—and our Director, Thomas Grabowski, MD, has made it his mission to provide an answer that makes sense to everyone and fundamentally reframes how the public thinks about these issues of brain health and aging.

Grabowski, a neurologist at the UW Memory and Brain Wellness Center, often starts his public science talks by clearing up a "fundamental and pervasive confusion in our society and the medical community between Alzheimer's disease and dementia." The distinction between these two terms has wide-ranging implications. In short, Alzheimer's disease names the biological process by which amyloid plaques and tangles of tau protein build up in the brain's medial temporal lobe and eventually spread throughout the entire brain. This process is often accompanied by vascular damage and other proteins, especially in very old people. Only in later stages of the disease does a person become dependent on the care of others to perform activities of daily life, a clinical state called dementia. Importantly, not all cases of dementia are caused by Alzheimer's disease or related pathologies; other less common neurodegenerative diseases, such as frontotemporal degeneration and Parkinson's disease, can also lead to dementia.

For perspective, while 1% of people aged 65 have Alzheimer-type dementia, 25-30% of adults aged 65 will show amyloid build-up in PET scans at least 15 years before the onset of dementia symptoms. According to the National Institute on Aging, the prevalence of clinically diagnosed Alzheimer's disease doubles every 5 years beyond age 65. Some people with these signs of pathology escape developing symptoms during life, and researchers are now on the hunt for the genes or aspects of life history that contribute to this resilience. Learn more on Page 18.

"So, if our plan is to advance the day when we prevent these threats to brain health, we really are going to have to intervene early, either with a strategy of primary prevention based on identification of early amyloid burden and genetic factors, or secondary prevention methods to treat early symptoms," says Grabowski.

In Grabowski's reframing of Alzheimer's disease, the long presymptomatic phase becomes a wide window during which lifestyle changes in exercise and other heart-healthy behaviors, and eventually, future therapeutics, can help improve or maintain cognitive function or delay dementia onset for many

years. In fact, the Lancet Commission on Dementia Prevention, which uses research from the UW Adult Changes and Thought Study, documents that not smoking and managing conditions such as obesity, hypertension, diabetes, hearing loss, and social isolation can help prevent dementia. In 2020, new additions to the list of preventable risk factors include head injury, heavy alcohol use, and air pollution exposure. Learn more on Page 20.

At the UW Memory and Brain Wellness Center clinic, our focus goes beyond slowing or preventing dementia; we take a strengths-based approach to helping people with early symptoms of memory loss find ways to leverage areas of strength that remain intact in the midst of decline. "The vast majority of older adults over 65 with early to mid-stage dementia symptoms typically have the capacity to live meaningful and engaging lives for many years in spite of the impairments," says Grabowski.

The aim to maximize the impact of strengths-based approaches to memory loss motivates certain unique areas of emphasis in our clinic. We are engaged in efforts to improve dementia diagnosis education for primary care physicians, so more people can access diagnosis and resources without referrals to specialty neurology centers. The clinic advocates for people living with memory loss and their families to participate in local dementia-friendly programs.

– Memory and Brain Wellness Center provider team, 2020







## An Interview with the ADRC's Founding Director

*George Martin, MD, Emeritus Professor of UW Pathology, has led a long and productive career at the University of Washington, where he received his BS and MD degrees and has been a member of its faculty since 1957. Martin's research has for many years been concerned with the development of genetic approaches to the study of aging and age-related diseases. At the UW, he is recognized for creating research opportunities in neuropathology and the biology of aging. By the time he founded the ADRC in 1985, he had already started the UW Medical Scientist Training Program in 1970 and the UW Genetic Approaches to Aging Research Institutional Training Grant, supported by the National Institute on Aging. At 93 years of age, George Martin is devoted to supporting research in aging and genetics and thinking critically about the most challenging issues in studying Alzheimer's disease and related neurodegenerative conditions.*

*He shares memories, fascinating insights about evolutionary biological theories of aging and genetics, and his hopes for the field of Alzheimer's disease research.*



Earl Benditt, MD in 1950. Courtesy, University of Chicago Library.

### HOW DID YOU FIRST BECOME INVOLVED WITH AGING AND GENETICS RESEARCH?

After I finished my medical residency at the University of Chicago, my late colleague and Associate Professor Earl Benditt, MD asked me to join him as a faculty member at the University of Washington in 1957. Benditt had been recruited to build an academic pathology department and jump-started research in the department on a modest National Institutes of Health grant.

I had developed an interest in the neurobiology of the genetic disorder called Wilson's disease in my medical residency, so I decided to connect with the chair of the Department of Medical Genetics and the late Professor Arno Motulsky, the founder of Medical Genetics here at the UW. I said: "I want to learn more about genetics!" They were very welcoming to me. I asked them to participate in our pathology course for the first time. So, I had to coordinate by bringing medical genetics experts in to give lectures to the new Department of Pathology.

At the time, I was working on an enzyme called caeruloplasmin, which is dysfunctional in Wilson's disease. Wilson's disease prevents the body from getting rid of excess copper, and these patients develop copper deposits in their liver and around their eyes. That work led to the cloning of the copper-transporting gene, *ATP7B*. Defects in *ATP7B* remain the only known genetic cause for Wilson's disease. And I said, "Hey, that's interesting! What about the element vanadium? It's a close cousin of copper." Our experiments indeed showed that vanadium made a tremendous difference in modulating organic compounds produced by the body, such as serotonin and adrenaline.

There was no predicting where that research would go. In a literature search, I came across the late Guido Pontecorvo, "Ponti." He was the first person who suggested it was possible to map human genes based upon his research on mitotic recombination in a fungus called *Aspergillus nidulans*! So, I took my whole family to Scotland for the year of 1961, where my young daughter developed a brilliant Scottish accent! —I worked with Ponti at the University of Glasgow for the entire year. That same year, the now famous paper by Leonard Hayflick came out on the Hayflick limit, or the number of times a normal human cell population will divide before cell division stops. Hayflick showed that there's a limited lifespan of cells and there's some evidence that it's related to aging. That's how I first got into aging research and genetics, and now I am trying to push research into how aging is the fundamental risk factor in all variants of Alzheimer's disease.

### WHY DID YOU TURN YOUR ATTENTION TO ALZHEIMER'S DISEASE AND DECIDE TO START THE ADRC WITH A FOCUS ON GENETICS?

It was the late Carl Eisdorfer, MD who first interested me in Alzheimer's disease at the UW. Eisdorfer started the Gerontological Research and Clinical Center at the VA Puget Sound Health Care System and served as chair of the UW Department of Psychiatry. He published the first UW paper on Alzheimer's disease in 1980, reporting on the immune system in people with the disease.

Around that time, my friend and colleague Rudolph Tanzi, PhD [now the Director of the Genetics and Aging Research Unit at Massachusetts General Hospital] published the 1983 study titled, *A polymorphic DNA marker genetically linked to Huntington's disease*. This linkage for Huntington's

disease really turned me on to the power and possibility of linking a gene to a neurodegenerative disease. My colleague Thomas Bird, MD, who founded the UW Neurogenetics clinic in 1974, was seeing more and more families with a history of Alzheimer's disease. So, we decided to apply to become an ADRC with the overarching theme of studying familial Alzheimer's disease.

I'm proud of what the original genetics team ultimately accomplished in the field of familial Alzheimer's disease. Our group's successful contributions came from individuals working collectively. Thomas Bird, Gerard Schellenberg, and Ellen Wijsman were key to our early work— as well as the post-doctoral fellows and many others. They made the contributions that we're seeing emerging from our Center today possible.

### WHAT IS A SCIENTIFIC MYSTERY OF ALZHEIMER'S DISEASE GENETICS THAT STILL FASCINATES YOU?

The Apolipoprotein E gene (*APOE*) poses interesting questions, and it's very complex. We have known since 1993 that *APOE*  $\epsilon$ 4, one polymorphism of *APOE*, is a substantial risk factor for late-onset Alzheimer's disease in the European population. Carrying an *APOE*  $\epsilon$ 4 allele doesn't guarantee someone will develop Alzheimer's, but the risk goes up circa three-fold with one allele and circa twelve-fold with two; the risky allele is present in about 25% of the human population.

I was impressed with the fact that *APOE*  $\epsilon$ 4 is actually the dominant and most common allele in non-human primates, who do not develop Alzheimer's disease! I became interested in how the risky allele variant is harmful in some environments, but it may actually be beneficial in others for evolutionary reasons.

When I was on a sabbatical with the late Joshua Lederberg, PhD [at Rockefeller University], I pursued an idea I had. Lederberg was interested in infectious disease and molecular biology. And I said, "Josh, I think that maybe that the reason non-human primates have *APOE*  $\epsilon$ 4 is that it protects them from some infectious disease." I said that because I knew that *APOE* codes for protein that is involved in transport of lipids in the blood and the central nervous system. I also knew of evidence that the *APOE*  $\epsilon$ 4 allele is not as effective at putting lipids into cell membranes, as are the *APOE*  $\epsilon$ 2 or  $\epsilon$ 3 alleles. Lederberg assured me that there were some fungal agents, such as *T. brucei*, that need the host lipids for them to survive because they can't synthesize the complex lipids on their own. So, if you—the infected host—have an *APOE*  $\epsilon$ 4 allele, then you wouldn't make the amount of lipids needed by the pathogen, moderating or preventing the disease and leading to a longer life and increased reproductive potential for you.

Now, there is more evidence for this hypothesis. My friend Caleb Finch, PhD at the University of Southern California argues that there may sometimes be positive reasons for carrying *APOE*  $\epsilon$ 4 in terms of cognition. While being an *APOE*  $\epsilon$ 4 carrier is the strongest risk factor to date of late-onset Alzheimer's and cognitive decline in industrial populations; it is associated with greater cognitive performance in individuals facing a high parasite and pathogen load, suggesting advantages to the *APOE*  $\epsilon$ 4

allele under certain environmental conditions.

In fact, there is evidence that children living in poor hygiene environments who carry the *APOE*  $\epsilon$ 4 variant are more resistant to diarrheal disease, including malaria, providing a survival advantage. This phenomenon may explain why some equatorial populations have a higher prevalence of this particular gene variant.

Remember, your risk for Alzheimer's disease is not only about genes, and it's not only about environments. It's gene-environment interactions, and it's gene-gene interactions. Genes elsewhere in the genome can make a big difference to whether that mutation is going to get you in trouble or not. And we don't know enough about all those background genomes. That's going to be a tremendous task in the future.



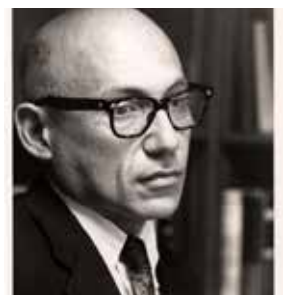
### WHAT IS YOUR HOPE FOR THE DIRECTION OF THE ADRC? IF YOU COULD DECIDE TO PUT FUNDING TOWARDS ANY AREA, WHAT WOULD IT BE?

I've been telling people my perspective for years, and even today not everybody agrees with me! I remember a moment at an international conference in 2009. In my talk, I said: "There are many different types of Alzheimer's, and this is a good heuristic notion." A famous researcher responded:

"Hey, George! There's only one type of Alzheimer's disease!" But I keep saying: Amyloid beta is important in Alzheimer's disease. Tau protein is important. Chronic inflammation is important. But what happens before that? There may be different biological pathways in different people. Even infectious disease might relate to changes in the brain's immune system, such as the herpes simplex virus, but it could be something else.

So, I would push for more work on the fundamental mechanisms of aging. Aging mechanisms comprise a big pathway, though not the only pathway. My dream would be that one day we'll be able to address a person's relative susceptibility to one of the numerous hallmarks of aging. For example, it would be useful to know if the person has robust retention of mitochondrial function, or if they have comparatively low rates of somatic mutation hallmarks of aging. After death, that estimate would give more meaningful context to the neuropathological findings from brain autopsies, brain imaging data, and genomics. You could say: "Hey, this guy got in trouble with Alzheimer's because of protein trafficking function." You'd have that full picture of an individual's risk and disease trajectory, but we don't have the financial resources for this approach currently.

Coupled with that biological information, we should capture data about the individual's background and environmental exposures in greater depth—for example, whether the person was exposed to a lot of toxins. We don't generally have that type of health information. We would need a universal health care electronic records system, so you could look up all those parameters for the question you'd like to answer. Let's hope we get there. I would love to see a research grant by the NIH supporting that kind of comprehensive dataset for research participants. >>> *Next page*



Joshua Lederberg, PhD in 1962



**WHAT IS YOUR OWN FAVORITE HYPOTHESIS?**

Epigenetic gambling. The best example comes from studies of wild-type *Caenorhabditis elegans* worms when grown in sterile suspension cultures. Their genes are identical, like identical twins. The environment is identical. In those experiments, biogerontologists have observed for many decades that, despite all efforts to control genotype and environment, there are substantial variations in the lifespan of individual worms. In fact, the expression of genes in a family of identical cells gets more and more different as an organism gets older. I raised a hypothetical mechanism for this observable variation: Nature wants to gamble with gene expression. I call that 'epigenetic gambling'.

In epigenetic gambling, random changes in cellular gene expression evolved as an adaptive mechanism to ensure survival of members of a group in the face of unpredictable environmental challenges. Once activated, it could lead to 'epigenetic drift', or changes in gene activity with aging, amongst all members of the group. I predict that while particular patterns of gene expression will be adaptive for a subset of individuals within a population early in life, continued epigenetic drift will result in variable patterns of disease over time. The weakness of this hypothesis is that we do not currently have a plausible molecular mechanism for the genetic 'randomizer' of epigenetic gene expression. My friend Dan Promislow, PhD [UW Department of Laboratory Medicine and Pathology] has informed me there's a name for epigenetic gambling in

evolutionary biology. It's called 'bet-hedging,' a concept which is very much in concert with my notion of epigenetic gambling.

And that's what I would like to test in Alzheimer's disease and other disorders in model systems. New technology to study gene expression in the brain is just exciting as hell. Jay Shendure, MD, PhD [UW Genome Sciences] can do what we call single-cell transcriptomes. You can see what's happening in the cells in the early stages of Alzheimer's disease, during the screw-up in the proteins that are transcribed. I wish I were a young man again with this technology. It's just unbelievable what you can do.

**WHAT IS YOUR HOPE FOR THE FUTURE OF BRAIN HEALTH AND DISEASE PREVENTION?**

If I had a lot of money and power, I would put a tremendous amount of money into early education. And it's the single most desperate thing that we need to do now: address inequality in education and the rampant misunderstanding of scientific evidence. Correlation is not causation. That's where we should put our money. I love what the mayor of New York City is doing. Mandatory education, preschool, beginning at age 3. The key is, you've got to give these teachers a lot more money, and you've got to train them in teaching critical thinking. Kids have curious little minds. And when they see something new or hear about something new, they'll say, "Gee, teacher, that's interesting." The teacher should then instruct them to automatically ask: How do we know that's

true? Can you imagine if every kid grew up in our democracy asking the question: "How do we know that's true? What is the evidence?" It would be a transformation.

**YOU ARE 93 YEARS OLD, REGULARLY ATTEND SEMINARS, CO-AUTHOR JOURNAL ARTICLES AND KEEP UP WITH THE LATEST ADVANCES IN RESEARCH. WHAT DO YOU ATTRIBUTE TO THIS INCREDIBLE SUPER-AGING?**

Your question is one that deserves a great deal of research. While we have gotten a good start on learning a bit about the phenomena of resistance and resilience to basic mechanism of aging and diseases of aging via the study of unusually healthy centenarians, we need more research on what I have named Unimodal Antigeroid Syndromes—the genetic and environmental basis for resistance and resilience to each of the numerous specific age-related disorders.

In my case, my number one hypothesis is good luck. I probably inherited a few good genetic variants, which I may share with a beloved Uncle who remains cognitively sharp and who will shortly become a centenarian. I also was lucky enough to have gotten outstanding teachers and fellow students from early primary school to postdoctoral training. On the other hand, when my Mom asked me if I wanted to pursue the option of attending kindergarten, my answer was "No, Mom, I want to have one more year to sleep late!" •



1984

The first NIH funded ADRC grant application is submitted. The direct costs requested for the entire proposed 5-year project period total \$6,697,620. Adjusted for inflation, that is over \$16 million today.



1985

The UW ADRC is established as one of the first 10 Alzheimer's Disease Centers originally funded by the National Institute on Aging.



1986

Dimensions newsletter inaugural issue is published, with the mission to link the public to ADRC information, outreach, and research opportunities. The title "Dimensions" was chosen to reflect the many stages and faces of Alzheimer's disease. Blue ink on yellow paper is thought to be most readable for people with dementia.



1987

Eric Larson and Bud Kukull are awarded an NIA grant to start an epidemiological model of an Alzheimer's incident case registry, similar to cancer registries. The Alzheimer's Disease Patient Registry is established. Named the Adult Changes in Thought study in 1994, it follows the lives and wellness of thousands of individuals in Seattle as they age to better understand sources of risk and resilience.



1988

An External Advisory Board comes to the ADRC for the first time to offer suggestions and critiques to prepare for submitting the Center renewal application. Members included Fred Plumb, Tony Phelps, Marilyn Albert, Amico Bignami, Kevin Cain, Robert de Mars, and Sherman Weissman.

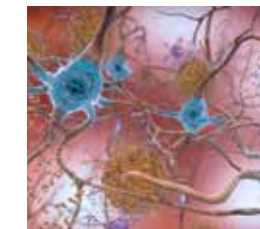
**ADRC Funds Pilot Studies**

ADRC funds the first 4 pilot projects, enabling young investigators to develop new areas of knowledge about Alzheimer's disease. Now called Development Projects, these funding awards, focused on junior investigators, are as robust as ever.



1989

The ADRC becomes a key gateway for patients to the fifty-five support groups running in WA State, mostly hosted by the local Alzheimer's Association.



1991

NIA grants ADRC \$5,100,000 over the next five-year funding cycle (adjusted for inflation, that is over \$10 million today). The funding supports the Center's community engagement and research projects, chiefly the search for Alzheimer's disease-causing genetic variants that requires cross-discipline expertise.



1992

The ADRC launches a mobile clinic led by Soo Borson, MD that would travel and assist underserved communities in King County and establish ties with diverse community organizations in the Seattle area, for the first time. (Picture date, 2007) Learn more on Page 16.

**TIMELINE OF ADRC HISTORY**



1978

Eric Larson and Burton Reifler open the first clinic at the University of Washington to evaluate outpatients with dementia.



1980

UW's first paper on Alzheimer's disease is a report on how the progression of dementia relates to the concentration of immune system cells. The study marks the beginning of UW's scientific effort to piece apart the causes of Alzheimer's disease.



1983

Rudolph Tanzi publishes a study linking Huntington disease to a gene on chromosome 4, sparking George Martin's curiosity and influencing the founding of the UW ADRC.





**FEATURE STORY**

# The Early ADRC's Search for an Alzheimer's Gene

How Creative Teamwork, Collaboration, Leadership, and Luck Set the Stage for Today's Approach to Biological Complexity

By Franklin Faust and Genevieve Wanucha

It was one of the longest distances that Thomas Bird, MD ever traveled for science—an eight-hour flight from Seattle to Amarillo, Texas, and a two-hour drive north into the Oklahoma panhandle to arrive at a small church in the small town of Beaver. It was 1987, which he still remembers because those two states were celebrating the 200th anniversary of the signing of the Constitution. He had come for the reunion of a large family he had come to know through phone calls to the UW Alzheimer's Disease Research Center and a previous visit.

The Reiswig family was unique, in a medical sense—at least twenty members had developed dementia over four generations, with ages of onset from 40 to 75 years old. This family had been described in 1979 by Robert Cook-Deegan, MD at University of Colorado, but their particular shared ethnic background had gone unrecognized. In the late 1980's, researchers were just beginning to understand that some cases of dementia linked to Alzheimer's disease likely had a genetic cause. While Bird knew that inherited or 'familial' Alzheimer's disease only accounts for a tiny fraction of cases, he also knew studying these unique families could open the door to better understanding the mechanisms of disease and, possibly, a treatment target for all cases.

That day, seated in the church pews, the Reiswig family listened as Bird explained the details of their neurogenetic study. The family signed consent forms to participate, and Bird took blood samples, which he sent back to the team's research nurse, Ellen Nemens (now Ellen Steinbart). The team would extract the blood cells' DNA and search it for what could be a faulty genetic factor. Importantly, the family shared their history so the researchers could create a pedigree, a family health history indicating relationships and disease cases using universal symbols.

Bird brought over twenty years of experience working with families with genetic disorders, such as Huntington's disease, at the UW Medical Genetics clinic, which he founded in 1974. Medical geneticist Ephrat Levy-Lahad, MD, who would later bring this family study to fruition in 1995, remembers: "Tom works so closely to the families that he sees as a physician, and while he's not a molecular biologist, he has that genetic vision – seeing families and seeing patients and thinking about problems in a genetic way. I really learned to take that approach at the ADRC, and I still practice it. The families and researchers share a goal in that kind of project, and that is very powerful to me to this day."

Bird knew that at-risk families often have a person who is particularly motivated to address the problem and seek help, a firebrand whose enthusiasm will inspire even hesitant relatives to open up about painful topics and organize them to join a research effort.

This family was no different. Ester May Reiswig was eager to help shed light on the disease that had recently taken her husband. "Thanks to her, the family reached out to us," says Bird. "They were concerned that they had hereditary Alzheimer's disease and that nobody was paying attention to it." Bird and Nemens fostered a dialogue. He listened to her as she spoke about her husband's ancestors and genealogy.

Reiswig's late husband's family was part of an ethnic group called the 'Volga Germans', who had moved from the Hesse region of Germany to the Volga River region in Russia at the behest of Catherine the Great in the 1760s. Later, amidst the political and economic tumult of the 20th century, many came to the US to settle in small villages along the trans-continental railroad. And the people busy catching up at the reunion weren't the only ones of Volga German ancestry with a history of Alzheimer's disease, she shared. Reiswig knew of two other families who had been documented as suspected genetic Alzheimer's cases, but no one had asked them about their background—as Bird was accustomed to do.

"As I was sitting there listening to her story, I remembered that one of our families back in Seattle had a German last name, and a relative who wrote a book called *The Volga Pilgrims*," says Bird. "It got me thinking." Bird continued to listen as Reiswig recalled that these affected Volga German families came from the same two tiny villages in southwestern Russia, Frank and Walter. "I realized that there could be many families whose ancestors migrated over from those same villages—distant relatives with a gene for Alzheimer's," Bird said. He quickly checked the families already

in the ADRC study, discovering three more families with a Volga German connection.

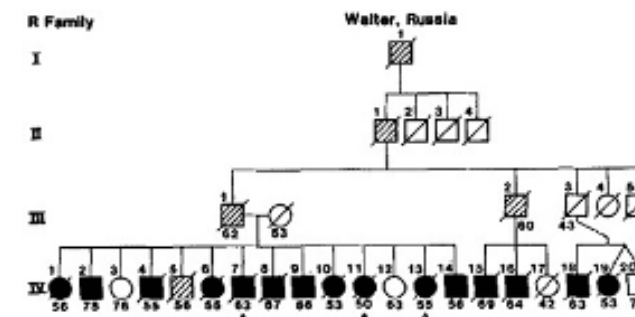
Over thirty years later, Bird would recall what he calls his "Eureka Moment." The Volga Germans would be a particularly useful collection of families in the search for an Alzheimer's disease gene because the affected family members would almost certainly share the same responsible gene; even more significant was that these family members could all be related to a common ancestor who first introduced the mutation into the family line. His question:

Which gene is it?

"I still remember the day when Tom came to my office really excited one morning, and he started telling me all about how he had visited this family and learned that they were Germans from Russia," says Gerard Schellenberg, PhD, now Professor of Pathology and Laboratory Medicine at University of Pennsylvania and Director of the Penn Neurodegeneration Genomics Center.

Nemens' degree in German became a valuable asset. She started digging through the ADRC

Registry, which is a large pool of potential research participants who agree to be contacted for research. She kept an eye out for families with German last names and contacted them to find out their place of origin or family's history. The fact that Nemens could pronounce the names of German villages surprised and delighted the families. By 1990, seven families of Volga German ancestry, all originating from the same two villages in Russia, made up one quarter of the families being studied by the ADRC team in the Center's first genetics project. >>> *Next page*



Part of the pedigree of the Reiswig family showing multiple persons over four generations affected by Alzheimer's. Courtesy, Thomas Bird.



1993

The ADRC expands its research seminar program to include faculty, postdoctoral scholars, and medical staff at the UW, Seattle Veterans Affairs GRECC, and Harborview Medical Center. They will be held on a bi-monthly basis.



1994

The ADRC joins a multi-site research study comparing the success of pharmaceuticals and behavioral management techniques in the treatment of agitation in Alzheimer's disease. Linda Teri, Rebecca Logsdon, Murray Raskind, and Elaine Peskind are the Principal UW Investigators.



1995

NIA awards the ADRC a \$8,100,000 grant for next 5 years. Adjusted for inflation, that is over 13 million today. The funding goes towards research on neurogenetics, brain structures involved in stress and agitation, proteins involved in Alzheimer's disease, APOE animal models, and investigations of estrogen's possible neuroprotective effects.

• TIMELINE



The vast majority of people of Volga German descent do not carry this genetic factor and do not necessarily live at a higher risk of dementia than the general population. Take for example Pacific Northwest natives Arlene and Al Noreen, who are known to many as active and cognitively sharp “super-agers” in their mid 90s. Arlene’s own grandparents immigrated with their family from the Russian village Walter on the Volga River to escape civil unrest. By the time the family reached the United States in 1901, the group included an infant who would one day become Arlene’s mother. They settled in Walla Walla, Washington State, close to other Volga German immigrant families.

Arlene, age 96, attributes her enduring health to several key factors now recognized to boost brain health and lower dementia risk. She has lived a life full of cognitive stimulation from a childhood spent playing in nature and learning in primary school, libraries, and then college at the University of Washington. Raising five children, volunteering in classrooms and museums, and serving as a mountain tour guide with her husband Al, Arlene has constantly embraced an intensely active and social life. But most importantly, she reports, the real secret to their health must have a lot to do with how they have supported each other in a difficult task: “We follow the doctor’s orders.”

Ever since Al, now age 95, developed high blood pressure in his 40s while working as engineer at Boeing in Seattle, the couple has eaten a very low salt diet and lots of fresh vegetables (though they still enjoy Arlene’s grandmother’s family recipes for sauerkraut with apple slices and beef-stuffed cabbage buns). Al still swims in the community pool for 45 minutes every morning and volunteers in a local botanical garden.

Arlene, who has helped to take the residents of a nearby memory loss facility on walks, says her heart goes out to the families of Volga German ancestry who were affected by Alzheimer’s disease, through simple bad luck. She sees these individuals who share her ancestral immigration story not as victims who succumbed to Alzheimer’s disease, but rather as brave individuals who helped researchers form a new framework of brain disease that considered risk as well as resilience.

## THE FOUNDATIONAL THEME OF THE ADRC

Several years prior, in 1983, this ambitious project on familial Alzheimer’s was a moonshot proposal. This longitudinal study aimed to follow research participants over time, collect and store biospecimens, and use emerging technologies in genetic analysis. The effort would require sustained, long-



Alfred and Arlene Noreen in 2019

term funding to have a shot at success. Fortunately, the National Institute on Aging had recently issued a new federal initiative that called on universities to apply to become Alzheimer’s Disease Research Centers (ADRCs). The NIA aimed to create many ADRC’s around the county, which would each have different specialties and themes to foster the study of Alzheimer’s disease from unique areas of expertise and institutional strengths. To this day, the ADRCs aim to provide a continuous infrastructure and necessary resources to support Alzheimer’s and neurodegenerative research, and the training of young scientists.

Bird soon learned that the plans for an ADRC at the UW were already falling into place, thanks to George Martin, MD, then a Professor in the UW Department of Pathology who was driven by an intense interest in the genetics of neurological diseases. Now age 93, Martin clearly remembers sparking the formation of the ADRC. Martin quickly garnered enthusiastic support from the UW School of Medicine Dean’s office. He started to form the team who would carry out the foundational project, and Bird quickly

signed on to lead the project in the genetics of familial Alzheimer’s disease.

“To build a good team, we started by looking for someone who was “hands-on with genetics,” says Martin. “I went to the late Dr. Ben Hall, a brilliant yeast geneticist and an old friend, and—actually—a talented gardener. I remember I used to go to his house to get fresh corn that he grew as a hobby.” Hall, in turn, recommended a post-doc named Gerard “Jerry” Schellenberg. He had received mentoring from Clem Furlong, PhD, UW Professor of Medical Genetics, an expert in gene-environment interactions.

“This is a guy who is now world famous in the Alzheimer’s field, but in 1983, he didn’t know what it was,” says Bird of Schellenberg. “I told him we needed somebody to isolate DNA and look at DNA markers in this little-known disease.” As it happened, Schellenberg was itching for a new challenge. He agreed to run the new ADRC Molecular Genetics Lab and develop genotypes—pieces of an individual’s full genetic profile obtained through the use of biomolecular tools at specific points in human DNA called genetic markers—represented in a chart with the numerical language that computers can understand.

“Bird knew I was getting interested in human genetics,” says Schellenberg. “I’d done bacterial genetics, but I’m interested in human genetics and the human gene mapping. He just came up to me and said, ‘Well, we’re going to put in this application to the NIA. Are you interested in working on this?’ And I said, ‘Fabulous.’ I cared more about genetics than Alzheimer’s specifically, and now it’s probably the opposite way around; I care more about Alzheimer’s than anything else. It was an opportunity to do what I really wanted to do.”

NIA reviewers traveled across the country to hear and evaluate the UW’s proposal in person. But when the initial site visit team arrived on campus in 1983, Martin was shocked. “There was not a single geneticist or cell biologist, which was very surprising, given the specific aims [of our project]” says Martin. “The site visitors, mostly geriatric psychiatrists, were very skeptical about the idea that there were major gene mutations responsible for Alzheimer’s disease. We were presenting a plan for genetics, cell biology, and epidemiology, and they were puzzled as to why we would



**Amidst Bird and Nemens’ search to find more Volga German families with a history of Alzheimer’s, the American Historical Society of Germans from Russia found a lead—a Russian by the name of Professor Plevy who had been working with his wife in the city of Saratov along the Southern reaches of the Volga River. They had been documenting the genealogy of Volga Germans still living in the area. On a visit to Seattle, Plevy gifted the ADRC five massive genealogical documents. Bird was fascinated to find family trees for five of the ADRC’s Volga German families that stretched all the way back into the 1700s. These records did not contain any health indications, but they are inspiring reminders of the human stories behind the research participants who are represented by numbers in research documents. Pictured: Thomas Bird examining historical Volga German family records, 2020.**

want to emphasize genetics in our Center because it was not considered a genetic disease. They thought we were out of our mind, and they did not recommend funding.”

The UW team only became more motivated to show the NIA that genetic family studies held the key for understanding the mechanisms of Alzheimer’s disease. The team persisted and prepared to shoot for a spot among the remaining five center allocations coming up the following year. Meanwhile, Martin impressed upon the NIA Program Manager the importance of including application reviewers who had an interest in genetics or biology.

## BUILDING THE CASE FOR THE UW ADRC

It was Bird who built a better case for their Center’s funding, following a research direction that would eventually lead him to the Volga German family a few years later. Families with a history of Alzheimer’s disease continued to be referred to him by Washington State neurologists who were puzzled by their shared predisposition to the disease. “Many of the Alzheimer’s-type dementia families referred to me during this time fortunately happened to have individuals who had undergone an autopsy, which was necessary for an Alzheimer’s diagnosis at the time,” says Bird. “Back then, ‘senility’ was still the normal term – you had to have an autopsy that proved the presence of Alzheimer’s plaques and tangles.” Today, brain imaging technology or spinal

fluid tests allow doctors to see this protein evidence in living patients, but a diagnosis of Alzheimer’s disease at the time required an expert look at the brain postmortem. Shuzo Mark Sumi, MD, a neurologist, neuropathologist, and lauded mentor, now Professor Emeritus of UW Neurology and Pathology, started to study the brain tissues from individuals in these families who had consented to brain autopsy when they died. The verified presence of plaques and tangles further strengthened the argument that these cases were truly Alzheimer’s disease.

When the NIA came back for the second round of visits, Bird was prepared to make what he hoped was an air-tight case. The team presented their relatively large cohort of research participants from these unique families, autopsy data from several individuals from these families, as well as their advanced genetic tools and qualified investigators who were ready to take on this large-scale challenge. “I remember saying: ‘These pedigrees show three or four generations. Males and females are both affected. It’s autopsy-confirmed Alzheimer’s disease,’” recounts Bird. “If that isn’t genetic, I don’t know what it is.”

“Tom, I think I’d buy a used car from you,” whispered Schellenberg after presentation to the site visitors. This ADRC application, a 537-page compendium of yellowing typewritten sheets, now rests on a shelf on the 14th floor of the Ninth and Jefferson Building at Harborview Medical Center, in the current Director’s office. >>> *Next page*





Marie Walters, 2020

“You have to remember that in the 1980s, before the era of computers, the grant applications were huge masses of paperwork,” said Bird. “This big center grant had to be put all together with a fax, copy, and Xerox machines, and the job fell onto the lap of Marie Walters, the first ADRC Program Manager. And she was able to

do it. I remember seeing tables with all the paperwork that was necessary for submitting the Center grant. And Walters was able to keep track of all of that really well, and keep the Center funded through the years.”

In 1985, under the founding directorship of George Martin, the UW received funding in the amount of \$6,697,620 (about \$16,000,000 by today’s standards) to become one of the first of ten NIA ADRCs in the country. Each directorship transition over the next 35 years would shift the ADRC’s major research themes and contributions. From Directors George Martin, MD (1985-1999) to Murray Raskind, MD (1999-2012), to Thomas Montine, MD, PhD (2012-2016), to Thomas Grabowski, MD (2016 – present, as of 2020), the Center built historic strengths in genetics and genomics, caregiving programs, fluid biomarkers, and neuropathology, and newer strengths in cell biology, stem cell model technology, genetic profiling of neurons, and brain imaging, along with transformative dementia-friendly community outreach at the UW Memory and Brain Wellness Center.

Through these successive waves of innovation however, the original family genetic research of the ADRC’s original Cores and Projects would stay a constant thread and foundation of future discovery. “The ADRC’s family study was one of the most long standing projects that the ADRC had during my time,” says Marie Walters, “which was unusual, because when an ADRC seeks a renewal of funding for the next 5-year cycle, the NIA evaluates progress, some projects stop, and others start. But, most other Centers weren’t approaching Alzheimer’s from a genetic angle. Our researchers were unique in our expertise in that area, among

the first in their fields to study Alzheimer’s in that vein.”

### HOW TO SEARCH FOR A DISEASE GENE

Chromosomes are groupings of the roughly 100,000 human genes, with 23 pairs occurring in every cell in the human body—one chromosome in each pair comes from Mom, and one from Dad. A gene is a unique section of DNA that codes for the production of a specific protein. Copying errors called mutations occur as cells divide, and result in slight variations in the DNA sequence. These mutations can result slightly different versions of the protein that a gene codes for. Most of the time, these slight variations are of little or no consequence to human health—like a word in a long sentence being replaced by a synonym. However, sometimes, the mutation may affect the meaning of the whole sentence—this can provide an advantage to survival, or a disadvantage (a disease). Unless the mutation has a severe effect in early life, it will have a 50% chance of being passed down to the next generation.

Currently, single gene mutations are known to cause an estimated 3% of Alzheimer’s cases and 10% of cases of Parkinson’s disease, amyotrophic lateral sclerosis, and frontotemporal degeneration. These ‘familial’ cases often follow patterns of ‘autosomal dominant’ inheritance, meaning that if a person carries the mutation, then there is a 50% chance they will pass it on to their child.

To study a familial neurodegenerative disease, such as those affecting ADRC families, researchers first need to identify the disease-causing gene. In the 1980s, the first step was to track down which of the 23 chromosomes the gene lived on. “Once the chromosome is revealed, the next step is to locate the actual gene, and then learn what process in the brain that gene is controlling. When we understand what process the gene is controlling, we may be able to alter the process or prevent it from occurring,” Bird described in 1989. “That’s clearly the long-term goal of genetic research.”

Fifteen years before that statement, Bird had used the knowledge of genetic inheritance to search for the location of a disease-causing gene in the human genome. Shortly after Bird’s founding of the first neurogenetics clinic at UW, he began searching for a mutated sequence of DNA in one of his first families of patients – a family with an unusually high occurrence of a rare neurogenetic condition called Charcot-Marie-Tooth (CMT) disease.

Bird started from a family pedigree—a map of the family tree that shows multiple generations of descendants starting from the earliest known relative and that denotes the presence or absence of the disease being researched (see Explainer). Through colors and symbols, it gives an overview of which family members had the disease, and which family members were spared. The pattern of inheritance looked autosomal dominant. To trace the disease gene down to a specific chromosome, he needed some sort of genetic marker—a piece of DNA whose known position can be compared to the inheritance of a disease.

At the time, a handful of genes that determined certain blood group types had been linked to specific chromosomes. Bird noted the family members’ blood group types on the pedigree. To his surprise, he found that a blood group called “Duffy” was always positive in family members affected by CMT and negative in unaffected members. The presence of the Duffy gene strongly correlated with the presence of whatever gene was causing CMT disease in this family.

The two genes appeared to be ‘traveling together’ from generation to generation. Bird knew that genes situated close to each other on the same chromosome are more likely to stay together through generations of chromosomal “cross-over”—an event preceding a sperm or egg’s formation. In cross over, each pair of chromosomes swap sections of DNA with each other before one of the chromosomes in the pair goes into an egg or sperm. So, the chromosomes that go into the sperm or egg cells contain a little bit of DNA from both of the grandparents. The likelihood that cross-over will split up genes onto separate chromosomes

depends on the genes’ physical distances to each other. Therefore, in Bird’s research case, it was likely that the Duffy gene and the mystery disease variant were located very close together, enabling the two genes to be passed down together for generations.

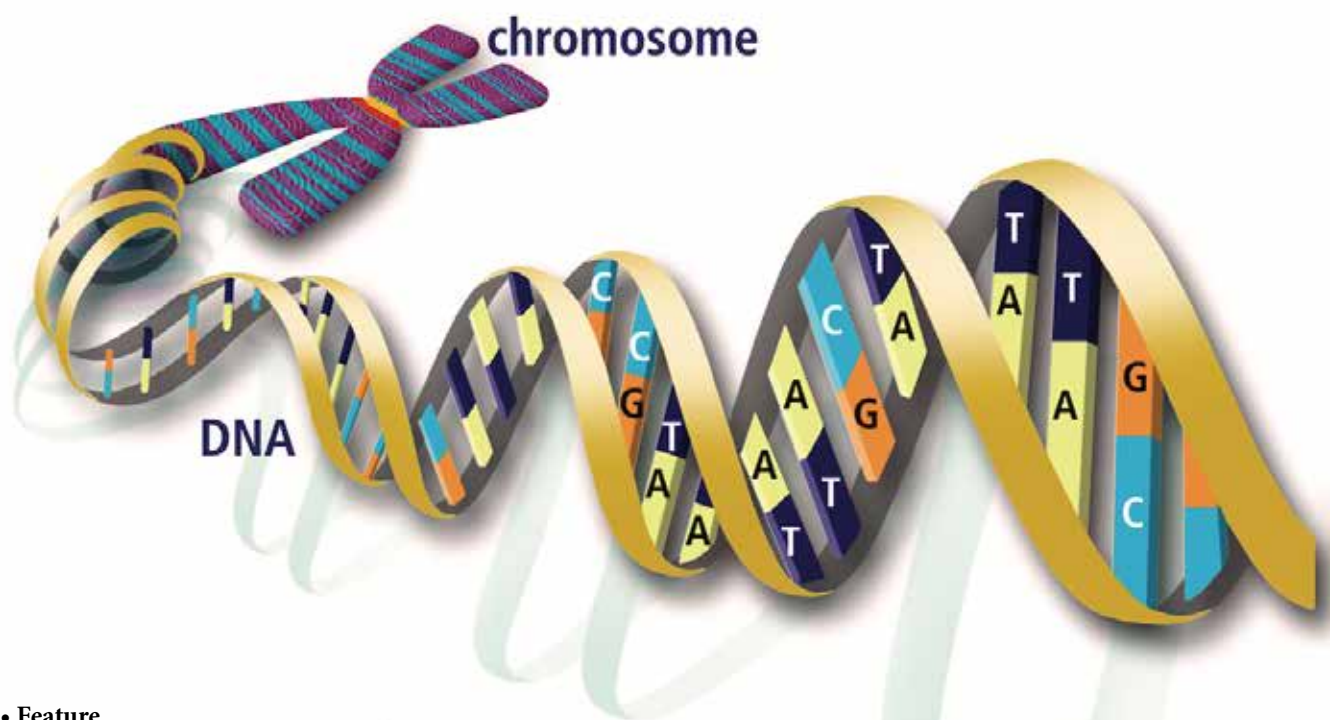
Fortunately, Bird had gotten lucky with Duffy. “When the Duffy blood group is positive, it actually puts a kink in chromosome 1, and you can see it under a microscope,” says Bird. “Because the two genes were traveling together so closely, we knew that the Charcot-Marie-Tooth disease gene had to be on chromosome 1 too.” Bird’s research took place before researchers knew the chromosomal “address” for many genes, so his successful linkage of a disease gene to a chromosome was fairly serendipitous. “Back then, if you didn’t happen to have a marker for the location of the gene, you were out of luck,” says Schellenberg. This success made Bird a candidate for leading the ADRC’s first familial genetics project.

By the time the ADRC launched in 1985, researchers had access to a more advanced method for tracking down a disease gene thanks to genetic advances of the Human Genome Project. “Brand-new research showed that we could take human DNA, chop it up into little chunks, and use them as markers for linkage studies,” says Bird. Those markers gave scientists genomic “addresses” for genes on every chromosome. With known locations for so many genes, scientists started using ‘genetic linkage analysis,’ a powerful new statistical method to detect the chromosomal location of disease gene, based on the understanding of genetic inheritance that Bird had used in the 1970s.

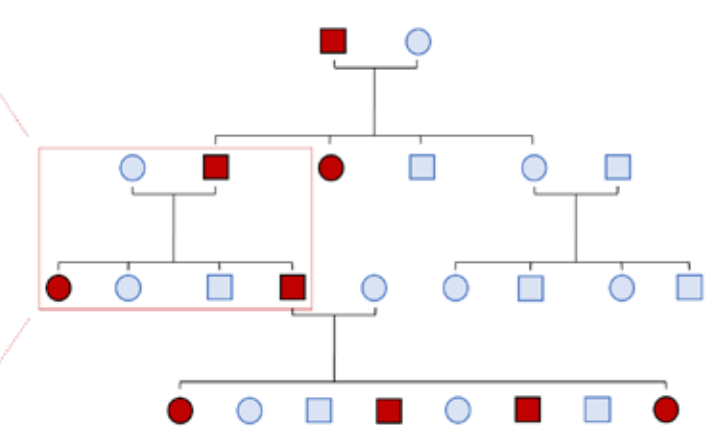
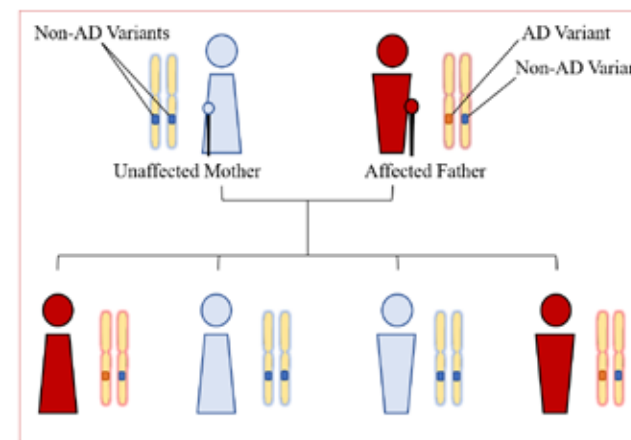


Dr. Thomas Bird in the clinic

>This article is continued on Page 26



### EXPLAINER: AUTOSOMAL DOMINANT INHERITANCE of ALZHEIMER'S DISEASE



Some genetic variants that increase the risk of Alzheimer’s disease (AD Variants) have an “autosomal dominant” pattern of inheritance. If one of a person’s chromosomal copies carries an AD variant, they have a 50% chance of passing that AD genetic variant down to their child, and a 50% chance of passing on the variant that does not increase a person’s risk for AD (Non-AD Variant).

In a medical pedigree, the pattern of a gene’s inheritance is shown with colors and shapes. In this hypothetical example, squares are male and circles are female. Red denotes individuals with a genetic variant that increases the risk of Alzheimer’s disease in adulthood, while blue denotes individuals with other genetic variants that do not increase the risk of Alzheimer’s disease in adulthood.





## Taking the Long Road

ADRC Efforts to Recognize Health Disparities and Better Represent American Indians and Alaska Natives in Alzheimer's Disease Research and Education

### FIRST STEPS

In 1992, ADRC psychiatrist Soo Borson, MD formed the Center's first effort to specifically reach out to disadvantaged minority groups in King County, particularly Asian Americans, creating a mobile clinic that provided free memory evaluations, care referrals, and opportunities to join Alzheimer's research at the ADRC. During this time, Borson began conversations with UW Institute for Health Sciences (IHS) to learn about the possibility and process of involving American Indians and Alaska Natives in Alzheimer's research. The IHS was the only UW entity with a memorandum of understanding with the Seattle Indian Health Service about developing research collaborations with tribal members. Borson connected the IHS with information about the mobile services and access to research participation available through the new ADRC effort to reach the underserved.

### GOING "OFF THE BEATEN PATH"

In 1999, the ADRC Education Core began to go the distance to help improve care for patients with Alzheimer's disease and their families living in rural areas and reservations in western states. ADRC psychologist Rebecca Logsdon, PhD presented a cross-country series of workshops on Alzheimer's disease, caregiving, and healthy aging to Native American and Alaska Native Communities. Focusing on communities without easy access to educational programs, her workshop series took her to rural Alaska, from the Aleutian Islands to Haines, Petersburg, and to Browning, Montana. This investment of time and effort began a long-term partnership with the Blackfeet Indian Tribe, to present talks about brain health and memory loss, provide educational materials, and consult with health-care providers about caring for elders with dementia.

### AN EYE TO CULTURE AND LIVED EXPERIENCE

Logsdon brought ADRC funding to a 2009 study with researchers from the Center for World Indigenous Studies. Together, they enrolled forty-two American Indian family caregivers of individuals with dementia, living on and off reservations into a trial of touch therapy. This intervention uses gentle pressure on energy points to resolve stress and promote physiological relaxation. In the Pacific Northwest, traditional medicine practitioners frequently employ hands-on healing, including energy healing and a variety of massage techniques. The trial found that touch therapy is an effective, implementable intervention for highly stressed American Indian caregivers, which fit with the cultural framework of beliefs and practices.



Rebecca Logsdon, PhD



Soo Borson, MD



Dedra Buchwald, MD



Lonnie Nelson, PhD



Astrid Suchy-Dacey, PhD



Meghan Jernigan, MPH

### BRINGING IN THE EXPERTS

Since 2015, the study of Alzheimer's disease and related conditions in American Indian and Alaska Natives has been a core theme of the ADRC. This focus is made possible by a collaboration with Partnerships for Native Health (P4NH), a local program with a mission of improving the health and well-being of Native people of all ages, directed by Washington State University's Dedra Buchwald, MD. Leveraging her leadership of the Cerebrovascular Disease and its Consequences in American Indians Study, the ADRC established a Satellite Core to gain further insights about Alzheimer's and related causes of dementia in these rural-dwelling study participants, as well as American Indians living in the Seattle area. Lonnie Nelson, PhD (Eastern Band of Cherokee Indians) kicked off the effort with an ADRC pilot project, using brain imaging to document changes in brain structures over time and their relationship to decline. His team aimed to establish diagnostic standards and estimates of prevalence for brain diseases in these underrepresented populations. Soon after, Astrid Suchy-Dacey, PhD joined the ADRC to improve the methods that researchers use to evaluate major modifiable risk and protective factors for cognitive impairment in Native communities, and ultimately, to suggest ways to address disparities and promote healthy aging.

### REACHING OUT WITH NEW RESOURCES

The present-day UW ADRC Outreach, Recruitment, and Engagement Core (ORE) is invested in an effort to reach out to American Indian and Alaska Native communities in the Pacific Northwest, in order to provide resources to people struggling with memory loss and educational materials to local clinic staff. Starting in 2016, Meghan Jernigan, MPH (Choctaw Nation of Oklahoma), then a staff scientist at P4NH, spearheaded an ADRC effort to foster culturally responsive clinical care and information about research participation and brain donation. Her work culminated in 2019 with the ADRC's Indigenous Aging webpage, which is tailored for American Indian and Native Alaskan communities. The site, found on the homepage of [uwadrc.org](http://uwadrc.org), offers education and material resources for clinicians, community health representatives, and Native caregivers. Jernigan also inspired the ADRC communications team to create the Indigenous Aging Brain Health series in issues of Dimensions, based on interviews with Native leaders in healthy aging initiatives, including traditional foods and culturally tailored exercise-based prevention programs.

### A RENEWED COMMITMENT TO INCREASING DIVERSITY AND INCLUSION

The persistent underrepresentation of Native populations in Alzheimer's and related dementia clinical studies and research is a complex issue. In part, this lack of diversity is linked to disparities in health, education, and socioeconomic conditions that limit access to a diagnosis of memory loss, and importantly, feelings of skepticism about medical research. Now, the ADRC is engaged in its strongest efforts yet to increase the diversity of research participants in order to learn about risk factors and resilience unique to these communities. Launching the Native Research and Resource Core in 2020, P4NH's Dedra Buchwald and Patrik Johansson, MD, MPH (Cherokee) aim to develop culturally acceptable data collection and data sharing protocols that also are of significant value to scientists and researchers. All elements of this endeavor are guided by the principles of participatory research methods, which foster a bi-directional exchange of ideas and knowledge, for example, by conducting focus groups and interviews with Native elders and caregivers about their perspectives and attitudes about participating in Alzheimer's research. In 2020, ORE Lead Kimiko Domoto-Reilly, MD was joined by P4NH's Ka`imi Sinclair, PhD, MPH (Western Cherokee) as co-Lead to promote community events and projects that ultimately aim to address longstanding inequities in access to medical care and actionable information about Alzheimer's and dementia.



Kimiko Domoto-Reilly, MD



Patrik Johansson, MD, MPH



Ka`imi Sinclair, PhD, MPH



Images, Krystal Koop (Makah)



Images (of carvings), Krystal Koop (Makah)





## TOWARDS AN ECOLOGY OF THE AGING HUMAN BRAIN: The Shared Project of the Adult Changes in Thought Study and UW ADRC

by Franklin Faust and Genevieve Wanucha

If you ask a group of Seattle King County locals over the age of 65, you can bet that several of them will have heard about the Adult Changes in Thought (ACT) study—they might even be enrolled as research participants or know a friend who is. That's because this study, launched at the early ADRC in 1986, has followed the physical and cognitive health of 5,750 members of major health maintenance organizations in Seattle for decades. At any given time, over 2,000 people are participating, with almost perfect rates of follow up for the check-ins that take place every 2 years. Of inherent interest to many aging individuals, ACT focuses on finding ways to delay or prevent dementia and declines in memory and thinking. It aims to deepen understanding of how the body, especially the brain, ages—and discover how people can age in the healthiest possible ways.

### A LIVING LABORATORY FOR BRAIN AGING

The ACT study functions as a population-based “living laboratory” for brain aging research. Researchers select participants at random from a pool of Seattleites who have reached age 65 and are in relatively good health, and then follow their cognitive trajectories until death. If a participant ever develops dementia, researchers can rewind that individual's history and look for clues as to what lifestyle, medical conditions, or local environmental factors may have contributed to their cognitive decline. There are also secrets to learn from “super-agers” whose minds show cognitive resilience to aging and disease and preserve their mental function remarkably well into old age. ACT's goal is to search for patterns in an aging population that point to lifestyle factors that act as risky pitfalls or supportive bridges on the journey towards lifelong brain health.

“ACT is the world's only study that can link outcomes for dementia, frailty, and aging to data that captures each participant's whole health history, including medical, laboratory, and pharmacy records,” says co-principal investigator of the ACT

Study, Paul Crane, MD, MPH, UW Professor of General Internal Medicine. “If you're really interested in the form of dementia that's in the community, the ACT study is the place to go,” adds Eric B. Larson, MD, MPH, now ADRC Associate Director and Senior Investigator and recent past Executive Director at Kaiser Permanente Washington Health Research Institute where he leads ACT.

The origins of ACT can be traced back to Larson's guiding motivations. As co-founder of the Geriatric Family Services Clinic in 1978, the first clinic on the West coast to provide impaired older persons with comprehensive evaluation for Alzheimer's disease, he already had decades of experience following the trajectory of people developing dementia by the time the ADRC began to form. The geriatrics clinic, along with outpatient clinics at the VA and Harborview Medical Center, became the primary source of research subjects in the ADRC's budding longitudinal study. A groundbreaking feature of an Alzheimer's study at the time, participants also gave consent to ultimately donate their brains for autopsy, enabling the ADRC to connect an individual's meticulously documented clinical history with neuropathological findings from their brain tissue.

However, Larson had always wanted to answer the question: “What can we learn from our research that will ultimately allow people to reduce age-associated cognitive decline and, ideally, prevent and delay the onset of Alzheimer's disease?” He knew that would mean reaching beyond a targeted cohort model, in which a volunteer's interest in participating was often based in already present symptoms or having a family history of dementia. “The vision of the ACT study was driven by the fact that in the early days of my work with Alzheimer's, there were a lot of findings that made a splash and then disappeared. They couldn't be reproduced because they focused on small populations and not on a community sample,” said Larson. He was eager to create

a study well suited for answering questions about dementia prevention in the general community. It would combine attributes of an observational population study and ADRC expertise in neuropathology and genetics.

The dream became a reality in 1986, when Larson and ADRC's Walter Kukull, PhD were awarded an NIA grant to start an epidemiological model of an Alzheimer's incident case registry, similar to cancer registries which have been used extensively to better understand cancers. They established the Alzheimer's Disease Patient Registry from a pool of 25,000 individuals aged 60 and older who were members of Group Health Cooperative, now Kaiser Permanente Health Research Institute. From this early registry, Larson and Kukull recognized that a true cohort study would be best to study Alzheimer's disease, akin to the cohort studies like the famous Framingham Heart Study and Honolulu Heart Watch. They then recruited a randomly selected community sample, formally named the Adult Changes in Thought study in 1994.

Today the ACT study maintains extensive data resources in collaboration with the ADRC, including an unrivaled population of people over 90 years old and a collection of over 850 brains—one of the largest in the world. The ACT team attributes the size and the richness of the data to the comprehensiveness of care provided in Group Health, now Kaiser Permanente Washington, and years of detailed medical records that are now stored electronically. The ACT study has learned many lessons to date, which has contributed data to 98 funded grants, with results published in over 350 scientific articles on brain health and dementia risk. See the next page for highlights of the most influential ACT findings on dementia prevention.



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Department of Pathology, Stanford University



C. Dirk Keene, MD, PhD, Associate Professor,  
Department of Laboratory Medicine and Pathology/  
Alvord Chair of Neuropathology, UW



Caitlin Latimer, MD, PhD, Assistant Professor,  
Department of Laboratory Medicine and  
Pathology, UW

### A GROWING STRENGTH IN NEUROPATHOLOGY

ACT is the only truly population-based study involving autopsy and the study of disease in the brain, or neuropathology—a unique feature that shows how ACT and the ADRC complement each other's strengths. “We truly intersect and interact synergistically at the level of the neuropathology program,” says Thomas Grabowski, MD, ADRC Director. It was Thomas Montine, MD, PhD, Director of the ADRC from 2012-2016, who did the heavy lifting of uniting ACT and the ADRC through common work in neuropathology, allowing ADRC expertise to make even more scientific use of each ACT participant's brain. “The way the ADRC Precision Neuropathology Core's workup looks these days bears Tom Montine's stamp,” says Grabowski.

When Montine accepted a new position at Stanford University, he turned over leadership of the core to C. Dirk Keene, MD, PhD, who has since launched a powerful collaboration with the Allen Institute for Brain Science to adapt tissue dissection and preservation protocols to next-generation technologies that can identify and measure pathology in autopsy tissue and analyze the patterns of gene expression in single neurons. Under Keene's lead, the Precision Neuropathology Core uses identical, state-of-the-art methods to analyze the donated brains of both ACT study and ADRC participants. This data resource has given researchers the ability to investigate the biology of common forms of late-onset dementia and make conclusions that generalize to the local aging community.

In a seminal ACT-ADRC contribution, UW Pathology's Joshua Sonnen, MD, now a neuropathologist at McGill University, along with Montine, Larson, and others, evaluated brain autopsies from ACT and other large population studies. Publishing the paper 'Ecology of the Aging Human Brain' in 2012, the team became the first to report a high prevalence of multiple different pathologies in the brains of cognitively normal older people and characterize it as a late, complex pathology in the community population.

Caitlin Latimer, MD, PhD, co-Lead of the ADRC Precision Neuropathology Core, added to this story in 2019, producing strong evidence for a little recognized factor behind the resilience or resistance to Alzheimer's pathology seen in some of ACT's oldest participants. Her most striking finding was that almost all of the brains from older people with symptoms of dementia showed buildup of a protein called TDP-43, yet the brains of age-matched people who were resilient or resistant did not. The field is now considering whether a secret to resilience to Alzheimer's disease in late life simply depends on never developing TDP-43 pathology. Researchers hope that this ecology of brain disease proteins in the aging brain will inform future biomarker studies and clinical trials with older individuals – setting the stage for new insights into the factors of risk and resilience that influence the susceptibility to common forms of dementia.

Since the complexity of the aging human brain became apparent, ACT and the ADRC have worked closer together to understand the common forms of dementia affecting the community. More powerful together than as separate institutions, the two projects paint a detailed picture of each individual who takes part in research, connecting the dots between cellular processes and lifestyle factors to arrive at a more comprehensive understanding of brain health and disease. “I don't think there's anything in the world that matches the richness of our data and the way we can go back so far,” says Larson. The emergence of this unique strength at the ADRC, and new ADRC/ACT collaborations with the Allen Brain Institute, is fulfilling ADRC Founding Director George Martin's early dreams of genetics and epidemiology coming together to benefit Alzheimer's research. • >>> **Read on to explore the most impactful take-home lessons from ACT!**





## PRESCRIPTIONS FOR PREVENTION

The Adult Changes in Thought study's longstanding commitment to epidemiological research, and collaborations with the ADRC, have helped to build a large body of work on brain health, aging, and disease that is relevant to public health policy. The fruits of that labor are now on the record in the Lancet Commission 2020 Report on Dementia Prevention, Intervention, and Care. Created by an international team of researchers, including UW's Eric Larson and former ADRC leader Linda Teri, PhD, the report is a comprehensive synthesis of the current science of preventing dementia. It provides policy makers, doctors, researchers, and the general public with evidence-based strategies for reducing dementia risk, and the authors recognize the barriers that many people face in accessing the vital components that support brain health at every age.

The report suggests that 40% of all dementia cases worldwide may be prevented by addressing a group of risk factors: high blood pressure, obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, social isolation, lower levels of education, alcohol consumption over 14 drinks a week, traumatic brain injury, and air pollution. "It's not a single thing that's going to lead to late-life dementia," says Eric Larson. "In the report, we emphasized this idea of the life course, with elements ranging from early life to late life that influence risk." Fortunately, existing public health interventions and personal lifestyle changes can directly address these risks. Some help preserve the mind by reducing damage to brain cells from pathology or inflammation; some help by constructing a cognitive "buffer" that keeps the mind functional in spite of the presence of disease in the brain; or, a combination of both fortuitous pathways. Behind the list of preventable risk factors in the 2020 Lancet Report is a history of ACT contributions to our modern understanding of aging and brain health. Highlighted below are some of the most significant findings about what's helpful and what's not.

### HEARING LOSS



- Receiving coverage in the *Washington Post* in 1989, one of Larson's first major studies of the local community population investigated the effect of hearing loss on brain health. Larson worked with UW School of Medicine's Richard F. Uhlmann MD, MPH on a study that found that a hearing loss of at least 30dB, equivalent to the volume of a whisper, was twice as common in people with dementia symptoms, and that the greater the hearing loss, the higher the odds of having dementia. This finding has stood the test of time, foreshadowing current evidence of a strong link between hearing loss and odds of dementia. The team speculated, as do modern-day researchers, that hearing loss could lead to disorientation, especially in socially isolated individuals, and it may predispose a person to loneliness and depression, which in turn can impair cognition, including perception, memory and judgment. *Uhlmann RF et al. Relationship of Hearing Impairment to Dementia and Cognitive Dysfunction in Older Adults*
- Larson worked with a team led by UW Otolaryngology's George Gates, MD for many years on hearing loss research. In 2011, they discovered that hearing loss caused by dysfunction of the auditory processing centers in the brain is a precursor to Alzheimer's disease-type dementia. They recommended that doctors consider referring older patients with hearing loss for neurological evaluation. *Gates GA et al. Central auditory dysfunction as a harbinger of Alzheimer dementia*

### EXERCISE & FITNESS

- People who get their heart rate up, or strengthen or stretch their muscles, for at least 15 minutes 3 times per week may be about 40% less likely to develop dementia than those who move their body less frequently, suggests a 2006 study led by Larson. "ACT was the first study to show the benefits of habitual exercise," says Larson. "And it didn't take much exercise to see the reduction in risk. It's really just about avoiding no exercise. This finding has held up over time." *Larson EB et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older*
- When a VA Puget Sound team scored the physical performance of the study's participants—based on fitness in walking, standing up, balancing, and grip strength—they found that those with low scores were roughly 3 times more likely to develop dementia and Alzheimer's disease during a 6-year follow up period than those who were more physically fit. The 2006 study suggests that the first signs of dementia in older people may be changes in physical function, which often appear before noticeable mental decline. *Wang L et al. Performance-based physical function and future dementia in older people*
- More exercise and activity research is on the horizon. Modern activity monitor technology now allows researchers to gather accurate data on sedentary activity, light exercise, and even circadian rhythms and sleep time from participants in the ACT Activity Monitor (ACT-AM) Study. A new goal of ACT-AM: search the "24-hour cycles" of participants for elements of daily activity tied to risk or resilience to dementia. Amidst the SARS-COV2 pandemic, Dori Rosenberg, PhD, MPH, leader of ACT-AM, is considering the investigation of how trends of isolation have affected the 24-hour activities of seniors. "With these new measurements, I think the ACT study is well positioned to help identify the key features of exercise that are beneficial to cognitive health," said Marilyn Albert, PhD of Johns Hopkins University in her keynote at the 2020 ACT Symposium. "Is the benefit just from aerobic activity? How much activity makes a difference, and at what age? I think ACT can help us communicate to the public about the factors critically important to brain health."



### VITAMIN SUPPLEMENTS & NUTRITION

- The ACT study has repeatedly refuted connections between antioxidant supplements and brain health benefits. In 2008, a team led by UW School of Pharmacy's Shelly Gray, PharmD, MS looked into the use of vitamins E and C, which were thought to be neuroprotective thanks to their antioxidant effects. They found no link to suggest that supplementation of E and C, whether taken alone or together, reduced the risk of dementia. *Gray S et al. Antioxidant Vitamin Supplement Use and Risk of Dementia or Alzheimer's Disease in Older Adults*
- Findings from the Kame Project, an ACT-associated effort that followed the brain health of Japanese Americans in King County, showed that those who drank fruit or vegetable juices at least three times a week might be less likely to develop Alzheimer's disease than those who drank such juices less often. However, these brain benefits were not observed in those who only took antioxidant-rich vitamin supplements (vitamins E, C, and beta-carotene). The study suggested that supplements may lack some neuroprotective chemical present in the juice, suggesting that supplements don't necessarily capture all of the benefits one can gain from including common, healthy foods in their diet. *Dai Q et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project*







## EYE HEALTH

- Researchers in the new EyeACT project think of the eyes as an “under explored window to the brain.” ACT’s unique access to participants’ ophthalmology records allows researchers to examine the link between eye disorders, corrective surgeries, and dementia risk. The team recently found that individuals with diabetic retinopathy, a deterioration of eyesight caused by diabetes, have an increased risk of microscopic strokes in the brain. *Lee CS et al. Ophthalmology-Based Neuropathology Risk Factors: Diabetic Retinopathy is Associated with Deep Microinfarcts in a Community-Based Autopsy Study*
- Cataract surgery, a quick outpatient procedure, prevents blindness, and it may also benefit the brain. At the 2020 Alzheimer’s Association International Conference,

UW Medicine’s Cecilia S. Lee, MS, MD reported emerging findings that cataract surgery is associated with decreased risk of dementia, suggesting a benefit to addressing cataracts as early as possible. *Lee CS et al. Cataract surgery is associated with reduced risk for Alzheimer’s disease. AAIC 2020 presentation*

## MEDICATIONS

- When a 2007 study showed that the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, could help prevent dementia, NSAIDs and dementia became a hot research topic with over thirty observational studies coming out in the following years. Most of these studies confirmed that NSAIDs seemed to lower dementia risk, but a handful of studies raised questions. The VA Geriatric Research Education and Clinical Center’s John C. S. Breitner, MD sought to clear up the confusion with one of the best resources available—a wealth of ACT study medication data that can often be traced back 10 to 15 years for each participant. He and his colleagues found that a history of sustained NSAID usage was associated with an increased risk of dementia and Alzheimer’s disease in elderly individuals, calling the drug’s status as a common preventative treatment into question. *Breitner JC et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort*
- To Larson, ACT’s most important finding concerning medication use emerged from a large study led by Gray in 2015. The study found a link between a significantly increased risk for developing dementia, including Alzheimer’s, and taking commonly used medications with anticholinergic effects at higher doses or for a longer period of time. Many older people take such medications—nonprescription diphenhydramine (Benadryl), for instance. Gray’s team backed up a similar finding of a French team with evidence from ACT’s gold standard drug-use dataset. “It’s now widely recognized that anticholinergics are a risk factor for late-life dementia,” says Larson. *Gray SL et al. Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study*



## SMOKING

- Examination of brains from research participants led to the first finding of a link between heavy cigarette smoking and reduced Lewy Body related neuropathology, supporting previous observational studies that showed a link between cigarette smoking and a reduced risk of Parkinson’s disease. The study found no relationship between smoking and Alzheimer’s pathology in postmortem brain tissue. Still, the Lancet Commission Report lists stopping smoking cigarettes as one of the most significant ways to help prevent the clinical syndrome of dementia, as well as cardiovascular disease. *Tsuang D et al. Association between lifetime cigarette smoking and lewy body accumulation*
- A 2010 ADRC study of the ACT population became the first to show a link between smoking and oxidative damage to the brain, a type of cellular damage caused by reactive oxygen sources that is linked to Alzheimer’s disease and vascular brain injury. The use of antioxidant supplements does not seem to change oxidative brain damage caused by smoking, vascular injury, or Alzheimer’s disease, suggesting that such supplements do not compensate for the risks that smoking poses to the brain. *Sonnen JA et al. Free radical damage to cerebral cortex in Alzheimer’s disease, microvascular brain injury, and smoking*

## TRAUMATIC HEAD INJURY

- Using self-reported data from ACT participants, Kristen Dams-O’Connor, PhD, Director of the Brain Injury Research Center of Mount Sinai, and ADRC collaborators were the first to show that traumatic brain injury (TBI) with a loss of consciousness increases the chance of another TBI later in life. This study’s discovery of the risk of repeated injury supported the need to monitor older adults who sustain head trauma. Today, we know that preventing blows to the head is important, as repetition of injury seems to compound the risk of dementia. Much of our knowledge in this area comes from non-ACT work led by ADRC member Elaine Peskind, MD who uses cerebrospinal fluid and brain imaging to study the link between repeated mild TBI, neurodegeneration, and dementia in American veterans. *Dams-O’Connor K et al. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study*
- A 2016 study led by ACT co-PI Paul Crane examined the relationship between TBI with a loss of consciousness and neuropathology in ACT and other longitudinal cohort studies of aging. The team found that this severity of TBI is linked to greater risk for Lewy body accumulation, as well as the progression of Parkinson’s disease and associated movement abnormalities, but they were surprised to find that the TBI link did not extend to Alzheimer’s disease. “These conditions are very common by the end of life, so we had enough power with our large population to find an Alzheimer’s story and we didn’t,” says Crane. “We found no association at all between head injury during life and Alzheimer-type dementia or the plaques and tangles of Alzheimer disease in the brain. It is a pretty strong negative study and contrary to what the field has found.” *Crane PK et al. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings*
- The science of TBI and dementia is complicated. To learn more, the ACT study collaborates with the Allen Brain Atlas’ Aging, Dementia, and TBI Project to better understand the long-term implications of traumatic brain injury. “So far, we haven’t found any signal of a significant link between one TBI with loss of consciousness and Alzheimer’s disease,” says C. Dirk Keene, MD, PhD, Lead of the ADRC Precision Neuropathology Core. “It’s important to keep in mind that the ACT study enrolls people who make it to the age of 65 without developing dementia. The bottom line is that people who reach 65, and who have had a serious whack to the head earlier in life, have the same risk of Alzheimer’s disease as someone without a TBI. I think that’s good news. However, we could be missing something in all that data, and we are still working on analyzing other measures.” *Edlow BL et al. Multimodal Characterization of the Late Effects of Traumatic Brain Injury: A Methodological Overview of the Late Effects of Traumatic Brain Injury Project*



## FALLS

Slipping and falling at home might lead to hitting the head. In 2004, the ACT Study looked at shoe surfaces and falls among elderly people and showed that falls are more likely in those who wear stocking feet or slippers around their house. Opting for a pair of hard-sole shoes while getting around at home seems to be a simple way to lower one’s risk for falls. *Koepsell TD. Footwear style and risk of falls in older adults*





## CARDIOVASCULAR HEALTH

- High blood pressure can put strain on the heart, and it seems that it may put a strain on the brain as well. A 2007 finding showed that high systolic blood pressure—the first and larger number you’re shown when your blood pressure is taken—was associated with a greater risk of dementia in people aged 65 to 74. *Li G et al. Age-Varying Association Between Blood Pressure and Risk of Dementia in Those Aged 65 and Older: A Community-Based Prospective Cohort Study*
- Two years later, a new association between high systolic blood pressure and cerebrovascular damage in untreated older adults aged 65 to 80 suggested that controlling high blood pressure with antihypertensives may reduce dementia risk by minimizing microvascular injury to the brain. “ACT is one of the first studies to demonstrate the association of vascular pathology to dementia risk, including Alzheimer’s disease,” says Larson. “Over the years, that information has encouraged people to control their blood pressure, avoid smoking, increase exercise, and do other things that reduce vascular risk that have also turned out to be valuable for brain health.” *Wang LY et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study.*
- Cholesterol comes in two varieties: “good” and “bad”. Specifically, “good” HDL cholesterol can lower your risk for heart disease and stroke, while “bad” non-HDL cholesterol raises these risks. In 2017, ACT researchers took advantage of the consistently collected cholesterol data obtained from patient visits to investigate how “good” and “bad” cholesterol might impact the brain. The study was the first to look at differences in neuropathological outcomes based on a snapshot of cholesterol levels at age 70. This led to the finding that higher levels of non-HDL cholesterol at this age were associated with Lewy Body pathology in the brain at autopsy. However, they found no association between HDL or non-HDL cholesterol and Alzheimer’s disease pathology. *Bettcher B et al. Association between Cholesterol Exposure and Neuropathological Findings: The ACT Study*
- In 2018, a team led by UW School of Pharmacy’s Zachary Marcum, PhD found that levels of “bad”, non-HDL cholesterol produced a “U-shaped” Alzheimer’s risk relationship in patients aged 60 to 79, where both higher and lower levels of non-HDL cholesterol led to heightened risk. The study found no association between “good” HDL cholesterol and Alzheimer’s-type dementia. *Marcum Z. et al. Serum Cholesterol and Incident Alzheimer’s Disease: Findings from the Adult Changes in Thought Study*
- ACT’s frequent linking of heart health to brain health hints at a potentially powerful route to preventing dementia. Current epidemiological studies show that the ages of onset for Alzheimer’s disease have pushed out about five years later than the generation 30 years ago experienced, and UW Biostatistics’ Ellen Wijsman, PhD, Lead of the ADRC Data Management and Statistics Core, thinks that gains to public heart health over that time might be pushing that trend. “The difference in the cardiovascular risk prevention profiles of those generations has made huge changes in overall health and has extended life expectancy,” says Wijsman. “It’s possible that the delayed onset of Alzheimer’s that we’re seeing is coming from the benefits of cardiovascular risk prevention.”
- Diabetes is a known risk factor for Alzheimer’s disease that jeopardizes the ability of the body to maintain safe, stable levels of blood sugar. In 2013, Crane led a study published in the *New England Journal of Medicine* that looked at blood sugar levels and dementia risk among ACT participants that found an association between higher blood sugar levels and Alzheimer’s disease in people with and without diabetes, suggesting that lowering blood sugar to safe levels through diet, exercise, or medical treatment, might lower the risk of Alzheimer’s disease. *Crane PK et al. Glucose levels and risk of dementia*
- Crane has just recently expanded off of this 2013 study with new, not yet published, research presented at the 2020 ACT Symposium that further solidifies his previous findings. His team has verified that the link between high blood sugar and dementia is consistent among people with differences in blood pressure and antihypertensive drug usage. Next up, Crane and other ACT researchers aim to see if the link between heightened blood sugar and dementia is consistent among people with different levels of cholesterol and classes of cholesterol medications.



## EARLY LIFE FACTORS & SOCIOECONOMIC HEALTH

- ACT research conducted in the early 2000’s pointed to early-life experiences having old-age consequences for the risk of dementia. Researchers hunted down birth records, census records, and other public records of their participants to find early-life data. When the data was compared to the rates of dementia in those participants later on, the researchers found that having more siblings, growing up in a non-suburban neighborhood, living in a household size of seven or more, and having a father employed in manual labor were all linked to the development of Alzheimer’s disease later in life. This early research raised awareness about the connections between socioeconomic status and the risk of developing Alzheimer’s disease. “Early life socioeconomic wellbeing probably lays down brain reserve,” says Larson, “so that when you get into the late part of life, you have more reserve to draw on before you develop cognitive decline that impairs function.” *Moceri VM. Early-life Risk Factors and the Development of Alzheimer’s Disease*
- Socioeconomic deprivation and racial discrimination lead to worse outcomes in physical and mental health. Over the past 34 years, King County’s socioeconomic and racial diversity has grown, and the ACT study is taking action to achieve a pool of participants that better represents our local population. This year, the study aims to increase its active cohort from 2,000 to 3,000 people, add 2 clinics serving socioeconomically diverse areas, and adopt a recruitment outreach plan that emphasizes racial diversity. With a more representative population, ACT discoveries of risk, resilience, and precision medicine will better serve and include all of Seattle’s vibrant communities.
- Larson and UCSF Memory and Aging Center’s Kristine Yaffe, MD are spearheading the new Systematic Multi-Domain Alzheimer’s Risk Reduction Trial (SMARRT) as another key part of ACT’s efforts to make this needed change. SMARRT directly oversamples from the racial and ethnic communities that are underrepresented in the ACT study of today. The goal is to see how lifestyle changes might be implemented to address the dementia risk factors that ACT has helped illuminate. SMARRT will test the effect of coaching interventions in preventing cognitive decline in a group of 200 older individuals. The personalized coaching will be focused on tackling the specific dementia risk factors present for each participant. Backed by decades of ACT contributions, SMARRT’s prescription for dementia prevention is on track to bring brain-healthy changes into all King County neighborhoods.

## EDUCATION

- In 1991, ACT research found that more years of education predicted a higher score on the Mini Mental State Examination, a common test used to screen Alzheimer’s dementia. Later in 2002, UW School of Public Health’s Walter Kukull, PhD led a team that found that attaining a higher level of education was linked to a lower risk of dementia. Subjects who had more than 15 years of education were at nearly half the risk of subjects with less than 12 years of education. These studies brought to light a difficulty in interpreting results about education and dementia risk. Cognitive screening tests are likely to have a favorable bias towards highly educated people. Education might support the health of neural connections that ultimately preserve a person’s test-taking ability, or it might engender cognitive flexibility or strategies that help them to perform well on tests despite the development of thinking and memory impairments in daily life. These studies remind researchers to consider that observed positive effects of education might reflect a failure of cognitive tests to detect early signs of dementia in highly educated participants. *Kukull WA et al. Dementia and Alzheimer Disease Incidence: A Prospective Cohort Study*
- After following 2,168 non-demented elderly participants for six years, a 2005 study found that lower level of education was associated with a rapid pattern of cognitive decline in individuals with two copies of the APOE4 allele, a genetic variant that increases Alzheimer’s risk. The researchers did not discover such a connection in people with only one copy of the risky genetic variant. The study, published in 2005, showed that lower levels of education could be particularly risky in people already genetically at-risk for Alzheimer’s disease. *Shadlen M et al. Education modifies the effect of apolipoprotein epsilon 4 on cognitive decline •*





...Continued from Page 15 [Article: *The Early ADRC's Search for an Alzheimer's Gene*]

### BUILDING THE MOLECULAR GENETICS TEAM

With Bird ready to do the sleuthing necessary to find more families, and Schellenberg prepared to scour subjects' DNA for clues, they still needed someone to find the answers in the treasure trove of genetic information. At the prodding of George Martin, the Dean's office stepped in to help and ultimately provided funding for the ADRC to recruit a young scientist from Stanford University, Ellen Wijnsman, PhD. She was a statistical geneticist who was uniquely equipped to operate in the worlds of mathematics and computers, as well as in population and disease genetics. "Genius, that one," notes Marie Walters. "I mean, I was in awe whenever I was with her."

Wijnsman's job was crucial. She would use new computing technology to run genetic linkage analysis, combing through

thousands of Schellenberg's genotypes in search of strong correlations between the inheritance of DNA regions and the development of Alzheimer's disease.

The UW ADRC's pioneering project was on the right track, with the right team in place: Bird examined patients and diagnosed Alzheimer's, and ensured quality clinical data, with help from Ellen Nemens, who obtained blood samples and helped evaluate and maintain contact with families; Gerard Schellenberg, molecular biologist, handled the DNA work of generating genotypes; and statistical geneticist technician Ellen Wijnsman developed computational statistical methods to analyze all the data collected from the research and search for genetic linkages to Alzheimer's disease. Technicians in the ADRC's Cell and Tissue Bank grew and maintained white blood cells—the source of DNA—from living patients' samples; and neuropathologist S. Mark Sumi, MD, the first leader of the Autopsy Core, along with others in UW

Department of Pathology, studied the brain tissues from deceased participants.

Also connected to the effort were people such as Eric Larson, MD, MPH, Associate Professor of Medicine in the UW Department of Medicine, who ran the ADRC's registry of patients living with familial and sporadic (non-familial) Alzheimer's who consented for eventual brain autopsy, complemented by a data bank of the clinical information on the subjects. This resource enabled work on many ADRC research questions. For example, Murray Raskind, MD, Associate Professor in the UW Department of Psychiatry and Behavior Sciences, soon to be joined by Elaine Peskind, MD, studied whether neurochemicals found in cerebrospinal fluid samples were different between familial and sporadic Alzheimer's patients.

Though the ADRC team were among the first in their fields to dive into Alzheimer's from the genetic angle, they were not the only ones looking for an Alzheimer's gene. >>> *Next page*

In 1985, researchers George Glenner, MD of University of San Diego, and Colin Masters, MD of University of Melbourne, isolated the plaques seen in the brains of people with Alzheimer's disease and found that they were made of amyloid beta protein. "So, researchers started looking for the gene that coded for amyloid beta," said Bird. "It turned out to be on chromosome 21, the same chromosome that is present in excess in Down's syndrome." This finding explained a curious connection between Down's syndrome and Alzheimer's disease.

For years, scientists had known that virtually all individuals with Down's syndrome eventually develop the hallmark plaques and tangles of Alzheimer's disease by age 40, and some, but not all, later develop dementia. As word of the finding spread, other researchers looked at their families with Alzheimer's disease and indeed came out with results showing a genetic linkage to chromosome 21.

The team at the UW ADRC followed suit in search of this linkage to chromosome 21 in their families. "We were looking for any joint inheritance of the disease with a single genetic marker, and we were using the developing gene mapping resources of the Human Genome Project," says Wijnsman. "Others were building maps and figuring out where these markers were. As they mapped those markers, our team would use them for linkage analysis to query each little region of the genome in search of a link to disease."

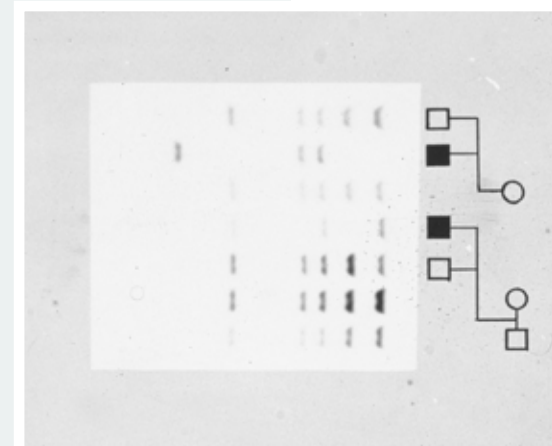
But the science didn't happen overnight. Bird set a high bar for enrolling patient families into the study, holding on to the same standard of requiring clear evidence that at least two patients per family had proven Alzheimer's disease, based on autopsy and tissue analysis.

The genotyping was another tall order. In 1988, the technology allowed Schellenberg to genotype about 1,000 genetic markers in a week—but there were many medical pedigrees to work through. Covering the genome to the best of their ability meant that each individual needed genotyping for nearly 200 genetic markers each.

Running linkage analysis on each one of those markers, one at a time, for their entire study population, added up to a huge computational challenge. "Back when I was getting started at the ADRC, I had a single PC that was completely inadequate. It had one Central Processing Unit, and one processor. It was slow, and some of our analyses took six months," says Wijnsman, who is now Lead of the ADRC Data Management and Statistics Core. "I was borrowing computer time from anyone I could find that could spare it."

"It's a real team approach—people with very special expertise," said Bird. "That's why it takes a lot of time and costs a lot of money."

The ADRC researchers rigorously studied pieces of DNA on chromosome 21 from the families in their cohort, including the Volga German family, but they did not find the linkage that



'Restriction fragment length polymorphism' technology (left) was used to genotype individuals represented on a medical pedigree (right).  
Courtesy, Wessex Reg. Genetics Centre

other studies had found. "There are a couple of possible reasons why we haven't found the linkage," Bird said at the time in 1989. "The Alzheimer's disease in our families may be genetic, but it may be caused by a different gene than in other families. Or perhaps all genetic Alzheimer's is on chromosome 21, but there are presently too few genetic markers to look at, so we haven't been able to see the connection yet. We're just not sure."

London researchers would identify the elusive mutation in the *APP* gene, located on chromosome 21, in 1991 and showed that it was the cause of Alzheimer's disease in two families in England and America. In the years leading up to this finding,

the scientific community at large surmised that all cases of familial Alzheimer's disease would be caused by this single gene on chromosome 21, but fortunately, some researchers at the UW ADRC were not so certain.

### A SHARPER FOCUS

While many in the scientific community were rallying around the easy link between chromosome 21 and Alzheimer's disease, Ellen Wijnsman was ready with a healthy dose of skepticism. "As a population geneticist, you're aware of how much genetic diversity probably exists underneath the biological hood of one disease category," says Wijnsman. "When I started studying Alzheimer's and working with Tom and Jerry, I very quickly became convinced that there was going to be more than one gene for familial Alzheimer's disease – that this was going to be more complicated than the field thought it would be."

The slow pace of research ended up being a blessing in disguise—she had the time and bandwidth to think critically. "It took a long time to generate the genotype data, so I had a lot of time to think about our study design," says Wijnsman. She crunched the numbers and found that it would take years to run statistical tests and look at genotypes for one genetic marker at a time for each case. Additionally, Wijnsman realized that if there were multiple different Alzheimer's genes in their study population, then they would compete for attention in the linkage analysis; it would be difficult if not impossible to get a strong signal for one genetic disease factor. "I sat down and started assessing the drawbacks of trying to do everything all at once, versus recognizing that there may be more than one gene and being prepared for that possibility," says Wijnsman.

Confronting these realities, Wijnsman called a meeting and made her case. "It was very obvious to me that we really needed to change our study design," she said. She made an argument to start dividing the patients up into groups based on how they differed in clinical presentation. Wijnsman wanted to focus on the early-onset cases, based on the availability of detailed medical data about the very first signs of disease and nature of symptoms. She split the cases up according to an under-appreciated variable at the time—how old they were the last time their family reported that they were clinically normal." >>> *Next page*

### • TIMELINE



1996

Faculty and colleagues publish what becomes the most highly referenced paper in ADRC history, with 2,998 citations as of fall 2020. The study shows that 3 different Alzheimer's-causing mutations are associated with significantly elevated concentrations of amyloid beta in blood plasma. The finding suggests that all of these mutations result in Alzheimer's through a common pathway.

ADRC researchers identify a mutation in the Tau gene and published the first report of a genetic cause of the neurodegenerative disease frontotemporal degeneration.

1998

The ADRC website launches, making it easier to learn about and get involved with Alzheimer's research.



1999

Murray Raskind succeeds George Martin as Director, bringing a focus on clinical trials and traumatic brain injury's effect on cognition.

ADRC researchers create the first transgenic mouse with a presenilin-1 mutation, opening up a new avenue for investigating the biology of the Alzheimer's-causing gene in a living organism. They demonstrate that the genetic change causes overactivation of neuronal receptors and subsequent neurodegeneration.





As it turned out, focusing on age-of-onset was a useful way to differentiate between the disease's familial forms. When they divided the patients up by age of symptom onset, they found that the late-onset families didn't seem to follow any strong pattern of inheritance.

"I saw that the later-onset families didn't always have a parent with Alzheimer's and then a bunch of adult children with it as well," says Wijsman. For the early-onset families, however, it looked like the offspring of a parent with Alzheimer's had been born with a 50/50 chance of inheriting Alzheimer's. The team reasoned that first focusing on the genetically straight-forward early-onset population would help them to interpret the data.

"While everybody else in the field was looking at all of their families at the same time, we started focusing in on these subpopulations and really using the data as efficiently as possible," says Wijsman.

The team moved their research in a pioneering direction. In 1990, Bird published a paper that shared the team's insights with the world. Bird plotted age-of-onset data for 31 familial cases out on a graph. It showed three distinct clusters - families with onset before age 50; families with onset after age 60; and families with variable ages of onset. For example, the Volga German families showed onsets between the ages of 40 - 75. It was not only useful, but actually critical, to group patients by the age they started showing symptoms.

"No genes had been discovered at that time in 1990, but I said, 'I'll bet that there are at least three genes for Alzheimer's disease,'" says Bird. This statement went against the grain of accepted wisdom in the Alzheimer's research field at the time.

"[Bird] was the one who opened the door to using age-of-onset [as a key differentiating variable] in our Alzheimer's research study," says Wijsman. "Everybody else followed eventually, because we were successful, and they weren't."

#### "DO-IT-YOURSELF GENOMIC SCIENCE"

The team was hoping that by focusing on subpopulations of early-onset cases, they would have "cleaner" data that would give them a higher chance of success. It was, as Schellenberg remembers, the age of "do-it-yourself" genomic science. "Nowadays, you can view the whole genome sequence online, but back then, the genes were not mapped, and the sequences were not available," he says. They got a lucky break in that regard thanks to James L. Weber, PhD, a collaborator who was working on the Human Genome Project and amassing DNA markers. A UW laboratory technician named Elaine Loomis went to Weber's lab to pick out points of interest in the human genome, run the genotypes from the DNA markers, and send those numerical representations of the genetic code to Wijsman for linkage analysis. Then, Schellenberg would use the results to generate a score of the data's significance for each individual family group. Schellenberg knew that their effort to narrow down the location of a familial Alzheimer's genetic abnormality to a single chromosome had no real guarantee of success, never mind finding its specific "address".

At the end of one long night, Schellenberg processed the one last genotype sent over from Weber's lab. "And I'm sitting there feeding data into my database and printing it out," said Schellenberg. "And I started to see big, positive numbers for a linkage to chromosome 14, and I was like, 'Oh my God!... That was my 'Aha' moment. I had figured that our genetic approach was going to work someday, but the fact that it worked on those early-onset families blew me away." They were the closest to discovering a gene than they had been since they started in 1986.

In 1992, the UW ADRC published the linkage of a familial Alzheimer's disease-causing gene to chromosome 14. While this finding did not involve the Volga German family samples, the finding was a big step forward. "I really credit a lot of our success to Tom Bird," says Schellenberg. Wijsman agrees: "Before the center was even funded, [Bird] was looking at early-onset Alzheimer's families. >>> *Next page*

His finding of those three clusters of ages of onset, and his suggestion that those represented different biological diseases, focused us on the early-onset families and got us in a place to find the linkage to chromosome 14. I credit those decisions as being partly why we made the progress we did make early on," says Wijsman. The team's choice to look at their data in a more selective way helped make success a reality.

#### AT THE CROSSROADS

At this point, the ADRC linkage study had opened the door to actually identifying the Alzheimer's genetic risk factor on chromosome 14, kicking up some scientific competition over who could find it first. A group of scientists at Harvard University and Massachusetts General Hospital followed up on the ADRC's findings and beat them to the identification of the disease gene in several families in 1995. The Harvard team named the gene "presenilin-1" (*PSEN1*) because the newly identified mutation in this gene nearly always led to dementia in people's 40s, at much younger ages than for the other genetic variants of Alzheimer's disease.

Despite the disappointment of not finding the *PSEN1* mutation first, the ADRC's linkage of the mutation to DNA on chromosome 14 allowed for the Alzheimer's research field to come to terms with larger, looming challenges. "Our finding really disturbed people because it showed that the genetics weren't going to be simple - that there would be more than one gene for familial Alzheimer's," says Bird. "The field wanted it to be simple, and everyone was disappointed that it wasn't going to be." Steering in a direction that would characterize the next two decades of ADRC research, the early molecular genetics team embraced the emerging complexities of Alzheimer's disease.

In a landmark paper published in 1989, *Evidence for Etiologic Heterogeneity in Alzheimer's Disease*, the team had suggested that there are multiple different genetic mutations behind familial Alzheimer's disease. They posited that while some families carry a mutation on chromosome 21, there would be other familial Alzheimer's mutations to discover still. The paper went beyond genetic mutations to introduce the influential idea of 'heterogeneity' in Alzheimer's disease, or the concept that several different genetic and environmental factors, such as toxins, trauma, or viruses, may act separately, or in combination, to result in a cognitive syndrome linked to the pathology of amyloid plaques and tau tangles. Genetic factors may act differently in the context of an individual's own biology and health issues, explaining the variability in the symptoms and ages of onset in familial cases, as well as the sporadic, later-onset forms of Alzheimer's disease.

For example, the ADRC team noticed that the Volga German families in their study showed wider variability in the ages of onset than other family groups. Some people developed symptoms at the age of 40 while others did not until age 72. The types of cognitive symptoms and duration of illness also differed from person to person.

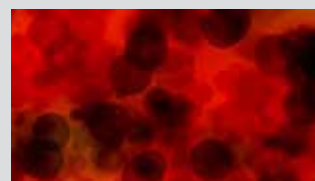
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## ON LOCATION



At ADRC's original offices in the Veteran's Administration Puget Sound Health Care System in Seattle, sets of filing cabinets fill up the floor space from wall-to-wall, stuffed with labeled folders containing decades of neurogenetics work. Inside these cabinets are the family files of the Volga German kindreds and about 2,000 other families that Bird and the ADRC worked with over the years. The knowledge and potential of these documents is unique. "They give you the power to find out who those people were, how they are related to each other, contact information, the whole pedigree," says Bird. "We need all of that information to answer important questions and to help the families' descendants who may have similar problems someday. And that's all in these files." Now, the legacy files are being digitized so that their important history can be preserved for the patients and questions of tomorrow.

#### • TIMELINE



2000

The National Alzheimer's Coordinating Center, funded by the NIA, originates in the UW Department of Epidemiology in 1999, with the ADRC's Gerard Van Belle and Walter Kukull, who remains Director to this day. NACC promotes collaborative research across Alzheimer's Disease Centers and is a freely available data resource to researchers.

ADRC funding renewed by NIA for \$11,200,000 over the next five-year period (adjusted for inflation, that is over \$16 million today).

2003

ADRC investigator Karen Swisshelm begins a new cell-culturing project. As project leader of the ADRC's Cell and Tissue Bank, she oversees a bank of blood and skin fibroblast lines from specimens derived from patients. She and her colleagues are working to develop ways to grow large numbers of cells that have characteristics important in studying Alzheimer's disease.



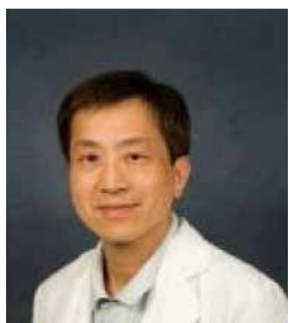


Ellen Steinbart, née Nemens  
(Picture date, 2008)



Ephrat Levy-Lahad, MD

“Telling my graduate students today about the technologies we used to sequence genes back then would almost be like describing how we used to have to mine our own salt or gather our own coals.”



Chang-En Yu, PhD

In the landmark 1989 paper, the authors suggested that the distinct manifestation of familial Alzheimer’s involves factors beyond the gene—even in cases in which a genetic factor was so strong that virtually all people with that mutation would someday develop dementia. This phenomenon of varying levels of resilience energized the idea that it is just as important to study the factors that counter disease pathology in the brain as it is to study the factors that cause it.

ADRC scientists of this early era honed in on the idea that each person has a different combination of biological and environmental factors that influence risk and resilience to neurodegenerative diseases and dementia. This concept of ‘biological heterogeneity,’ from a genetic perspective, was the central theme of the original ADRC – and the researchers soon discovered that the genetics of Alzheimer’s disease would be more complicated than anyone expected. Now, in 2020, the newly renewed ADRC continues a thematic focus on biological heterogeneity, using new tools such as pluripotent stem cells. These in-vivo models allow researchers to probe the mechanisms of genetic variations in the context of an individual patient’s biology and identify therapeutic drug targets.

ADRC researchers now study genes whose variants may contribute some level of risk or resilience to Alzheimer’s: *UBC*, *SORL1*, *MSUT2*, and *APOE*, as well as newly identified risk factors of frontotemporal degeneration and ALS. In this light, the story of the early ADRC embodies the evolution of the field - from a view of Alzheimer’s disease as a single gene phenomenon, to a condition that varies across individuals involving many different underlying factors that converge at cognitive trouble, and ultimately, will require different treatments.

### COLLABORATION LEADS TO DISCOVERY

In 1994, the team was still looking for the genetic cause of Alzheimer’s disease in the affected Volga German families. Schellenberg and Wijsman had ruled out the amyloid gene on chromosome 21 and the presenilin gene on chromosome 14. The data suggested the Volga German families carried a third, as-of-yet-undiscovered gene for Alzheimer’s disease—a gene that had been flying under the researchers’ radar. Eager to bring new energy to the Volga German family mystery, Schellenberg asked Ephrat Levy-Lahad, an up-and-coming post-doctoral researcher in the medical genetics program, to head the project. Under Schellenberg’s guidance, Levy-Lahad prepared and sent the genotypes to Wijsman, who started digging through the data for a correlation between DNA and disease. They started making progress immediately.

“I remember Ellen [Wijsman] came to me with the news,” says Bird. “She said, ‘We’ve got it – a linkage in these families. [Their disease gene] is linking to the long arm of chromosome 1. It’s pointing to a new gene for Alzheimer’s disease. We’ve got to report this.’ They wrote up a paper and *Science* started reviewing it.

After seven years of trying, genetic linkage studies on these Volga German families had finally led the group to an area on chromosome 1, but they had still not identified the gene itself. “We couldn’t look it up—nobody knew what genes were in that particular region,” says Schellenberg.

Levy-Lahad refers to the technology that they used at the time as “prehistoric.” “Genetics has undergone a total revolution since then. Today we have the whole human genome, we know where all the genes are, and we can sequence them in a week,” says Levy-Lahad. “Telling my graduate students today about the technologies we used to sequence genes back then would almost be like describing how we used to have to mine our own salt or gather our own coals.”

Mapping out the different genes within that region on chromosome 1, at the time, required yeast artificial chromosomes, called “YAC” clones, which are human-engineered DNA molecules used to clone DNA sequences in yeast cells. This technology would allow the researchers to run many experiments on their DNA sequence of interest. Fortunately, Maynard Olson, PhD, now Professor of Genome Sciences and of Medicine, had arrived at the UW in 1992 and created an impressive YAC clone library, now at the ADRC’s disposal.

## Missing Alzheimer’s Gene Found

SCIENCE • VOL. 269 • 18 AUGUST 1995

*“This summer, research on Alzheimer’s disease, the memory-loss disorder that affects 17 million to 20 million people worldwide, has sizzled as much as the weather.” —Marcia Barinaga, Science Magazine, Research News*

The team also had help organizing the YACs that they would need to cover the linked region on chromosome 1, thanks to Chang-En Yu, PhD, a researcher who still works as Research Associate Professor in the Division of Gerontology & Geriatric Medicine at the VA.

Levy-Lahad got to work. “We had to take these YACs and start sequencing them to try and figure out which genes were there,” she says. “At first, we were going through them, one by one, just like we had been doing for the chromosome 14 gene.” It took sixty YACs to cover the candidate region on chromosome 1; finding the genetic mutation would be akin to searching for a needle in a haystack.

It is at this moment that external collaboration became a rung on the ladder of scientific discovery, with a call from Wilma Wasco, PhD and Rudolph Tanzi, PhD, who had both worked with the Harvard team that followed the ADRC’s lead to identify the mutation in the presenilin-1 gene on chromosome 14 in their group of early-onset families.

In spite of the previous competition, they collaborated with the ADRC team and gave them a clue that would prove critical in their probe into the genetics of the Volga German families: Wasco and Tanzi had recently found a genetic fragment with a sequence highly similar to the presenilin-1 gene located on chromosome 14. The fragment was a “homolog,” or a genetic cousin of the chromosome 14 gene. The similarity between the two gene sequences suggested that the proteins they encode may have similar functions that could be important to Alzheimer’s biology.

The implication of Tanzi’s message was that, perhaps, searching for this homolog in the Volga German family DNA may lead the ADRC team to the mutation site.

It was far-fetched. The ADRC team was skeptical.

“The significance of the homolog was just that there was something specific to look for,” says Levy-Lahad. “If you would have asked Jerry and I, we would have said that the chances looked really slim.” She searched the YACs in the chromosome 1 region for the homolog gene, and, remarkably, she found it. The homolog was right there, hiding away in the DNA region that the team had pinpointed as the likely site of the Alzheimer’s variant in the Volga German family members. “That was like a sledgehammer to the forehead,” Schellenberg told medical reporters at the time. “It went from being a ho-hum project to... ‘this is the gene’.”

Schellenberg calls the subsequent search to find the gene in the Volga German families “a slam dunk.” He still remembers the moment of discovery, when Levy-Lahad and Loomis were looking at the genetic sequencing data that came out on giant X-ray films, which measured about 14 by 18 inches. “I saw them holding this thing and going into the lab, laughing and giggling and smiling,” he says. “They wouldn’t tell me, but I knew they had the gene.”

“There’s so much of an element of luck in these things,” says Levy-Lahad. “I was working 18-hour days to find this gene, and it could have been a project of a few years if there wasn’t that homolog.”

The team finished the job within a few days, with help from David Galas, PhD and colleagues at Darwin Molecular, a biotech firm in Bothell, Washington. They were able to sequence the gene from the Volga German family members and, critically, confirm that the mutation was only present in the gene in affected family members and absent in unaffected



members. “The genetics all fit together so nicely,” says Schellenberg. “It was incredibly rapid.”

A small genetic change had proven responsible for the Volga German families’ history of Alzheimer’s disease: a single mutation, N141I, within the gene that was named “presenilin-2” for its similar biological structure to the presenilin-1 gene. The ADRC researchers described the discovery in the August 18, 1995 issue of the journal *Science*, and received coverage in *Science Magazine*.

The team toasted their achievement. Their decade-long effort had paid off in the discovery of a new Alzheimer’s gene mutation, fulfilling the aim set out in the original 1985 ADRC application to identify important genetic factors. “The VA didn’t allow alcohol into the building,” said Levy-Lahad, “So we took our bottle of champagne and celebrated in the parking lot.” The popping of the cork didn’t just mark one scientific achievement. It ushered in an era of even more fruitful and expansive research in Alzheimer’s disease genetics.

> *This article is continued on Page 45*



# Celebrating the Stories of ADRC Research Participants

*"I want to do everything I can to help others who come along into this diagnosis."*



**Stuart Du Pen**

Stuart Du Pen, a retired anesthesiologist, lives on the Olympic Peninsula with Anna, his wife of 30 years. After receiving a diagnosis of Alzheimer's disease in 2017, the couple decided to join the ADRC study and look into opportunities to participate in other studies. As medical professionals, they are both familiar with end of life situations, when people often talk about leaving a legacy or donating organs. "Developing the science forward into the future for others is a kind of legacy that both of us really want for him," says Anna Du Pen, who works as an oncology nurse.

For Du Pen, participation in research goes along with lifelong interest in helping others through medicine. "I want to do everything I can to help others who come along into this diagnosis," he says. "I think the least we can do is work together—the researchers and the people living with the disease—to find the answer." It's also about surviving challenges, which, he says, is in his blood. Du Pen is the grandson of a man who survived the sinking of the Titanic, the only one of his group of 5 seamen to live. He went on to serve in World War II as a Captain in the US Navy.

Getting to the ADRC at Harborview takes commitment for the Du Pen couple, who travel two and a half hours each way. Anna says that the ADRC staff make their participation possible, especially research coordinator Yeung Tutterrow. "She understands that it is going to be a long day for us. She organizes our day so that we can go to the ADRC research visit and a memory clinic appointment, all on the same day. She did all the footwork, so I didn't have to make those phone calls. It shows she understands that we need help."

Adapting to new challenges, Du Pen keeps his mind active with games like Quarkle, doing the laundry and housework, and caring for a new puppy. He maintains a vegetable patch in a raised garden bed and enjoys watching birds. The couple feels lucky to live close to family, including nine grandchildren. If you ask whether the diagnosis of Alzheimer's disease changed his marriage in any way, Du Pen will tell you: "We're probably closer now than we've ever been in the past. And we were close before." •



**Vivian Lee**

Vivian Lee was the first African American student admitted to the 4-year Bachelor of Nursing program at the UW in 1955, as well as the first African American registered nurse hired at the Seattle VA hospital. She went on to be a trail blazer in nurse practitioner training and public health for low-income communities of color. As a leader in the U.S. Public Health Service for 20 years, she implemented women's health research projects and clinics in the Pacific Northwest.

Lee, 82, has been volunteering in ADRC research for over 20 years. "I wanted to volunteer, even before my mother developed Alzheimer's symptoms at age 89," says Lee. "I just felt the need for more women of color, especially African American women, to be involved in medical research." She suggests that the ADRC could increase the diversity of the research cohort by setting up study sites in central or southern areas of Seattle, such as Columbia City and Beacon Hill.

Lee takes after her mother, Alvarita Little. Alvarita grew up in a southeastern Texas farming community, receiving education in a school for African American children that did not provide access to high school. She would later pursue social work and become a community service leader in Seattle. She gained support from the city to fund and establish three girl's clubs, including the Alvarita Little Center 1969, now home to the YWCA GirlsFirst Program.

As her mother aged, Lee and her husband moved next door to support her. So, Lee noticed when Alvarita forgot how to make her famous Texas-style potato salad and faltered in managing her budget. Yet, clever, resilient, and resourceful, she was able to score normally on cognitive tests, escaping a diagnosis of Alzheimer's again and again. It would be a long time until a doctor finally agreed with Lee that Alvarita needed dementia care.

It is her mother's long-delayed opportunities to access needed resources that shape Lee's vision for Alzheimer's research: "I hope for earlier diagnosis, and I hope that primary care physicians will become more astute at looking for symptoms and referring families to proper care." Lee says she hopes to follow in her mother's footsteps in one more way: "I hope I will be a super-ager too." •



**Carolyn Chapel**

Carolyn Chapel's journey to ADRC research participation is a family story. Both her mother and her mother's sister had an atypical form of Alzheimer's. They experienced difficulties getting a diagnosis, partly because they retained their verbal abilities. After her mother died of pancreatic cancer, Chapel fulfilled a wish and gave the UW the most precious gift there could be: her mother's brain.

As a retired educator and President of the Substitute Teacher's Organization in the Edmonds School District, she is proud of all the procedures she helped institute upon returning to the workplace after raising two children. But she is also proud of her mother.

Chapel remembers the moment when the research team showed her the report on her mother's donated brain. "Seeing her brain image made me proud of her," says Chapel. "I said out loud when I read it: 'Mother, you did so well with what you had.' It was very moving to me because I hadn't realized how well she had done with this great amount of damage."

Attuned to her family history of Alzheimer's disease, Chapel decided to join the ADRC study. "I am optimistic that there will be discoveries for future generations," she said. "So, if I can help the researchers in some little way, I will." Chapel has had good experiences with the ADRC, remaining committed even as her own symptoms of Alzheimer's affect her. "The research study team has always treated me like I was special person and seemed to enjoy having me as they put me through various tests and exercises."

A correct diagnosis from the UW MBWC clinic gave her the information needed to make important life changes. She stopped driving, moved with her husband Roy into an assisted living facility, and accessed community resources.

She points to MBWC neuropsychologist Kristoffer Rhoads, PhD, who gave a talk about sleep and brain health. This motivated her to get tested for sleep apnea, which led her to use an apnea machine every night. "I'm still plugging along with it, and I don't need to take naps as much as I had to in the past," she says. "All in all, I'm sleeping better at night." •



**Dixie Wilson**

Participating in ADRC research is just one of the many gifts of time, effort, and funds that Dixie Wilson has given to the UW, her alma mater. Upon returning to the Seattle area over two decades ago after a career in sales and marketing, Wilson began to volunteer in community service roles at UW Medicine, Seattle Children's, and other organizations. Her support for Alzheimer's disease started in 2001, when she joined the UW Friends of Alzheimer's Research, a group dedicated to supporting the ADRC. She soon stepped into a leadership role as a board member, chaired the UW Friends of Alzheimer's Research Petite Wine Auction. From there, she and her husband established the Steven G. and Dixie Y. Wilson Endowment for the ADRC, a fund that supports research to better detect early signs of Alzheimer's.

Wilson's specific interest in Alzheimer's disease comes from her family's experience. Her father was one of five siblings who developed the condition. At a fundraising function, the Wilson's met Thomas Bird, MD, a leader at the ADRC. "When I told him a little bit about my family history, he asked me if I'd ever be interested in participating in research. I took his card, and when my dad passed away, I reached out to Dr. Bird. That's how I got started."

Beyond concerns about her family history, Wilson's passion is larger than herself. "I also have an overreaching need to do whatever I can to eradicate the disease, and I am in the position to contribute and speak up. Back when my family was dealing with Alzheimer's, no one was talking about it. Alzheimer's was not something that was openly discussed. The stigma around it really bothered me, and I wanted to do what I could to try to put a voice to the common experience."

Wilson continues to provide insights and support to the UW Medicine Strategic Initiatives Committee and the UW Medicine Scholarship and Student Support Committee. Alzheimer's takes center stage in her advocacy, because she knows the investment will pay off. "I do believe that in short order, we are going to have drugs in the pipeline that might be able to ward off the disease for some of us." •





## The Far Reaching Legacy of Non-Pharmacological Interventions and Caregiving Programs at the Early UW ADRC

By Genevieve Wanucha

“A big tangled knot” is how Linda Teri, PhD has long thought about the daily life challenges of both the person living with dementia and the care partner. This simple visual describes her approach to helping those dealing with behavioral issues, such as agitation, depression, and sleep disturbances, as well as the social factors that worsen or improve challenging home situations. Teri, now Professor Emerita in the UW School of Nursing, served in the past as Director of the former UW Geriatric Family Services Clinic, faculty in the UW Department of Psychiatric and Behavioral Sciences, and ADRC leader in medical and caregiver education for over twenty years. “I’ve always been interested in taking the knot and pulling it apart,” she says. “If you pull a few strands out, it’s still a knot, but maybe it’s less tangled. What strings can we pull from this amorphous, scary tangle of challenges that will actually help people?”

ADRC-affiliated researchers have a history of pulling on those “strings.” In the early 1980s Murray Raskind, MD, ADRC Director from 1999-2012, found that family support groups could resolve feelings of isolation and fear for spouse caregivers. Susan McCurry, PhD focused on sleep and showed that scheduled, regular exercise and light exposure during the day were powerful strategies in managing sleep disturbance in Alzheimer’s disease. Peter Vitaliano, MS, PhD studied the health effects of caregiving psychological stress and coping. Michael Vitiello, PhD studied the link between sleep disruption and cognitive changes and the use of sleep EEG for diagnosis of early Alzheimer’s disease, as well as treatments for caregiver sleep problems. Rebecca Logsdon, PhD

worked with Teri and McCurry on testing behavioral therapies and teaching skills to alleviate depression and anxiety.

Through the 1980s and 1990s, the study of behaviors in the Alzheimer’s field was outside the mainstream. Teri remembers the attitude of other researchers that dementia was a cognitive disorder, so behaviors were simply epiphenomena, or by-products of a disease process: “Why bother studying them?” “We were still the only group with a non-pharmacological focus on dementia behaviors,” said Teri. “At the same time, families were being told there was nothing they could do about their loved one’s behaviors, except to give medications with side effects and limited benefits.” It was this under-recognized human need that motivated her to identify the most effective strategies for caregivers to improve their home situation.

Teri began her research career at the early ADRC tracking the kinds of behavioral problems affecting research participants and their care partners who came through the Clinical Core. She soon ran into a research roadblock: there were no good measures of behavior, no scoring systems for caregiver reports about their loved one’s behaviors. This lack of objective measures limited researchers’ ability to define observable types of behaviors, rate severity level, compare groups of patients, and ultimately detect declines or meaningful improvements during an intervention or treatment study. As a psychologist, Teri also wanted a way to understand how the caregiver’s response can affect the emotional state and behavior of a person living with dementia.

Doing her homework, Teri reached out to Steve Zarit, PhD, a pioneer in the study of caregivers at Pennsylvania State University. He allowed her to use and improve his behavior measurement system: “Whatever you think will make it better,” he told her.

In 1992, Teri, along with Zarit, Logsdon, and Vitaliano, published the ‘Revised Memory Behavior Problem Checklist,’ a 24-item caregiver-reported measure of observable behavioral problems in dementia patients. Today, the tool is recommended by the American Psychological Association as a reliable and valid assessment of both the behavior problems in dementia patients, and the extent of caregiver distress related to those problems, and it has been translated into five languages.

“I think it has gotten a lot of attention because the checklist captures the behaviors and the caregiver’s reactions to them,” says Teri. Being able to “capture” a picture of the behaviors in the context of a patient’s social environment allowed her and her team to tackle those “tangled knots.” They could better identify the threads to pull to most effectively unravel the complex knot of challenges affecting care partners. These non-pharmacological approaches that grew from this foundation stand as one of the historical legacies of the ADRC and parallel efforts that have had the farthest reach into the most intimate and difficult parts of people’s lives.

### DOING THE ABCs

In the early years of the ADRC, Teri and Susan McCurry, now a research professor and vice chair of research at the UW School of Nursing, drew from social learning theories in psychology to create a framework for understanding the behavioral changes that occur in individuals with dementia. They called it the ABCs, where a Behavior is determined by its Activator and its Consequences. With this formula, caregivers can “get active” to change the behavior by either changing the situation that triggered it or the event that follows it. The team found that common “activators” and “consequences” of behaviors revolved around caregiver communication styles, such as arguing or holding unrealistic expectations about loved one’s ability to remember or perform tasks, which can produce a vicious cycle of worsening interpersonal conflict.



Back row: June van Leynseele, Piruz Huda, Joanne Webb, Linda Teri, Ph.D..  
Front row: Cathy Blackburn, Julie Cleveland, Ray Houle, Adam Templeton.

ADRC RDAD Team, 1990

NIH funding in 1993 made possible the first application of the ABCs to a behavioral intervention designed to reduce physical disability and behavioral problems in patients with Alzheimer’s disease. A group of ADRC-affiliated investigators, including Teri, McCurry, Logsdon, Eric Larson, MD, MPH, and Wayne McCormick, MD, joined together to conduct Reducing Disabilities in Alzheimer’s Disease (RDAD). Rather than focusing on one area of impairment, RDAD tested the first-ever integrated mix of medical, behavioral, and psychosocial interventions, such as exercise. This first study enrolled patients in the Alzheimer’s Disease Patient Registry, a group of Group Health Cooperative members willing to participate in research, created by Larson and Kukull in 1986 to better understand Alzheimer’s disease in the wider community. Over time, RDAD evolved into its present-day form: a home-based exercise program, combined with caregiver training in problem-solving strategies, practical communication, and pleasant events that can improve the lives of cognitively impaired participants and their caregivers.

“I cannot stress how much this program has helped me. It saved our family’s sanity,” an RDAD participant named Tom told the team. Tom had joined the study to get

better support and guidance in caring for his father, an African American man living severe dementia and depression. At the end of the intervention, Tom and his father were exercising together four days a week, and his father was now strong enough to get off and on the toilet by himself. Tom reported that using the ABCs helped him solve some of his most vexing caregiving problems. After Tom worked to identify and modify the activators for his father’s habit of undressing at family functions, he was soon able to react calmly, redirect, and assist his father back into clothes.

Studies of RDAD show that the home-based intervention increases physical activity and reduces stress for people living with dementia and their care partners. It has since evolved through various iterations, thanks mostly to funding from the National Institute on Aging, but also state contracts to train Areas Agencies on Aging senior home care staff in Washington, Oregon, and across the country.

In 1999, Teri received a 5-year Pioneer Award from the Alzheimer’s Association to take ABC behavioral management approaches that they had been testing in families living at home and bring them into assisted living settings.

>>> *Next page*



The team launched Staff Training in Assisted Living Residencies (STAR), the first program to address the challenges of providing care to residents with dementia in assisted living. “STAR was a game changer,” says Teri. At the time, there were no training or education programs for staff in assisted living care facilities who interacted with people living with dementia, and often depression and anxiety, every day.

As a staff training program, STAR required hands-on work by ADRC team members. Piruz Huda, RN then working as a psychiatric health provider and research study consultant, helped develop the manual and video training components, distributed through the ADRC, used in assisted living facilities. As a STAR trainer, he engaged care staff in role-playing and discussions. “When people describe to me what hasn’t worked, I like to work with them to teach them some simple skills, and find a way that does work,” Huda said at the time in 1999. “To see their appreciation, that they feel better working with the resident, and especially that the resident feels better, is very rewarding.” This and future work resulted in publications that showed STAR improved resident outcomes, reduced dementia-related problems, and improved staff skills and job satisfaction.

### ADAPTATIONS

Today, many different versions of RDAD, STAR, and STAR-Caregivers (STAR adapted for family caregivers) are part of a group of popular validated non-pharmacological interventions, known collectively as Seattle Protocols, widely adopted in homes, clinics, and facilities throughout the country and world.

“I’ve never felt like I owned these interventions. My goal was always to give it away, to get it into the hands of the people who needed it,” says Teri, who left her role in the ADRC in 2009 to expand RDAD at the UW School of Nursing. She is now focused on helping other researchers to adapt these ABC-based programs for those who may need them the most.

Inspired by the effectiveness of RDAD, Karen I. Fredriksen Goldsen, PhD, Professor at the UW School of Social Work, teamed up with Teri to design and integrate specific components of the intervention to address the unique needs of the aging LGBTQ population and evaluate its effectiveness in an ongoing clinical trial named the Innovations in Dementia Empowerment and Action (IDEA) Study. In this free six-week cognitive behavioral intervention program, a care partner and a person living with dementia are matched up with a coach, who helps both the caregiver and the person experiencing symptoms to develop strategies to solve problems that may arise. The intervention is being offered in Seattle, San Francisco, and Los Angeles.

STAR-Caregivers is undergoing similarly robust expansions and improvements. Currently, UW School of Public Health’s Robert Penfold, PhD is working with Teri and McCurry to pilot a less expensive, shorter, virtual version with patients and caregivers at Kaiser Permanente Washington. This effort, STAR Caregivers: Virtual Training and Follow-up, is a NIA-funded clinical trial to improve the behavioral and psychological symptoms of dementia and reduce caregiver burden without the use of anti-psychotic medications. Alongside Penfold, Maggie Ramirez, PhD of the UW School of Public Health is adapting the STAR-Caregivers program to fit the cultural needs of Spanish-speaking Latino family caregivers and developing a mobile app to ensure easy access to the program.

As Teri reflects on the widened landscape of behavioral interventions and culturally-tailored caregiver resources that exist today, she points to a sign of their positive impact. “One encouraging thing I’ve seen over the years is that the idea there’s “nothing you can do” has become less common, while the idea that caregivers can learn helpful behavioral skills has become much more common.”

Despite the relatively increased availability of resources, dementia caregiving will always present some form of the “tangled knot of challenges,” as Teri calls it. “I expect in many ways that the emotional burden for caregivers hasn’t changed from 20 years ago and is probably as intense as ever,” she says. For this reason, the ADRC team continues to honor and build on the long-reaching legacy of the Center’s past foundational work in non-pharmacological interventions. The ADRC, in partnership with the Memory and Brain Wellness Center (MBWC) clinic, serves as a point of referral to the IDEA Study and STAR-Caregivers and spreads the word about these and other opportunities to the general public and ADRC research participants. The MBWC regularly offers a free program, Powerful Tools for Caregivers, as well as many community wellness talks and workshops.

Infused with the MBWC’s emphasis on resilience and mindfulness, these resources help people learn new habits to take care of their own selves while they care for a loved one. At heart, the Center shares Teri’s enduring goal: to support and empower family caregivers to examine their own tangle of physical and emotional challenges, pulling on the loosening threads, until things get a little easier. •



### • TIMELINE

ADRC makes a push to promote caregiver self-advocacy, drawing from the National Family Caregivers Association. They make caregiving and self-care key topics of the 19th ADRC Public Forum.

ADRC receives a 5-year NIA funding renewal of about \$15 million, enabling new research including projects to map new genes involved with late-onset Alzheimer’s disease and modify the age of onset, and work to characterize cerebrospinal fluid proteins in geriatric dementias.



Former and current ADRC faculty and staff successfully launch the Alzheimer’s Disease Genetics Consortium, an initiative to bring genetics data from Alzheimer’s Centers around the country together to run large-scale association studies in search of new genes influencing late-onset Alzheimer’s disease.



NIA renews ADRC funding for next 5 years for \$12.6 million, adjusted for inflation.

*Self care isn't a luxury. It is your right as a human being....remember your own good health is the very best present you can give your loved one.*

2004

2005

With consultation from ADRC’s Rebecca Logsdon, the WA Department of Social and Health Services starts a project to develop dementia caregiving programs, as well as consultation and counseling services in order to reduce caregiver distress and improve quality of life for individuals with dementia and their caregivers.



2006

The ACT Study publishes a groundbreaking study which suggests that regular exercise can prevent or slow the onset of dementia in the elderly. Read more on Page 21.

2007

ADRC’s Jing Zhang, Elaine Peskind, and colleagues make a major step on the path toward early and accurate diagnosis of several neurodegenerative brain diseases. Using an advanced analytical technique, they have identified proteins in the human cerebrospinal fluid that may serve as biomarkers for Alzheimer’s and Parkinson’s diseases and Dementia with Lewy Bodies.

2009

The ADRC celebrates research participants by giving “The Research Longevity Award” to the oldest research volunteer who is 103 years old. “The Above-and-Beyond Award” goes to the person who has had the most lumbar punctures (spinal taps) for the biomarker studies; this award went to a volunteer who had seven. “The Research Perseverance Award” went to two people who had each participated for twenty-two years in ADRC research.

2010



NIA funds the Pacific Northwest Udall Center for the study of Parkinson’s disease. Several UW ADRC faculty join the new Center in investigating the cognitive impairments seen in Parkinson’s disease. The present-day Pacific Udall Center is based at Stanford University and maintains ADRC collaborations.



Are Females at a Higher Risk of Alzheimer’s Disease?



Back when the Alzheimer’s research field was in its infancy, researchers were working to understand the scope of the disease’s consequences for public health. Prevalence studies took “Alzheimer’s censuses,” which showed a higher number of females living with Alzheimer’s disease than males, igniting the widespread idea that females are at higher risk. Other researchers thought that more females may be affected because they tend to live longer than males, and the risk of disease increases with age. The complex problem sparked curiosity among researchers, leading to efforts to crack what is now an age-old question: how does biological sex affect dementia risk?

Haydeh Payami, PhD, Professor of Neurology and Genetics at the University of Alabama, prior research scientist at Oregon and Health Sciences University’s Alzheimer’s Disease Center, and collaborator with the UW ADRC, waded into this scientific debate in 1996 with a study examining two familial Alzheimer’s disease kindreds. She found that the females in these families were more likely to develop Alzheimer’s with age, and that they tended to develop the disease at a younger age than the males.

Payami investigated the trend further, looking specifically at the risk tied to *APOE*  $\epsilon$ 4, one of three key alleles (variants) of the *APOE* gene, the strongest known risk factor other than age for late-onset Alzheimer’s disease in European populations. Her research showed that males had no significant added risk from carrying a single copy of *APOE*  $\epsilon$ 4, but that females did. The study suggested that this sex-based *APOE*  $\epsilon$ 4 effect might be a factor that put females at a higher risk for Alzheimer’s disease than males.

In 1997, an influential meta-analysis out of Boston University School of Medicine, supported the UW ADRC’s findings. The team crunched the numbers on thousands of Alzheimer’s disease cases and controls pooled from clinical studies with volunteer participants, producing an analysis that established a sex difference in *APOE*  $\epsilon$ 4’s influence in these participants, showing that females with one *APOE*  $\epsilon$ 4 allele have a fourfold higher odds of Alzheimer’s disease than male carriers. “That paper fairly firmly settled the field’s acceptance of the hypothesis that sex effects were interacting with *APOE* genotype effects to put women at greater risk,” says

ADRC’s Ellen Wijsman, PhD, Professor of Biostatistics, who collaborated on Payami’s papers in 1996. For a time, she notes, the study largely put the debate to rest. This paper ended with a caution about the generalizability of the results to risk in the population at large, and the need for prospective cohort studies to provide estimates of absolute risk of Alzheimer’s disease.

In 2017, the possibility of elevated female risk was called back into question. New data sources became available thanks to the Framingham and Rotterdam studies, two long-running longitudinal cohort studies that continuously recruit, in mid-life, and follow groups of individuals as they age. Whereas clinical studies select for demographics more likely to volunteer for research, these cohort-based longitudinal studies take participants earlier and at random from a larger community – resulting in a less biased, more complete picture of risks to individuals.

**Sex may not affect overall risk of Alzheimer’s dementia, but more recent findings from the ADRC and elsewhere indicate that male and female brains may tend towards different neurological hazards as they age.**

Wijsman points to a 2017 study that analyzed the Framingham and Rotterdam data and found little to no evidence that males and females get Alzheimer’s disease at different rates, regardless of *APOE* status. “The best data today shows that if you have a seventy-year-old man and a seventy-year old woman, their risk of Alzheimer’s disease does not seem to be different,” says Wijsman. “That’s a change from what we thought 30 years ago.” The bottom line: Current evidence suggests that the overall risk for Alzheimer’s disease is no different for females than it is for males. Researchers now look forward to results from the Atherosclerosis Risk in Communities Study, which includes non-white populations.

Sex may not affect overall risk of Alzheimer’s dementia, but more recent findings from the ADRC and elsewhere indicate that male and female brains



Elaine Peskind, MD

may tend towards different Alzheimer’s-associated neurological hazards as they age.

In 2017, longtime ADRC researcher Elaine Peskind, MD, Professor in the UW Department of Psychiatry and Behavioral Sciences, brought her unique expertise to bear on the question of how differences in sex and *APOE* status affected the presence of biomarkers for Alzheimer’s and vascular disease in cerebrospinal fluid (CSF).

The ADRC study found that females carrying a copy of *APOE*  $\epsilon$ 4 variant had more Alzheimer’s protein in CSF, while males, regardless of *APOE* genetics, had larger indications of vascular injury to the brain—both of which are factors that are thought to put a burden on the brain and contribute to dementia.

Recent research out of University of California San Francisco, including two major figures in ADRC history—UW’s Walter Kukull, PhD and University of Pennsylvania’s Gerard Schellenberg, PhD—found evidence to suggest that differences in male and female neurogenetics may be important for predicting disease progression. This finding adds even more complexity to the longstanding question of what determines sex-based differences in dementia risk.

There are likely to be many sex-related factors at play in the trajectory of a person’s cognitive wellbeing, and fortunately, our Center has the tools to tackle complex, biological problems. Guided by a framework of biological heterogeneity, ADRC scientists will continue to work to make sense of these risk profiles and progress the science towards precision medicine treatments that benefit the brains of each sex and the wide variety of biological factors therein. •



## High Standards

By Franklin Faust

Ellen Wijsman will admit that she doesn't have all the answers, but she might just have all the right questions. As Professor of Biostatistics in the UW School of Public Health and UW Division of Medical Genetics/Department of Medicine in the School of Medicine, she has a healthy skepticism for new scientific discoveries about Alzheimer's disease. If something doesn't add up during a science talk—whether it's an unsubstantiated assumption, a subtle methods glitch that complicates the interpretation of the science, or a study population too small to detect a robust correlation between a hypothetical risk factor and disease—Wijsman speaks up, asks questions, and ultimately improves understanding by exposing logical flaws and offering solutions. The moment her voice fills the room at a presentation, ADRC researchers turn in their seats, anticipating an incisive reality check.

Wijsman focuses on using statistical analysis for defining the inheritance patterns of Alzheimer's disease and identifying connections between a risk factor and disease in distinct population groups. In other words, she uses mathematical models to find meaningful patterns and insights into disease risk hidden within massive amounts of medical data.

In the lab, as in meetings, her reputation for scientific rigor and high standards proceeds her. "In our lab, she is famous for saying, 'Nice result—now can you make it go away?' She always encourages us to double check assumptions and think through their implications," says Nicola Chapman, PhD, a research scientist in Wijsman's laboratory who has worked with her for 25 years, "She has definitely nurtured in me a deep skepticism of surprising results, which in the end results in better science." By repeatedly holding herself and others to a gold standard, Wijsman brings out the best in those around her.

She first arrived at the UW ADRC in 1987 to fill the role of liaison between statistics and genetics on an ambitious project to identify

genes involved in familial Alzheimer's disease. For 15 years, Wijsman has served as Lead of the ADRC's Data Management and Statistics Core (DMS), directing data support for many ADRC projects and providing assistance with statistical analysis to junior researchers. Her retirement from this position marks the end of 33 years of direct involvement with our Center. As she moves on to a role of collaboration and consultation, she

leaves behind a large pair of boots to fill. Her work as a mentor, teacher, and scientist has advanced scientific discovery and elevated the careers of those around her in a way that continues to help our Center thrive.

### A KNACK FOR STUDY DESIGN

The scientific integrity of a study, and credibility of its findings, starts with a good plan. A study design is a research road map that plans out how the data generated for a study can be effectively analyzed and interpreted. Without a solid framework, researchers cannot answer the questions about links between genes, health, and disease that they

were inspired by in the first place.

Wijsman's passion for refining study designs has helped a countless number of researchers to course-correct their plans for successful interpretation of data. Whether it's her real-time feedback at scientific presentations, fielding of investigators' project pitches as the manager of the ADRC's DMS Core, or feedback on grant proposals made to the many review panels she has served on, such as the Center for Inherited Disease Research Access Committee, Wijsman has consistently given her colleagues strong feedback when she sees a better path to answering their research questions. "She'll tell you your approach to the study is wrong, and she'll tell you why it's not appropriate. She'll be critical, and then she'll give you alternatives," says Elizabeth Blue, PhD, Associate Professor of UW Medical Genetics, and one of Wijsman's longtime collaborators. "She's not telling you not to do it. She's telling you how to do it better. And she's usually right. She's always got her eye on the ball."



Wijsman's many years of criticism and constructive feedback have had a tremendous impact on the field, one research plan at a time.

In fact, the ADRC's first genetics project benefited from Wijsman's eye for good study design, as it led to a new recognition of the genetic complexity of familial Alzheimer's disease. She took a critical eye to the Center's familial Alzheimer's disease dataset and found differences in the patterns of inheritance from parent to child, particularly in the ages at which people developed dementia. Wijsman intuited that the search for a single Alzheimer's gene was overly simplistic. She suspected that varying patterns of genetics and biology seen in different populations all converge on the similar syndrome of Alzheimer's-type dementia, a phenomenon termed genetic heterogeneity.

She urged the team to use age-of-onset data to group families into subsets, which made it possible to detect the genetic signals they were looking for and find the distinct genetic variants that promote Alzheimer's disease in individual families. In that first project, Wijsman set the course for the Center's early achievements in identifying single gene causes of Alzheimer's disease and frontotemporal degeneration. "Wijsman was indispensable to the breakthroughs in the genetics of Mendelian Alzheimer's disease that established us as a successful Center," says Thomas Grabowski, MD, ADRC Director.

Over thirty years later, Wijsman now plays an important role in sorting out the genetic puzzle of late-onset sporadic Alzheimer's disease through her work in the Alzheimer's Disease Sequencing Project (ADSP), a massive scientific effort to tease out the genetic factors influencing the more common form of Alzheimer's disease. Researchers think that the patterns of disease inheritance in late-onset Alzheimer's disease family pedigrees are more complicated than for early-onset disease because the development of the late-onset disease may be influenced by multiple genetic variants and environmental factors. To have a chance at understanding this complex pattern of genes and disease, statistical analyses require a larger sample size—more genetic data from more people. One problem is that the task of searching for complex genetic relationships in big populations with massive amounts of genomic data requires long computer

processing times, making it more difficult to carry out the analyses. Wijsman has been a leader in trying to make these analyses work.

**"In our lab, she is famous for saying, 'Nice result—now can you make it go away?' She always encourages us to double check assumptions and think through their implications."**

"Ellen is developing novel solutions to real world problems that the whole field is going to have," says Blue. "Her guiding question is: 'How can we make a resource for other people so that they don't have to spend 2 years doing the work that we had to?'" While building statistical tools to analyze the ADSP's massive and complex genetic data sets, Wijsman found a blind spot. There was a gap between the data collected and the analyses that needed to be performed to find genetic variants that increase disease risk. "We couldn't see the differences in the genetic variants between the Alzheimer's cases and the controls," says Blue. "But Dr. Wijsman's work shifted the way they handled the follow-up study so that we could have the data we needed to move forward." Wijsman's diligence led to the ADSP's addition of a "Discovery Extension Phase" that gives researchers the data they need to progress in the search for genetic variants that increase the risk for late-onset Alzheimer's disease. Over more than thirty years of research on both early-onset and late-onset forms of Alzheimer's disease, Wijsman's laser-focus on identifying problems in research and addressing them with new methods and ideas has pushed the field forward time and again.

Developing some of those statistical analysis tools took decades of dedication, largely stemming from the struggles Wijsman faced in her early years at the

ADRC. "The data analysis was very challenging in those early years," she says. "The challenge drove my interest in the development of a methodology that would eventually allow computations to be done in practical amounts of time." Wijsman collaborated with Elizabeth Thompson, PhD, Professor Emerita in the UW Statistics department, and Adjunct Professor Emerita in UW Genome Sciences and UW Biostatistics, to develop new statistical tools that could better model complex genetic traits and make analysis more manageable. Some of their first projects leveraged the heart disease research family pedigrees of Arno Motulsky, MD, a founder of the field of medical genetics whose work originally attracted Wijsman to move to the UW.

Over the next 27 years, through waves of new genetic and computational technologies, Thompson and Wijsman continued to build new tools, such as software and lines of code that have given researchers more power. Their innovations allow for detection of genotyping errors in pedigrees, statistically sound assignment of genetic background to individuals who lack data in large pedigrees, and an improved ability to use data from multiple points in the DNA at once, to name a few outcomes. With the tools to leverage new genetic technologies, Wijsman and Thompson's colleagues have been able to investigate questions about complex interactions of genetic and environmental risk factors in human diseases that were previously out of reach.

"Dr. Wijsman embraced the interface of statistics and neurogenetics, and the particulars of neurodegenerative disease. She is an inspiring example of how enabling a true interdisciplinary commitment can be," says Grabowski.

Through the career-long collaboration, Wijsman linked Thompson's statistical expertise to the expertise of medical geneticists and neurogenetics researchers at the ADRC. "Working with Ellen let me bring statistical models and computational methods to address real biological problems," says Thompson. The two collaborators have unraveled some of the mysteries behind Alzheimer's disease, heart disease, prostate cancer, and alcoholism, finding new genetic and environmental factors that may increase the risk of these conditions. >>> *Next page*





Ellen Wijsman, 1987

### A MENTOR'S DEDICATION TO TRAINING THE NEXT GENERATION

When Wijsman arrived at the University of Washington, the institution did not have a structure in place to train new statistical geneticists. "What was lacking was training of the next generation of statistical geneticists," says Thompson. To help ensure the future of their field, Wijsman and Thompson started a training track of statistical genetics courses in UW Biostatistics and Statistics Departments. They worked for decades to instruct new generations of researchers. "Her training in quantitative and population genetics, and also her great ability and enthusiasm for it, connected people on the medical side to the broader statistical genetics world. She continually strives to bring those worlds together," says Thompson. At a scientific crossroads, Wijsman has provided statisticians a bridge to explore medical questions and has helped medical geneticists use mathematical models to draw conclusions from real-life data about disease risk. People trained and instructed by

Wijsman have gone on to use statistical analyses to find genetic variants and epidemiological risk factors that influence susceptibilities to a wide variety of human diseases.

Wijsman's past students remember her capstone course in statistical genetics as a fundamental part of their training, without which their education would not be complete. "Ellen taught her students the value of being a statistician in solving real scientific problems. I think Ellen must have been a role model for so many of them," says Thompson. France Gagnon, MSc, PhD, Research Professor and Associate Dean at University of Toronto's Dalla Lana School of Public Health, whose research leverages modern molecular technologies and analytic approaches to identify genetic influencers of heart disease, recalls the enthusiasm that Wijsman brought to the classroom. "She spends more time preparing for class than most people in her class probably spend learning the material. She is passionate about statistical genetics and it shows in the way she teaches," says Gagnon. Wijsman's teaching record shows her commitment to lifting up and challenging others in her field to improve.

Wijsman's passion for statistical genetics and skill in teaching its fundamentals and application to medical questions shined in the laboratory as much as the classroom. "Ellen was really my most influential mentor that I've had in my career," says Weiva Sieh, MD, PhD, Associate Professor in the Departments of Population Health Science & Policy and Genetics & Genomic Sciences at the Icahn School of Medicine at Mount Sinai. Under Wijsman's guidance, Sieh worked to search for the genetic players in a fatal dementia complex that affects the Chamorro people of the island of Guam as well as other Pacific Island populations. "She was such a good role model for scientific integrity as well as personal integrity. Some of the most lasting lessons that I learned about how to conduct myself as a scientist, what it means to be a mentor and a researcher, how to balance having a child and maintaining a high-level career, I learned from just modeling Ellen," says Sieh.

As Wijsman asked hard questions of her lab mates, she kept an open door for trainees to ask their own. "I felt like nothing was off limits and that she would be willing to answer my questions honestly," says Sieh. Wijsman also consistently participates in a trainee-mentor lunch with the International Genetic Epidemiology Society (IGES), a society in which Wijsman served as President in 2005, where trainees come to get an outsider perspective on their questions or anxieties about the field and their careers.

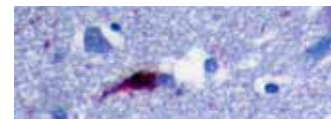
The effect of Wijsman's exemplary training did not stop with the researchers she trained, for those people have internalized her approach to mentorship. Gagnon largely credits her emulation of Wijsman's teaching style for the Graduate Teaching Award that she received from the University of Toronto in 2014. "My trainees commented that they felt comfortable, that they were able to ask lots of questions, and that I helped them grow as an independent scientist," she says. "When I saw that, I said, 'Wow, that's Ellen Wijsman there.'" Wijsman's personal guidance fostered her mentees' curiosities and helped them grow into their lab coats, and they now carry that same spirit in working with their own scientists-in-training.

Wijsman equipped her trainees with the tools to collaborate with those who work in applied medicine, and they have continued to do so. "Back when I was training with Ellen, there were very few people in the statistics field collaborating so genuinely with clinicians and wet lab scientists," says Gagnon. "I carry her influence into my work today, pushing for new research projects in my role, and working very closely with wet lab scientists, clinicians, and clinical psychologists to make sure we are thinking outside of the box when talking about solving problems." Wijsman's spirit of collaboration and willingness to learn and lean on the expertise of others persists in those she has trained.

As Wijsman prepares to retire from the ADRC DMS core, she looks forward to continuing to consult on various ADRC projects and share her perspective in scientific meetings. But her legacy speaks for itself, in generations of capable researchers who apply statistical tools to new medical questions. With their memories of Wijsman as a guide, these researchers will continue to advance our understanding of disease risk in the wider population and train the leaders of tomorrow. •

### • TIMELINE

2011



ADRC faculty and colleagues publish "The Ecology of the Aging Human Brain," reporting the prevalence of disease in the brains of community adults who died without a dementia diagnosis. The study is groundbreaking in its reveal of the widespread incidence of complex, converging pathologies of brain disease in older adults without dementia.



Debby Tsuang, Geriatric Psychiatrist at the UW ADRC, becomes the Director of the Geriatric Research, Education, and Clinical Center at VA Puget Sound. Tsuang continues to guide the Center's contributions to research, education, and clinical care in aging and neurodegenerative disease.

2012



Thomas Montine becomes ADRC Director. Under his leadership, the Center becomes the first ADRC in the country to focus on a precision medicine approach. Montine unites the ACT study and the ADRC through common work in neuropathology, allowing ADRC expertise to make even more scientific use of each ACT participant's donated brain.

2013



UW Memory and Brain Wellness Center (MBWC) opens at Harborview Medical Center with the mission of promoting the well-being of persons living with memory loss and their families, by providing exceptional care, advancing scientific understanding at the ADRC, and building dementia-friendly communities. Director Thomas Grabowski serves as a neurologist in the clinic.



2014

Sherry Willis and colleagues publish results from the Advanced Cognitive Training for Independent and Vital Elderly Trial, the first to show that cognitive training interventions yield benefits to subjects' cognition five years down the road and suggests those benefits transfer to improvements in daily function.

2015



A new ADRC Satellite Core, led by Dedra Buchwald, is founded to examine the risks and consequences of vascular brain injury in surviving participants of the Cerebrovascular Disease and its Consequences in American Indians Study.

2016



Thomas Grabowski, the Director of the MBWC, becomes the Director of the ADRC. He brings a new vision of "strengths-based reframing" of dementia, and a new approach to investigating biological heterogeneity based on his imaging expertise. He oversees the launch of the MBWC website and social media accounts, as well as the 5-year NIA funding renewal of about \$15 million. Suman Jayadev is appointed as co-Lead of the Clinical Core with Gail Li. Kimiko Domoto-Reilly becomes Lead of the Outreach, Recruitment & Education Core; C. Dirk Keene assumes leadership of the Neuropathology Core and Targeted Testing Core. The ADRC welcomes 10 new ADRC Affiliate Members from different UW departments. ADRC programs move to Harborview Medical Center, while some scientific labs remain at the VA Puget Sound Health Care System.



ADRC/MBWC faculty led by Kristoffer Rhoads help to shape the development of the WA State Plan to Address Alzheimer's Disease and Other Dementias, approved by the Washington State Legislature to bring about statewide innovation in dementia care policy.



Jessica Young joins the ADRC to lead an ambitious precision-medicine project: transform the skin cells of research participants into neurons with induced pluripotent stem cell technology, and study that participant's precise, genetically determined neurobiology in a petri dish.



• **TIMELINE**

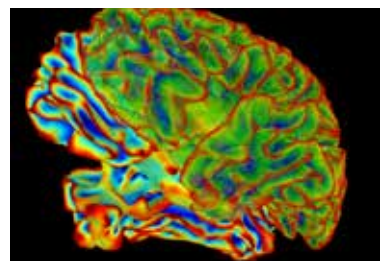
**2017**



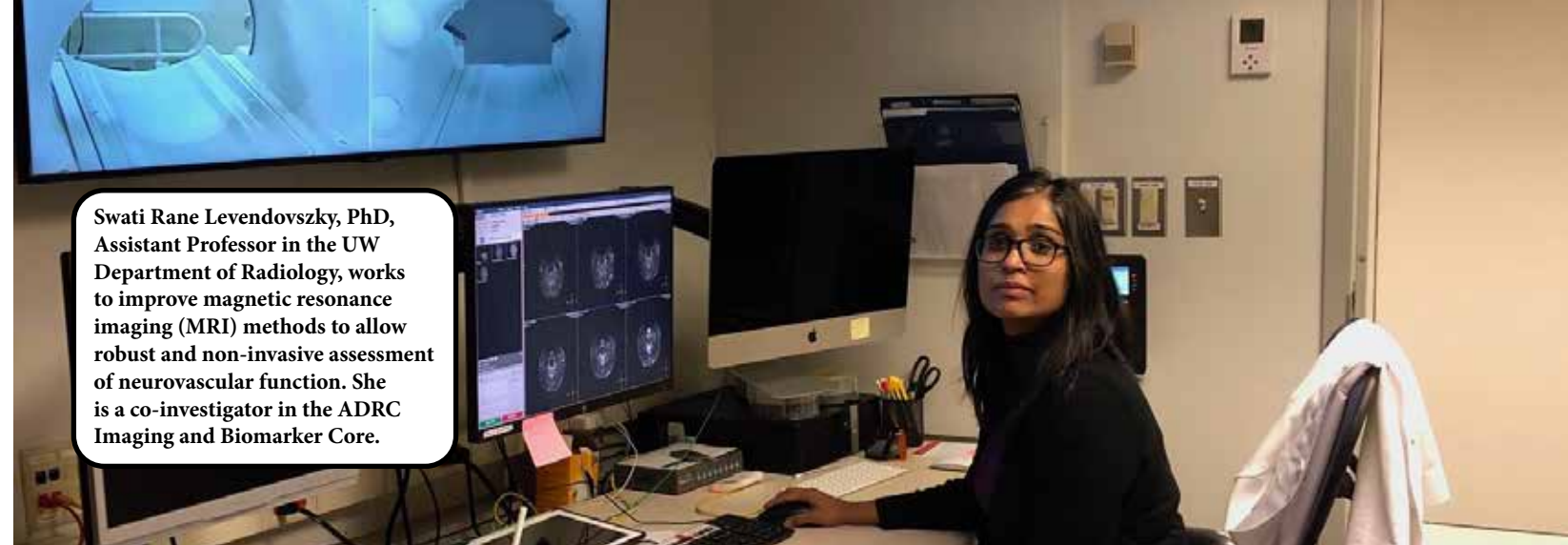
The MBWC partners with Seattle Parks & Recreation to start the Garden Discovery Walks, a free program for people with memory loss or dementia, and their partners, to explore a public garden and enjoy light exercise and time spent in nature.



Thomas Grabowski, ADRC Director, testifies at the US Senate Appropriations Subcommittee Hearing, 'Saving Lives through Medical Research' in Washington DC on the importance of NIH/NIA funding for Alzheimer's research. A \$400 million increase in Alzheimer's research funding was soon signed into law, increasing NIH federal funding to nearly \$1.4 billion.



The ADRC Neuropathology Core, Allen Institute, Group Health Research Institute (now Kaiser Permanente), and UW Medicine's collaboration in the Aging, Dementia, and Traumatic Brain Injury Study results in the release of a publicly available databank resource for studying the later effects of TBI on the aging brain.

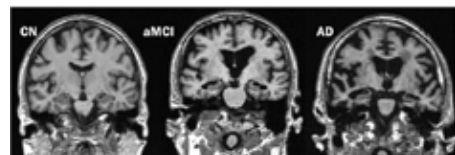


Swati Rane Levendovszky, PhD, Assistant Professor in the UW Department of Radiology, works to improve magnetic resonance imaging (MRI) methods to allow robust and non-invasive assessment of neurovascular function. She is a co-investigator in the ADRC Imaging and Biomarker Core.

**2018**



The MBWC becomes a Lewy Body Dementia Association Research Center of Excellence, a comprehensive network of twenty-four research centers to conduct Lewy Body dementia clinical trials, provide community outreach, and expand professional continuing medical education efforts around Lewy Body dementia. Kimiko Domoto-Reilly is site Principal Investigator.



The NIA commits \$3.73 million to the ACT Imaging Records project, allowing researchers to gather existing MRI scan data from the ACT study's well characterized cohort of older adults. The project will illuminate how patterns of brain atrophy, as shown on MRI, relate to a person's underlying disease pathology and type of symptoms. The findings could help researchers distinguish between different disease subtypes and diagnose with precision. The leaders of this new effort are Eric Larson, Christine Mac Donald, and Paul Crane.



The MBWC holds the first FTD Education Day, offering resources, support, and arts showcase for people affected by frontotemporal degeneration, the leading cause of dementia under 60 years of age. The event included a showcase of art created by persons living with FTD.

**2019**



ADRC's Outreach, Recruitment, and Education Core launches the ADRC Indigenous Aging webpage, which is tailored for American Indian and Alaska Native communities. The site, found on the homepage of [uwadrc.org](http://uwadrc.org), offers education and material resources for clinicians, community health representatives, and Native caregivers. The resources reflect the work of Partnerships for Native Health's Meghan Jernigan. Read more on Page 16. Image, Krystal Koop (Makah).



Jeffrey Iliff joins the ADRC to focus on neurodegeneration, the glymphatic system, and traumatic brain injury research. He becomes Associate Director for Research at the VISN 20 Mental Illness Research, Education, and Clinical Center at VA Puget Sound Health Care System.



Thomas Bird publishes the book *Can You Help Me?: Inside the Turbulent World of Huntington Disease*. This comes two years after Eric Larson, current Co-Associate ADRC Director, published his book, *Enlightened Aging: Building Resilience for a Long, Active Life*.

...Continued from Page 31 [Feature article: *The Early ADRC's Search for an Alzheimer's Gene*]

A year later in 1996, the team published another genetic study on presenilin-1 and presenilin-2 that is now the most highly cited paper in ADRC history. In 1998, the genetics group identified a mutation in the Tau gene, and published the first report of a genetic cause of the neurodegenerative disease frontotemporal degeneration. Returning to the study of presenilin-1 in 1999, ADRC researchers created the first mouse model of dysfunction in this gene, opening up a new avenue for investigating the biology of the Alzheimer's-causing gene variant in a living organism.

In the current day, presenilin work is as productive as ever and directly proceeds from the studies of the 80s and 90s. Bird's protégé, Suman Jayadev, MD, Associate Professor of Neurology and ADRC Clinical Core Lead, and her team recently uncovered evidence that age-related changes in the way presenilin-2 generates transcripts (the instructions for making proteins) may be involved in later onset Alzheimer's risk in the general population. Now, an ADRC Development Project is deploying the newest genetic technology to expand the understanding of presenilin-1 and 2 variants in different forms of both familial and sporadic late-onset Alzheimer's disease, which may reveal new functions for these genetic factors. The researchers see this project as a possible first step on the path to a new treatment involving the preservation of genetic function.

**NEW TOOLS FOR A NEW FRAMEWORK OF BIOLOGICAL HETEROGENEITY**

The themes of the ADRC have remained remarkably consistent since its founding, while also growing and changing to tackle new challenges. Starting in 1985, the ADRC approached familial Alzheimer's by thinking outside of the box about the role of genetics in Alzheimer's disease and pushing the boundary of what genetic technology could reveal. As the decade-long story of the ADRC Molecular Genetics team reflects, this quest led to a better understanding of the heterogeneity in genes, pathological proteins, and clinical phenotypes inherent in age-related neurodegeneration. Past progress has fundamentally shifted how the Center defines the very disease that it studies.

Alzheimer's disease is the most common cause of a dementia diagnosis. But now, thanks to neuropathology research at many ADRCs across the country, we have a much better understanding

of the disease's heterogeneity and its massive implications. Researchers now recognize that more often than not, patients with a diagnosis of Alzheimer's disease have different mixtures of brain pathologies and spatial patterns of disease spread. This heterogeneity across patients complicates diagnosis, treatment, and clinical trial design. To adapt, the NIA now funds ADRCs to study Alzheimer's Disease and Alzheimer's Disease-Related Dementias (ADRD), which include Alzheimer's disease, frontotemporal degeneration, Lewy Body dementia, vascular contributions to cognitive impairment and dementia, and mixed etiology dementia.

The ADRC will continue to refine the field's understanding of heterogeneity. In May 2020, the NIA awarded the ADRC a 15 million dollar funding renewal for the next 5 years. The application states its driving scientific focus as "investigating the biological heterogeneity of ADRD – the mechanistic and biological underpinnings of the pathophysiology of disease as well as the factors countering degeneration and dementia." The study of how the brain withstands the disease could never have been imagined as a research focus back in 1985.

The tools to investigate biological heterogeneity also bring new power to questions with a long history. The immense scientific challenge of understanding the biological heterogeneity of ADRD calls for the development of new, modern technologies: brain imaging with Positron Emission Tomography (PET) and magnetic resonance imaging (MRI). Much like genetic linkage analysis in 1985, brain imaging today is an emerging, resource-intensive technology that requires immense skill and expertise in cutting-edge database design and "big data" statistics to process the massive data flow generated by brain scans—and to detect the meaningful patterns therein. The goal of the ADRC's new Imaging and Biomarker Core—led by current Center Director, Thomas Grabowski, MD, a neurologist and national leader in imaging science through his creation of the UW Integrated Brain Imaging Center—is to use imaging technology to better understand different spatial patterns of disease (and lack of disease) in the brain. This Core's findings and resources will be used both by bench scientists, to guide experiments into mechanisms of ADRD, and by clinicians, in order to better monitor and predict trajectories of disease for each individual. Ultimately, the Center aims to factor the spatial pattern of disease into our understanding of the genetic, neuropathological, and cognitive dimensions of ADRD. >>> *Next page*



## A RECIPE FOR TODAY'S SUCCESS

The ADRC today faces challenges inherent to an ambitious project, yet they pale in comparison to the strong headwinds confronting the Center's first project. Recall that the NIA of 1985 initially rejected the idea of an ADRC focused on Alzheimer's disease genetics—until Bird presented an evidence-based research rationale. Today, the ADRC swims with the current as a national leader in Alzheimer's research, thanks in part to continuous, reliable federal funding. Still, the solution for a successful project lies in a strongly collaborative team who, together, have the right mix of expertise in several disciplines, a common dedication to a project that may take years, and unyielding persistence, positivity, patience, and open-mindedness in the face of roadblocks and delays.

Indeed, when asked to reflect on the success seeded during the early years of the ADRC, Founding Director George Martin brings it back to the people. "Our group successes all came from individual contributions. And collectively, it makes a big difference," he says. "The genetics research of Tom Bird, Jerry Schellenberg, and Ellen Wijsman were key – as well as the successes of the post-docs and many others. They made the science and Center of today possible."

Wijsman describes the successful structure of the genetics linkage team as a "three-legged stool": "Tom [Bird] brought the clinical expertise, Jerry [Schellenberg] brought the molecular expertise, and I brought the statistical genetics expertise. We would sit down, listen to each other, talk things through, and make our decisions by equal vote," she says. "I think George Martin was certainly a part of creating that environment that guaranteed that people would truly work together." Besides the personnel, the Directorship of the ADRC has a special role to play in any successful project. Wijsman credits some of the first Center projects' success to its Founding Director.

As historical documents and testimony from colleagues show, Martin provided not only a vision of focusing on genetics but also an environment conducive to tackling questions that bridge basic science and medicine. His framework involved strategic inclusion of researchers with diverse skill sets and expertise in different disciplines, all united by an interest in Alzheimer's disease. Martin explains it best in the 1984 ADRC application to the NIA:

*"A major impact of the proposed ADRC will be to galvanize a subset of the geneticists and molecular biologists to channel their energies towards the elucidation of the pathogenesis of familial forms of Dementia of the Alzheimer's Type. Another major impact will be to bring together investigators and practitioners from a wide variety of disciplines. This has, in fact, been accelerating rapidly as a result of preparations for this application and has been a source of considerable satisfaction to clinicians and basic scientists."*

The ADRC Director must oversee the federally mandated effort to build a rich data resource for the entire field, maintain a cohort of research participants suitable to inform current hypotheses, connect to the public and medical community, educate young investigators, as well as contribute to scientific challenges in different projects. The job demands creativity and compromise, as the story of the ADRC's genetic project from 1985 to 1995 reveals. Martin's model of fundamental collaboration and thoughtful team building continues to be the foundation of the ADRC's success to this day. >>> *Next page*

## CREATIVE PARTNERSHIPS

The seeds of creative collaboration in neurodegenerative disease research planted over 3 decades ago are now blossoming into prosperous partnerships that could not have been imagined in 1985. The ADRC has always drawn staff and scientists from UW Medicine Departments of Neurology, Pathology, and Psychiatry and Behavioral Sciences—but now more than ever, the ADRC engages in UW-based and external collaborations that enable many avenues of research and innovation to proceed simultaneously. These efforts include: creating human cell models to screen potential drugs with the Institute for Stem Cell and Regenerative Medicine; leveraging expertise in new technologies at the Allen Institute for Brain Science in order to understand cellular vulnerability or resilience to disease; providing needed education and outreach to local American Indian and Alaskan Natives with the Partnerships for Native Health; creating research education programs with Sage Bionetworks; making progress on better understanding and treating frontotemporal degeneration with the University of San Francisco; embarking on new projects in cell biology, big data, and neuroimaging with funding from the Weill Neurohub, and creating inclusive approaches to wellbeing and resilience with the UW Memory and Brain Wellness Center and Garvey Institute for Brain Health Solutions.

As the force supporting all of these partnerships, ADRC leadership provides an environment where researchers, staff, and scientific ideas flourish. Inevitably, a Director's perspective and expertise shapes a Center's chosen scientific questions. In addition to his role in the ADRC, current Director Thomas Grabowski is also a neurologist and Medical Director of the UW Memory and Brain Wellness Center, where he has introduced the concept of "strengths-based reframing" of dementia in order to empower the agency of people living with memory loss, promote wellbeing for patients and families, and counter the stigma surrounding dementia.

In research, Grabowski also seeks to shift the ADRC's frame of reference to the "topographic" patterns of neurodegeneration over the brain space. This approach takes the heterogeneity of Alzheimer's and related diseases head on, to discover the links between patterns of brain atrophy, cognitive symptom profiles, and predictive genetic factors. This clarity is needed for the dream of a precision medicine approach to deliver targeted treatments or interventions to different biological subgroups of individuals, before symptoms have emerged.

While the ADRC is now positioned at the field's technological cutting edge, its early history lives on through the families who first joined the founding genetics project and still contribute. About three years ago, an old friend and classmate of Grabowski's read in the UW alumni magazine that he had become ADRC Director. She reached out to him to disclose that she belongs to one of the Volga German presenilin-2 families.

"After our follow up conversations, she met Tom Bird, who was fabulously generous with his time," said Grabowski. "It's obvious to me that Tom's loyalty and commitment to these families was a big factor in the success of the program. More generally, this team was, and continues to be, amazingly talented and open. Open to meeting participants where they are. Open to each other's talents and contributions. Open to the data and to thinking differently about Alzheimer's disease. The legacy of this project continues in our Center. Members of these families, and others in which the genetic cause is still unknown, continue to participate in our studies and come to autopsy, and we bring ever more sophisticated approaches to bear on our questions about Alzheimer's disease and the path to prevention and treatment. The long arc of this work, and its continuing relevance to current Alzheimer's disease research, are a tribute to those who built a strong foundation years ago. We are all indebted to their critical thinking, standards of excellence, and perseverance." •

*Special thanks: George Martin, Thomas Bird, Ellen Wijsman, Gerard Schellenberg, Ephrat Levy-Lahad, and Alfred and Arlene Noreen.*



Thomas Grabowski, MD



# 2020



UCSF-UW ADRC Science Day, Nov 2019

The Weill Neurohub, a consortium of UCB, UCSF, UW Medicine, launches with projects in cell biology, big data, neuroimaging, and neural engineering that require combined strengths of these three public institutions. Three of the five inaugural projects have an Alzheimer's disease focus. UW researchers include, Suman Jayadev, Jessica Young, Bing Brunton, C. Dirk Keene, and Thomas Grabowski.



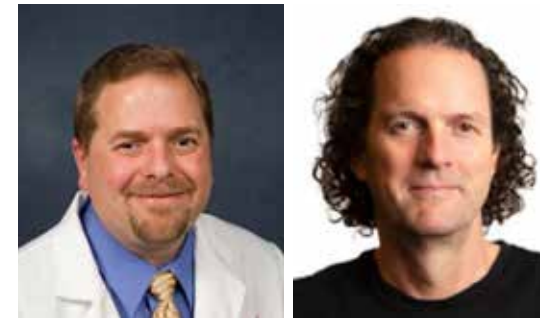
Amidst the new challenges and restrictions of the SARS-CoV-2 pandemic, the MBWC, in partnership with the ADRC, creates virtual adaptations of educational programs and expands video offerings. Learn more at [depts.washington.edu/mbwc](https://depts.washington.edu/mbwc). In October, Carolyn Parsey and colleagues publish a study about the effects of the pandemic on older adults, including policy implications: *Caring for Washington's older adults in the COVID-19 pandemic: Interviews with organization leaders about the state of social and healthcare services*, funded by the UW Population Health Initiative's COVID-19 Economic Recovery Research Grant.



The Memory Hub: A Space for Dementia-Friendly Community, Collaboration, and Impact is announced. Bringing together people, programs and partners, the new MBWC initiative on First Hill will operate as a vibrant dementia-focused programs and events venue, collaborative workspace and training center. This project is spearheaded by MBWC's Marigrace Becker and made possible by a leading gift from the Richard M. and Maude Ferry Charitable Foundation. Learn more at [depts.washington.edu/mbwc](https://depts.washington.edu/mbwc).



The ADRC, in partnership with the Memory and Brain Wellness Center, is gearing up to launch several new studies of potential therapeutics and treatments, under the leadership of Charles Bernick, Director of Clinical Trials. "Many patients are interested in participating in research, and we want there to be an appropriate clinical trial or study opportunity for everyone we encounter," says Thomas Grabowski, ADRC Director.



The Allen Institute, UW Medicine, ADRC, and Kaiser Permanente launch a massive new Alzheimer's research collaboration. Supported by \$40.5 million in funding over the next 5 years, the project will investigate the basic function of brain cells at the earliest stages of Alzheimer's disease in order to find new biological clues and cellular mechanisms to inspire future research. C. Dirk Keene and Ed Lein are leaders of this endeavor.



The MBWC Clinic launches the UW Project ECHO Dementia (Extension for Community Healthcare Outcomes) program, a learning model in which front-line care providers in WA State learn from each other in a virtual conference room format, with input from experts in memory loss and dementia. The ECHO Dementia team is led by Kristoffer Rhoads, Nancy Isenberg, and Allyson Schrier. Learn more at [depts.washington.edu/mbwc](https://depts.washington.edu/mbwc).



The ADRC launches the new Research Education Component for the training of scientists in the Alzheimer's disease research field. The project is led by Jeffrey Iliff and Brian Kraemer. Learn more at [uwadrc.org](https://uwadrc.org).



The ADRC receives a \$15 million funding renewal for the upcoming 5 years. New Cores and Core Leads are listed on Page 2. This pattern of continuous NIA support speaks to the unique, intergenerational presence of scientific expertise and organizational leadership that has made the Center successful over the past 35 years—and that our current researchers, clinical specialists, and directors have the privilege of continuing into the future. •



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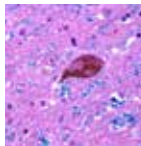


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