
# Mind MATTERS

SANDERS-BROWN PUBLICATION ON AGING | Fall 2021

*in this issue*

## ESTABLISHING A LINK BETWEEN ALZHEIMER'S AND POLYPHARMACY

Sanders-Brown Center on Aging

# PROGRESS TOWARD OUR MISSION

**Welcome to the 2021 Sanders-Brown Center on Aging magazine, *Mind Matters*. I invite you to enjoy this magazine, where you will learn about some of the remarkable programs we have here at Sanders-Brown, including our thoughtfully curated caregiving programs, our work with individuals with Down syndrome, and the efforts underway to optimize medications to preserve memory functions.**

Despite the unique challenges presented throughout 2020 and 2021, we have remained steadfast in advancing our mission of enabling healthy brain aging for all adults in Kentucky and beyond. The 2021 year has brought continued funding from the National Institutes of Health of our Alzheimer's Disease Research Center, funding us for years 36-40! In addition, we broke ground on a new, state-of-the-art clinic facility in Lexington that will allow us to provide care to more patients and their families and allow us to make more discoveries that will lead to our goal of maintaining a healthy brain as we age. Finally, thanks to investment from the state of Kentucky, the University, UK HealthCare and philanthropic donations, we have been able to plan significant modernization and rebuilding of our research building.

The Sanders-Brown Center on Aging remains a global leader in the study of Alzheimer's disease and related dementias. Our continued growth and new discoveries are only made possible by the tireless work of our faculty, staff and trainees and by the thoughtful gifts we have received through philanthropy. Without the generosity of people who share our vision of healthy brain aging, we would be a lot further away from our goal of delaying the onset of dementia and slowing disease progression. I welcome your questions and comments, and our amazing team would be happy to tell you more about our work, our needs and/or provide a tour of our facilities.

Regards,
Linda J. Van Eldik, PhD | *Director, Sanders-Brown Center on Aging*

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# Aging in PLACE

WRITTEN BY RENA BAER | PHOTOGRAPHY BY PETE COMPARONI & MARK CORNELISON

Alzheimer's disease and related dementias (ADRD) take a toll on not only the person with the disease but also those who care for them. At the University of Kentucky's Sanders-Brown Center on Aging, researchers are continually exploring evidence-based interventions to support caregivers—both professional and family members—with a toolbox that enables them to provide more optimal care.

That much-needed support results in a better quality of life for both the person with ADRD and those caring for them. It can also lengthen the amount of time a person with ADRD can live at home in a familiar environment.

People with ADRD require a caregiver as they progressively lose their memories and abilities to think. "It's very, very different from somebody who has, say, kidney dysfunction," says Dr. Gregory Jicha, MD, PhD, who is director of UK's Telemedicine Cognitive Clinic and director of the Sanders-Brown Center on Aging Clinical Core. "Even going on dialysis, that person is still able to manage their own disease, feed themselves, make their own doctors' appointments and visits, and make their own choices in medical outcomes."

If the caregiver is not prepared for the role or knows little about ADRD and its effects, it impacts the person with Alzheimer's, says Dr. Jicha. It often accelerates problems associated with the disease such as depression, anxiety and psychosis. This, in turn, creates an even larger burden on the caregiver and becomes part of a vicious cycle.

"We realized in order to provide optimal care, we have to not just treat the patient, but we have to educate and care for the caregiver as well," he says.

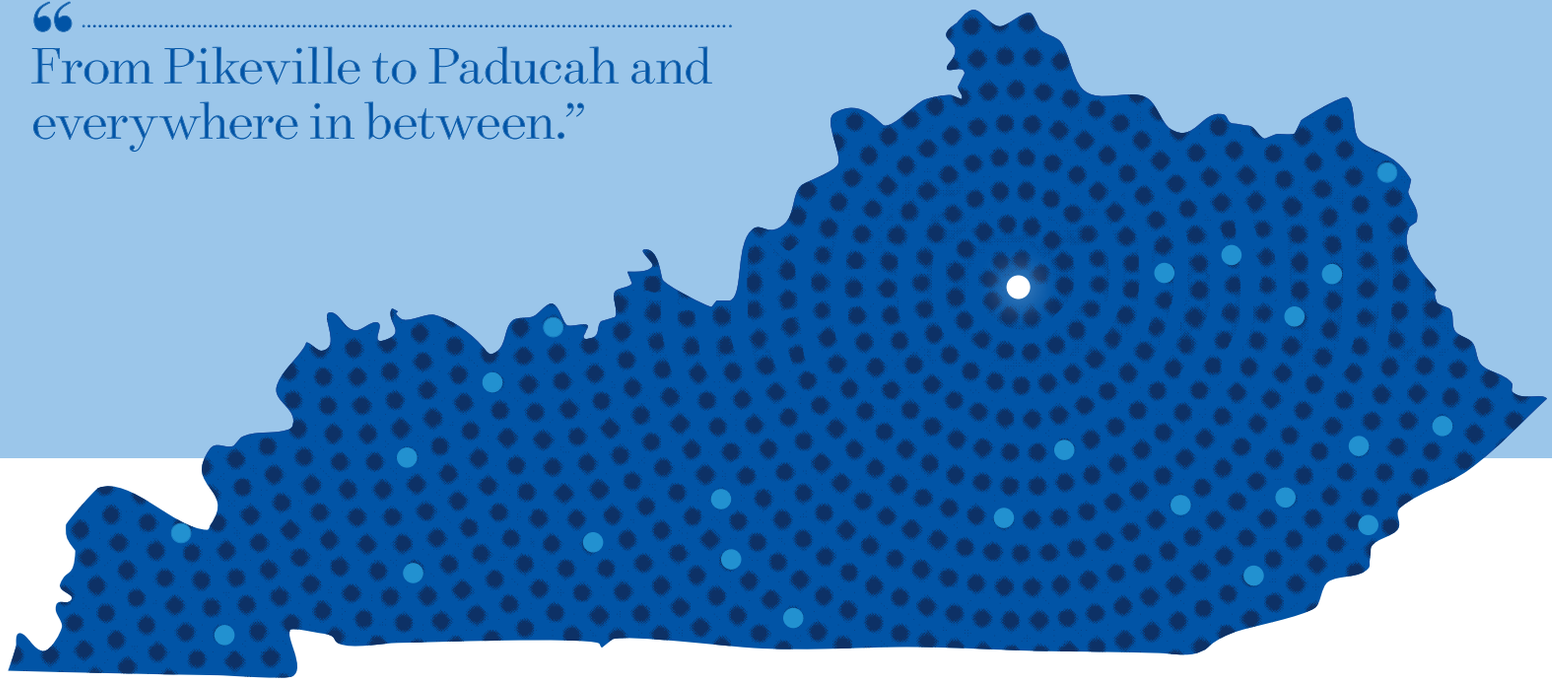
In Lexington, if someone were diagnosed with Alzheimer's, they might call the Sanders-Brown Center on Aging, where they would be told about the local Family Caregiver workshops that are held in partnership with the Alzheimer's Association, Sanders-Brown, Baptist Health here in town and other organizations, says Dr. Jicha.

These free, interactive all-day workshops are held quarterly in Lexington and are offered in a handful of Kentucky's other bigger cities. The workshops include multiple speakers who educate participants on topics such as how the disease progresses, what caregivers can expect, ways dementia is being treated, managing the financial complications, and how caregivers can support and care for themselves. "But if you're living in Hazard or Olive Hill or Morehead or Corbin, you're not going to have that kind of a resource," says Dr. Jicha.

Though the Sanders-Brown Center on Aging is convenient to those in Lexington, it can be much more difficult for caregivers to receive this support who live in the more rural and far reaching areas of the state. In an effort to increase its outreach, and also reach patients/caregivers where they are most comfortable, Sanders-Brown currently provides three complementary telehealth programs that allow caregivers in rural and remote areas to access its expertise and support: the Rural Caregiving Telemedicine Program, KEEN-CDC (Kentucky Enduring Education and Care Network for Collaborative Dementia Care) and Harmony at HOME (Help Online Modifying the Environment).

Dr. Jicha began the Rural Caregiving Telemedicine Program 16 years ago, which provides the same information as the Family Caregiver Workshops through continual telehealth programs coordinated in tandem with 14 medical hubs

> From Pikeville to Paducah and everywhere in between."



"from Pikeville to Paducah and everywhere in between." The approach differs in that the quarterly programs are 90 minutes and focus on different subjects requested by residents in those rural areas. A panel of experts on each subject is put together to lead each presentation, which is followed by a question-and-answer session. Participants who can't get to a hub to join the teleconference can now link up through Zoom.

The Kentucky Enduring Education and Care Network for Collaborative Dementia Care, known as KEEN-CDC, borrows telehealth elements of the Rural Caregiver Program but is instead tailored to staff of certified nursing facilities, from physicians to nursing aides. The three-year accredited online program, which presents topics quarterly, provides continuing education credits for professionals but anyone caring for patients with ADRD at certified nursing facilities can attend. Though it's not a state or federally mandated training like HIV or opiate abuse, the KEEN-CDC program provides education that is paramount in providing optimal support to patients with ADRD, says Dr. Jicha.

> If we can help one professional caregiver who cares for dozens of Alzheimer's patients, then we have helped dozens of Alzheimer's patients," he says. "That's magnified by those thousands of professional caregivers we reach out to."

The program is rooted in a grant Dr. Jicha wrote and received from the Centers for Medicare and Medicaid Services and Kentucky's Office of the Inspector General to provide ADRD education using funds from nursing homes that were fined for suboptimal care—often related to caring for patients with dementia. KEEN-CDC has transformed from a state program directed at violators into its current iteration, which because of COVID and its online accessibility, has created nationwide interest.

"It's been a boon in terms of increasing outreach to skilled nursing facilities," says Dr. Jicha. "There was not only a shortage of staff to help care for our elderly [during COVID], but there were no training opportunities because people couldn't go to live in-person training programs. And what are you going to do when you're in a place like rural Kentucky, where no training programs are available? So the Centers for Medicare and Medicaid Services asked us to open the program to a national audience so we could meet this new COVID challenge of training caregivers at skilled nursing facilities across the nation, wherever this was needed, because COVID was disproportionately affecting the elderly, especially those with dementia."

The 12-part series covers a broad range of topics from proper nutrition to bathing and hygiene to palliative and end-of-life care. The series is also being converted into "enduring materials" available to a broader audience, such as colleges that can use the archived program, or particular topics covered, in healthcare education.

"This is hands-on, practical training with tools that one can use in their day in, day out workflow as a professional caregiver to not only help the person they are caring for but to help them feel an increased satisfaction in doing their job, which is work that is often ignored or goes unappreciated," says Dr. Jicha.

The most recent research program is Harmony at HOME (Help Online Modifying the Environment), which is funded by a grant through the NIH/NIA in partnership with the Emory Roybal Center for Dementia Caregiving Mastery (NIH/NIA P30AG06400).

Harmony at HOME trains caregivers of people with moderate to severe ADRD in the skills of assessing and modifying homes to promote "person-environment fit." It is based on the idea the environment (such as lighting, noise level, temperature), especially when combined with individualized support, contributes to or even shapes behavior.

Also delivered via telehealth, Harmony at HOME is specifically targeted for rural Appalachia in Kentucky, a region with the poorest healthcare options for older adults in the country and plagued with extremely high rates of co-morbid conditions, including ADRD. Access to quality caregiver training, in-home caregiver support and respite care is significantly limited in this region.

"We're bringing in occupational therapy techniques that help to improve the quality of life for both the caregiver as well as the person with Alzheimer's using sensory-based approaches for the caregiver to learn and be able to implement in their own home," says Dr. Jicha.

Right now, Elizabeth Rhodus, PhD, OTR/L, who played a significant role in developing the program, is completing a proof of concept clinical trial as part of her postdoctoral fellowship supported by the NIH T32 AG057461 "Training in Translational Research in Alzheimer's and Related Dementias (TRIAD)" grant under Drs. Linda Van Eldik and Paul Murphy with mentorship by Dr. Jicha. She is working with 30 caregivers on a weekly basis to form and solidify the constructs of Harmony at HOME.

"We want to give an intervention that teaches caregivers how to continually assess the relationship between the person with cognitive impairment and their home environment," says Dr. Rhodus. "As normal, healthy adults, we can turn on the air conditioner if we're hot, or we can turn down the lights if we feel a little stressed. People with cognitive impairment don't necessarily have that same ability. They lose the ability to make themselves more comfortable. And at times, that can make people agitated, upset, or just not comfortable within their home. If we can teach the caregivers how to better assess the home environment, then they can increase comfort for the person they are caring for."

This work will enable the investigators to establish the feasibility of the program and to demonstrate its capacity with a population of caregivers that is in particular need and

"We're teaching caregivers to assess their environment and actually implement changes to be able to help lessen or reduce the severity of the symptoms that their loved ones are experiencing in the home."

difficult to reach, says Dr. Jicha. "We hope in our future grant iteration, when we're done with this work with the Emory Roybal Center for Dementia Caregiving Mastery, that we're going to be able to introduce this program nationally for a multi-site validation study across different geographic areas with disparate populations. This will really increase the armament we have to support not just the person with Alzheimer's disease but also provide support indirectly through educating and training their caregivers."

Also, telehealth occupational therapy services are a billable healthcare service.

"It's a great option because one of the challenges with these caregiving type interventions is that a lot of times they don't fall into a billable service," says Dr. Rhodus. "We can create caregiver techniques and programs, but the follow-through, from a clinical standpoint, doesn't always happen if the programs are not reimbursable. Harmony at HOME can have increased practical implementation because it is built from a healthcare framework."

Harmony at HOME includes a social work component, as well. For the pilot study Drs. Jicha and Rhodus have been working with assistant professor Allison Gibson, PhD, MSW. Dr. Gibson describes her role as helping take theory into practice.

"My role with social work is really more the emphasis on adapting the OT aspects of the intervention to be translatable and trainable for the caregivers," she says. "We're teaching caregivers to assess their environment and actually implement changes to be able to help lessen or reduce the severity of the symptoms that their loved ones are experiencing in the home."

Dr. Gibson says behavioral disturbances for people experiencing Alzheimer's disease and dementia are very prevalent and increase caregiver burnout, which can impair their own ability to care for themselves.

"We are giving them a tool belt, and caregivers can pull out different tools throughout their day so that those symptoms are much more manageable," says Dr. Gibson. "That's obviously going to mean they may be able to sustain that arrangement of living in their own home for a much longer period. If you're stressed out, you're burned out all the time. And, you're not able to take care of yourself as a caregiver. It's going to be much more likely that you're going to end up having to place someone in long-term care."

Dr. Rhodus says the goal of all caregiver programs offered at the Sanders-Brown Center on Aging is for people to be able to "age in place" and to support them at every level in that process.

When we say age in place, we mean, ideally, people want to live at home, but for a lot of people with cognitive impairment, that's not an option," she says. "The programs we offer at Sanders-Brown cover the continuum of care from people who are just diagnosed with mild cognitive impairment or a new diagnosis of dementia to those in the last stages of the disease process. We have options to train caregivers on how to care for the person with cognitive impairment in their environment to promote comfort and successful aging in place for as long as possible." ■

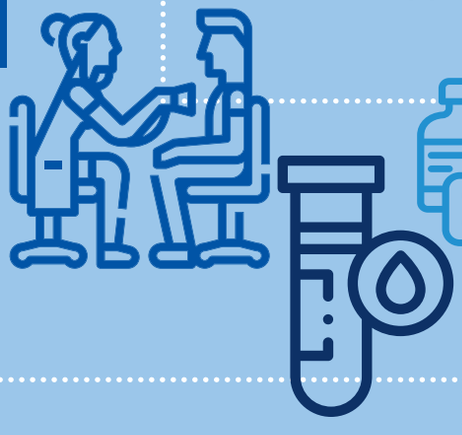
WHAT TO EXPECT

# *a visit to the* RESEARCH CLINIC

Longitudinal Study clinic visits are only three, maybe four, hours out of one day, once a year. But what we've been able to learn over decades and hundreds of participants has added up to give incredible insights into brain aging and Alzheimer's disease. **What do our participants do during that short time with us that has yielded such great results?**

## THE UNIVERSITY OF KENTUCKY SANDERS-BROWN CENTER ON AGING CLINIC

2199 Harrodsburg Road
Lexington, Kentucky 40504



1 Generally their first stop is with one of our phlebotomists for a **blood draw.** We're checking for drug effects, along with typical metrics like A1C and cholesterol. We're also evaluating for general research purposes—blood biomarkers for Alzheimer's, for instance.

2 A **physical exam and general health check** is next, where we'll get an updated health history and check vital signs, along with an abbreviated eye exam.

We follow with a **neurological exam** that includes a mental status assessment, checks for motor function and balance, sensory examination, and cranial nerve evaluation.

## OFF-SITE SERVICES

**Participants may also receive off-site services during their visits:**

- mri
- pet scan
- drug infusions

PARTICIPANT STATS

# 735 PARTICIPANTS

*reasons why* PEOPLE VOLUNTEER

1. Relative with Alzheimer's
2. Want to be a part of a longitudinal study

**55 to 95+** YEARS OLD

**from 5** STATES

**40%** RURAL **60%** URBAN

**416** WITHOUT MEMORY PROBLEMS

**193** MILD COGNITIVE IMPAIRMENT (MCI)

**125** DEMENTIA

**30** PARTICIPANTS A YEAR TRANSITION FROM NOT HAVING MEMORY PROBLEMS TO MCI OR MCI TO DEMENTIA.

3 **Memory and thinking testing** represents a significant portion of the visit. Our participants take a series of tests over a 90-minute period that assess learning period and recall period, among other things.

4 We also gather data on our participants' **walking, gait and balance.** We conduct tests that measure footsteps, speed and walking patterns that can give an indication of issues in the brain.

## ADDITIONAL TESTING

**Depending on the participant, we may conduct some additional tests during their visit**:

- retinal image scan to check for the presence of amyloid plaques and tangles
- cognitive testing with an EEG
- lumbar puncture to check drug penetration

This graphic has been designed using resources from Flaticon.com

*Research* STORY

WRITTEN BY LYNN DAVY | PHOTOGRAPHY BY PETE COMPARONI

# ESTABLISHING A LINK BETWEEN ALZHEIMER'S AND POLYPHARMACY

## Sanders-Brown researchers seek to reduce medications to prolong healthy brain function

**When Dr. Daniela Moga came from Romania to the U.S. to pursue her PhD in 2007, she was surprised by the number of television ads for drugs aimed at older adults. A medical doctor with interest in pharmacoepidemiology, Moga found the ads deceptive and potentially dangerous.**

Since then, she has made it her ambition to help older adults monitor and reduce the number of medications they take so they cut the risk of detrimental drug interactions. Today, she and Dr. Greg Jicha are working together to study the possible connection between polypharmacy and degeneration of the brain.

"We want to see if by reducing drug interactions and inappropriate drugs we can delay the onset of Alzheimer's so that people can live independently for a longer time," says Dr. Moga, an associate professor at the University of Kentucky College of Pharmacy who collaborates with Sanders-Brown researchers. "They may still develop Alzheimer's, but we want to see if we can give them more time to live independently."

Drs. Moga and Jicha's project is called INCREASE, which stands for Intervention for Cognitive Reserve Enhancement in delaying the onset of Alzheimer's Symptomatic

Expression. This study expands on an earlier study (the new study focuses on all meds and follows participants for a year) and offers hope that a simple reduction or even tweak of medications ingested by an older adult could dramatically change the trajectory of their life.

Ninety participants were recruited, all 65 years of age or older, with no signs of dementia. Most of these participants live near the UK campus, and all of them take at least one medication on the Beers List of Potentially Inappropriate Medications. A brain scan was performed at the beginning of the study to establish neurological health, including the presence of amyloid plaques and neurofibrillary tangles.

These plaques and tangles can be a sign of disease onset and progression, but researchers also know that cognitive reserve can help to compensate for the presence of these plaques and tangles, thereby supporting healthy memory function. However, some medications may interfere with cognitive reserve, which could be detrimental to the patient's long-term health.

"We estimate that 40 percent of seniors are taking inappropriate medications, so it follows that if there are 40 million seniors in our society, then 16 million are at risk for memory problems related to inappropriate medication use. This figure is astounding and should wake us all up," says Dr. Jicha. "How can we fix this problem? We can't picket the hospitals and pharmaceutical companies, but maybe we can help seniors to be more aware of the risks and educate doctors and pharmacists."

Patient recruitment for the INCREASE study wrapped up shortly before the coronavirus pandemic shut down the UK campus, which was fortunate because although participants could not come to the university for their visits, they could still use telehealth to speak with doctors and pharmacists about their medications. One lady in the study group took 12 chronic medications at the beginning of the study, including two medicines on the Beers List. Thanks to counseling and medical review of her medications, she had the opportunity to stop some medications and greatly reduce some others. The medical review found that she needed a certain medication that she was not receiving previously.

> "Study participants grew up during a time when people didn't have a lot of information about drugs at their fingertips," says Dr. Moga. "As a result, they rely on professionals to provide this information, which doesn't always happen in a timely fashion. It's estimated that older adults and frail people take up to 15 medications a day. How many of these medications could result in negative drug reactions?"

Researchers are in the process of reviewing the data collected as part of the INCREASE study, and they presented an analysis of these data in July at the Alzheimer's Association International Conference. Because this study expanded the number of medications surveyed and allowed for a more extended follow-up period, Dr. Moga is hopeful that the results will be insightful. They have already provided Drs. Moga and Jicha with ideas for subsequent studies, which will include participants from rural areas, as well.

"There was a lot of very positive communication that occurred between participants and the research team, and it did influence medication regimes," says Dr. Moga. "We are excited to see if there was also a change in memory and thinking."

One study currently in planning will admit participants with signs of dementia, as well as their caregivers. Drs. Moga and Jicha want to work with participants to reduce medications and help caregivers understand the function of various drugs and how to ask healthcare providers about possible interactions.

"Although the medical system is evolving, and healthcare teams are breaking out of their silos, there is still a lack of communication between doctors and pharmacists and patients that can create situations in which a patient is taking inappropriate medications," says Dr. Jicha. "It's often not the medication that has changed, but the way the patient's body responds to the medication, and this must be addressed. We are working on prevention, on reaching a solution sooner." ■

SANDERS-BROWN

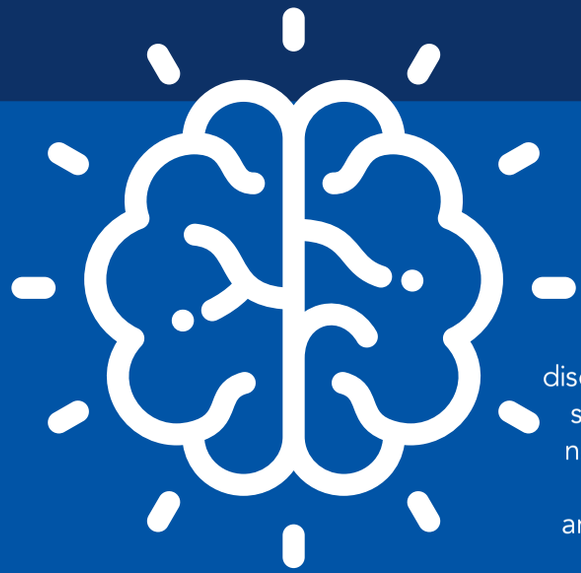
# Contribute to a CURE

## DEMYSTIFYING BRAIN DONATION

Since 1989, our team of doctors, psychologists, family care specialists and other staff has been studying memory and thinking to better understand healthy brain aging and Alzheimer's disease. Over this time, we have followed more than 1,000 people from Lexington and surrounding communities who have agreed to undergo annual examinations and brain donation at the time of death. With their help, we are closer than ever to finding a cure for this devastating disease. **You can help, too!**

## WHAT IS A BRAIN DONATION?

Brain donation involves the post-mortem removal and study of brain tissue and fluids. Our donors arrange for us to have their brains after their deaths, which enables us to give their families a full diagnosis of their loved one's condition, study their disease in detail and bank their brain tissue for future research efforts.



## WHY DONATE?

Simply put, researching brain tissue is the best way to understand the effects of dementia and other diseases on the brain, and even one donated brain can support dozens of clinical studies across laboratories nationwide. The more research that can be done, the better our understanding of the brain's pathology, and, in turn, the better our chances are of developing treatments for Alzheimer's and other diseases.

## WHAT ELSE IS BEING DONE ACROSS THE NATION?

**Sanders-Brown's biobank has provided more than 33,000 donated biosamples to over 175 labs across the country since 2010, including nearly 100 labs at the University of Kentucky.**

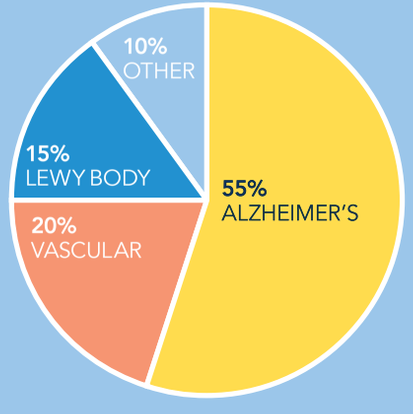
## WHAT IS A *biobank?*

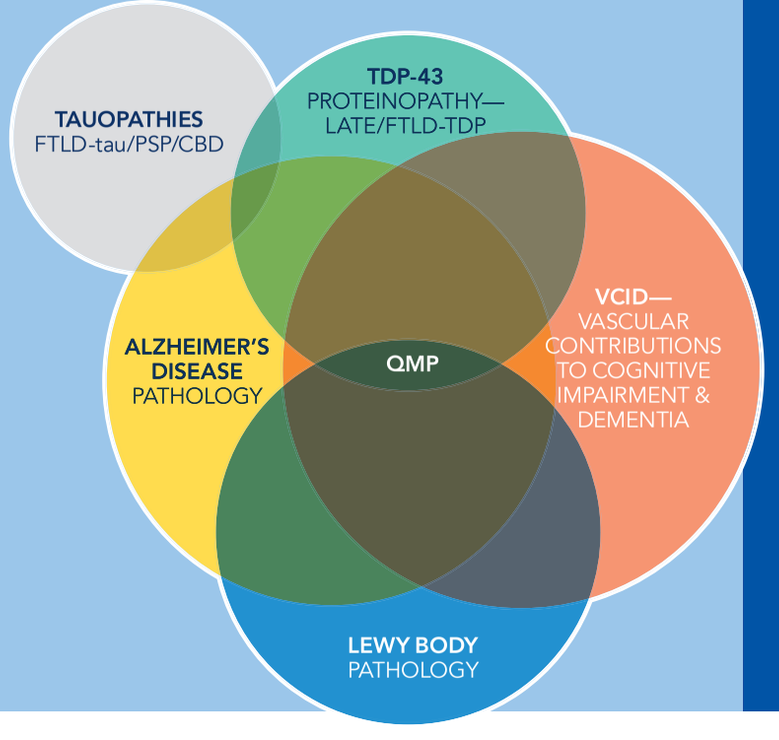
*A biobank is a large collection of tissue samples that includes brain tissue, blood, and cerebral and spinal fluids that can be accessed by researchers. The Alzheimer's Disease Center Biobank at the UK Sanders-Brown Center on Aging has been a critical driver of scientific advancement in this area of study and has been successful in altering basic perceptions in the field about dementia and Alzheimer's.*

# WHAT HAVE WE LEARNED FROM **BRAIN DONATION?**

The previous paradigm was that "you had it or not."
What we know now is that AD isn't just one thing.

**REDUCTIONIST VIEW OF DEMENTIA** **VS** **THE *real* PICTURE OF DEMENTIA**




# WHERE ARE WE GOING **FROM HERE?**

## Decoding brain pathology is the key to therapies & a cure.

The key to a cure is to understand what's going on so we can deploy tailored therapeutics for the various subsets of the diseases.

Sanders-Brown Center on Aging

*Research* STORY

WRITTEN BY LYNN DAVY | PHOTOGRAPHY BY PETE COMPARONI & MARK CORNELISON

# PROBING THE CONNECTION BETWEEN DOWN SYNDROME AND ALZHEIMER'S DISEASE

Researchers at Sanders-Brown hope to understand this link to help those with Down syndrome and the general population combat dementia

**People with Down syndrome are living longer and fuller lives thanks to medical advances. But there is still much to learn about the Down syndrome brain, including why those with the genetic condition are more likely to be diagnosed with Alzheimer's disease as they age.**

Researchers at the Sanders-Brown Center on Aging have been studying the mental thinking abilities and brain evolution aging of people with Down syndrome for more than a decade. They know that roughly 20 percent of people with Down syndrome show signs of Alzheimer's brain pathology by the time they are 20, and that virtually all of them have this brain pathology by the time they reach 40.

But they don't know why some members of this group never actually develop full-blown Alzheimer's. This is one of many questions that medical experts hope to answer as part of a multi-center research project known as the Alzheimer's Biomarkers Consortium-Down Syndrome, which kicked off in 2020 and is scheduled to continue into 2025.

Since people with Down syndrome develop symptoms of Alzheimer's disease earlier than people without the genetic condition, researchers hope they can also help the larger population defend itself against the disease. Roughly 6.2 million people of all ages are estimated to have Alzheimer's disease in the U.S.

"There's a lot of excitement about finding treatable conditions that could reduce the risk and allow those with Down syndrome to live longer, healthier lives," says Frederick Schmitt, PhD, professor of neurology and researcher at the University of Kentucky's Sanders-Brown Center on Aging. "We hope that this project will also help us to find remedies for people in the general population who are also affected by Alzheimer's."

It was only in the 1970s and 80s that scientists started to actively investigate possible connections between Down syndrome and Alzheimer's disease because up until then, most people with Down syndrome died around 40 years of age, before signs of the disease manifested. Now that people with Down syndrome are living into their 50s, and 60s, and even later, scientists can track disease progression.

For the past decade, Dr. Schmitt and the research team have worked with other researchers at Sanders-Brown to monitor 120 people with Down syndrome. Kentucky has one of the highest rates of babies born with Down syndrome in the nation, and so work in this area, and advances made, have a direct impact on residents. Local families are grateful that their loved ones can participate in studies: for the social contact, medical care, and extra support.

Most study participants look forward to their meetings with researchers and doctors because they interact with new people, observe the work of sophisticated medical machines such as MRIs, and play cognitive function games. Over the years, they become friends with researchers and doctors.

"I think it's wonderful because the more information we have, the better Frances, and others, are going to be cared for," says Linda Perkins, whose sister, Frances Dillion, was a participant for seven years in the studies at Sanders-Brown before her death and brain donation to further advance scientific knowledge. "Other children and adults with Down syndrome will hopefully have a better life because of what the researchers are discovering through these studies. It gives me great hope for the future."

During the past year, almost all the visits and meetings related to studies were moved to a virtual format due to Covid-19, but this has not slowed down researchers or their work. They continue to recruit new volunteers for the study (they are currently focused on recruiting candidates as young as 25 years of age), analyze medical data, and process questionnaires that participants and their families fill out. While progress has continued, everyone misses seeing volunteers in person because of the joy they bring.

"People with Down syndrome and their families are special and one of the wonderful things about working with them is their genuine expression of emotion," says Dr. Schmitt. "They give you hugs, and they tell you they love you. It's really rewarding work."

Recently, Drs. David Powell and Kate Van Pelt, two members of the research team at Sanders-Brown have been looking closely at blood flow to the brain, and why the flow tends to diminish in people with Down syndrome as they age.

"If we could understand what is causing these changes in blood flow in the brain, then we could begin to understand how it impacts thinking and eventually see if these blood flow changes could be a target for treatment," says Dr. Schmitt.

Working with people with the genetic condition takes patience. They often require help preparing for blood draws and MRIs, which can promote anxiety and be frightening. Researchers also work with families to help them better understand the way Alzheimer's shows up in people with Down syndrome, which is different than for those in the general population.

People with Down syndrome who have Alzheimer's typically begin to withdraw from social interactions, become more aggressive, and develop irrational fears. One participant developed an irrational fear of water, even though he used to love swimming and spending time in the water. This participant died at an early age because of Alzheimer's, which was a tragedy for his family and friends.

Dr. Schmitt and his team are driven to help those with Down syndrome live longer lives, without the threat of dementia and Alzheimer's. Research shows that a protein called beta-amyloid begins to build up in the brain of people with Down syndrome beginning at about 20 years of age. As the presence of the protein grows, so do plaques that disrupt cell function and lead to dementia and, possibly, Alzheimer's.

Scientists believe that the presence of the third chromosome 21 that is unique to people with Down syndrome may play a role in the earlier accumulation of the beta-amyloid protein. The third chromosome 21 creates other medical conditions, some of which scientists and doctors can now control with medicine, including thyroid problems and inflammation buildup in the body.

Medicine that diminishes the effects of Alzheimer's disease for some members of the general population does not work in people with Down syndrome, which is another mystery that scientists hope to solve as part of their research. Dr. Schmitt and other researchers are "scratching their heads" to understand if this is due to other "processes or brain injuries" that are occurring in people with Down syndrome.

> "Can we identify the most important components of the third chromosome 21 and then make a difference so people with Down syndrome don't develop dementia and Alzheimer's?" asks Dr. Schmitt. "If we could, there could be ramifications for those without Down syndrome, as well." ■

# About
## OUR TEAM

## DOWN SYNDROME TEAM

*(From left to right)*
Markeda Yarbrough
Lisa Koehl, PhD
Jennifer Wells, MS, LPA
David K. Powell, PhD
Roberta Davis, MA
Briana Williams
Katie McCarty
Frederick Schmitt, PhD

*Not pictured*

**Physicians**
Donita Lightner, MD
Richard King, MD, PhD
Gregory Jicha, MD, PhD

**Brain Imaging**
Brian Gold, PhD
Riham El Khouli, MD, PhD

**Core Collaborators**
Jordan Harp, PhD
Kate Van Pelt, PhD

*Research* STORY

WRITTEN BY JEN NEWTON | PHOTOGRAPHY BY PETE COMPARONI & MARK CORNELISON

# THE KEY TO ALZHEIMER'S MAY BE IN YOUR GENES

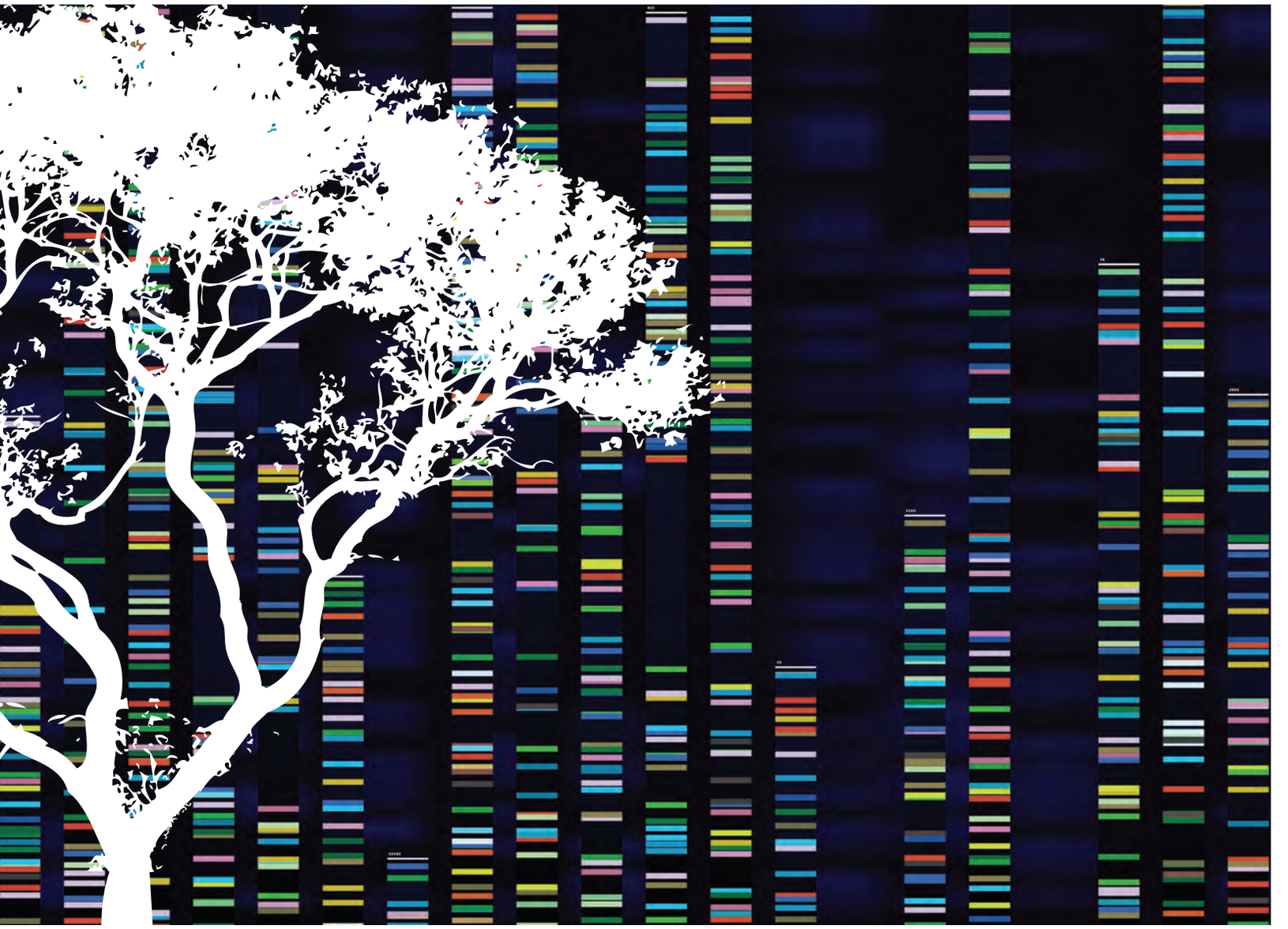
**For years, researchers have sought out the cause of Alzheimer's disease in the hopes of finding a cure. What has become clear is that there is likely no one universal cause, but a complex set of factors that influence development of the disease. From amyloid plaques and tau tangles to vaccines, researchers are exploring multiple avenues, including the field of genetics, which is showing promise. At the Sanders-Brown Center on Aging, the multidisciplinary research team is exploring genetics from diverse points of view to understand how they affect the Alzheimer's disease process and how they could be used to target therapies, diagnostics and a cure.**

According to Steven Estus, PhD, Professor of Physiology, "When you break down Alzheimer's disease risks, probably 60 percent of risk has a genetic basis." The genetic nature of the disease means it does run in families, but simply having a gene associated with Alzheimer's does not mean a person will develop the disease.

"There are between 30 and 40 genes that have been implicated in Alzheimer's disease. But for most of those genes, all we know is that the gene is somehow involved," says Mark Ebbert, PhD, Assistant Professor of Bioinformatics. "What we don't have for most of these genes is an actual mechanism for how the gene is driving disease."

"If we better understand the biological mechanism that is driving the downstream problems, then we can address that specifically, and we can design therapeutics to act as preventive measures," says Dave Fardo, PhD, Professor of Biostatistics and Stephen W. Wyatt Endowed Professor of Public Health.

By understanding how the genes work, the team hopes to turn data into laboratory testing and ultimately into clinical trials that will lead to therapies. And the goal isn't just to develop effective treatments, but also to develop diagnostic tools that can detect the disease before symptoms ever appear, when the disease could be preventable.



## THE DIFFERENCE BETWEEN CAUSE AND RISK

Some genes have a causal effect, meaning people with these genetic mutations will most likely develop the disease. Other genes do not directly cause Alzheimer's but have been identified as risk factors. And some genes have protective qualities.

Genetic mutations in three genes —amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2)—have been found to cause hereditary forms of early-onset Alzheimer's.

One of the greatest risk factor genes is apolipoprotein E (APOE), which has three forms. APOE-3 is the most common but is believed to have a neutral effect on Alzheimer's. "APOE-4 is present at about 20 percent frequency in our population. If you have one copy of APOE-4, that increases your risk of Alzheimer's about threefold," says Dr. Estus. APOE-2 is the rarest form. It has the opposite effect. "APOE-2 is protective. It cuts the risk of Alzheimer's by about 40 percent," he says.

While these genetic variations have been known and studied since the 1990s, many new genes have been identified since 2005 when new technology enabled large-scale genome-wide association studies (GWAS). These studies test hundreds of thousands of people for multiple genetic variants at one time.

## UNDERSTANDING HOW GENES WORK

From a physiological perspective, Dr. Estus' research focuses on genetic variations that occur at a single point in the DNA sequence, called single nucleotide polymorphisms (SNPs), and how they affect gene function.

One gene Dr. Estus and his team are studying is CD33, a known risk factor for Alzheimer's. They discovered that a CD33 genetic variant was creating a protein that didn't function, and the result was a decrease in disease risk. In fact, a 40 percent decrease in CD33 provides a 20 percent decrease in risk. So, Dr. Estus and his team are proposing that blocking CD33 more completely could cut the risk in half.



"We try to understand genetic risks and how they affect the protein so we can understand how to inhibit or activate them," says Dr. Estus. This research also carries pharmaceutical implications. "If you have a genetic validated target, a drug is about four times more likely to get FDA approval," Dr. Estus says, meaning sooner access for those suffering from the disease.

On the bioinformatics side, Dr. Ebbert is working to identify large structural variants or functional mutations that involve 50 or more nucleotides. Previously cost- and time-prohibitive, he utilizes cutting-edge technology known as long-read sequencing to look for mutations in tens of thousands of nucleotides at a time.

Once identified, Dr. Ebbert can collaborate with scientists in the wet lab, like Dr. Estus, to look at how the mutation is affecting the cells and what can be done to alter its effects. The implications become, "On the therapy side, now that we have a mechanism, how do we then intervene in that mechanism?" On the diagnostic side, "If it's at the genetic level, then we can screen individuals early in life. Say you have this variant that is likely to cause disease; now we can start intervening long before symptoms begin and maybe even before disease starts," says Dr. Ebbert.

In the Biostatistics department, Dr. Fardo uses statistical methodologies to test for association with recently discovered proteins that cause problems with brain function. "If we have those protein measurements, we can be much more specific about what has happened in that particular person's brain and correlate that to the genetic predisposition," he says.

Ultimately, the more researchers understand, the more Sanders-Brown can help patients understand their risk and their options.

> "It's a complicated disease and what it's really going to take to make a difference is a team that's genuinely working together, which is what we have here at Sanders-Brown, the University of Kentucky. And as part of that team, the resources, the community, the families and individuals who are affected by this disease are part of that team. We can't do this without them," concludes Dr. Ebbert.■

*Student* PROFILE

WRITTEN BY HILLARY SMITH | PHOTOGRAPHY BY PETE COMPARONI

# DREW FARR

**Drew Farr began working with the University of Kentucky's Sanders-Brown Center on Aging as an MD/PhD student. UK's MD/PhD program trains the best and brightest in the skills, intellectual tools and science of both clinical medicine and ground-breaking biomedical research. As part of that program Farr completed his two years of classroom work for medical school and is now in the midst of his PhD training. Once that is complete, he will return to medical school to complete his clinical rotations.**

Prior to joining the prestigious program at UK, Farr received his undergraduate degree in economics from the University of Georgia. During his time at Georgia, he worked in a behavioral neuropharmacology lab. Now he finds himself working in Chris Norris' lab at the Sanders-Brown Center on Aging for his PhD training with an interest in the neural processes that underlie the encoding, potentiation, retrieval and decay of memories over time.

Farr says he chose this type of work and finds motivation from his own memories.

> "As a child, I had a close personal relationship with my great-grandmother 'MeMa'. She grew up in Dalton, Georgia, worked for decades at a carpet factory, loved to dance and lived into her late 90s. She experienced memory loss related to an Alzheimer's disease diagnosis."

Farr says despite her diagnosis, without fail, his MeMa called family members every year to sing them 'Happy Birthday' on their special day.

A desire to help in the search for answers, treatments and ultimately a cure for Alzheimer's disease made Sanders-Brown a perfect place for Farr to pursue his doctorate degree. "My favorite part of Sanders-Brown is collaborating with outstanding faculty, staff and fellow students."

Whatever the future holds for Farr, he says he will be taking some invaluable lessons with him thanks to his time at UK. "Chris Norris has devoted considerable time teaching me to write fellowship grants, which led to successful applications." Additionally, Farr says he has learned several techniques for scientific research from other members of the Norris Lab.

# ALZHEIMER'S *in* KENTUCKY

Alzheimer's disease is a growing public health crisis in Kentucky. Without an effective treatment or cure, the impact of Alzheimer's will continue to rise, and the numbers in Kentucky are escalating.

NUMBER OF PEOPLE
**AGED 65 AND OLDER**
living with Alzheimer's in Kentucky

*estimated*
**14.7%** CHANGE

2020 **75,000**
2025 **86,000**

**149,000**
*family caregivers*
bear the burden of the disease in Kentucky

**69.6%** of caregivers have chronic health conditions

**27.1%** of caregivers with depression

**$803 MILLION**
is the cost of Alzheimer's to the state Medicaid program

**6th LEADING CAUSE OF DEATH**

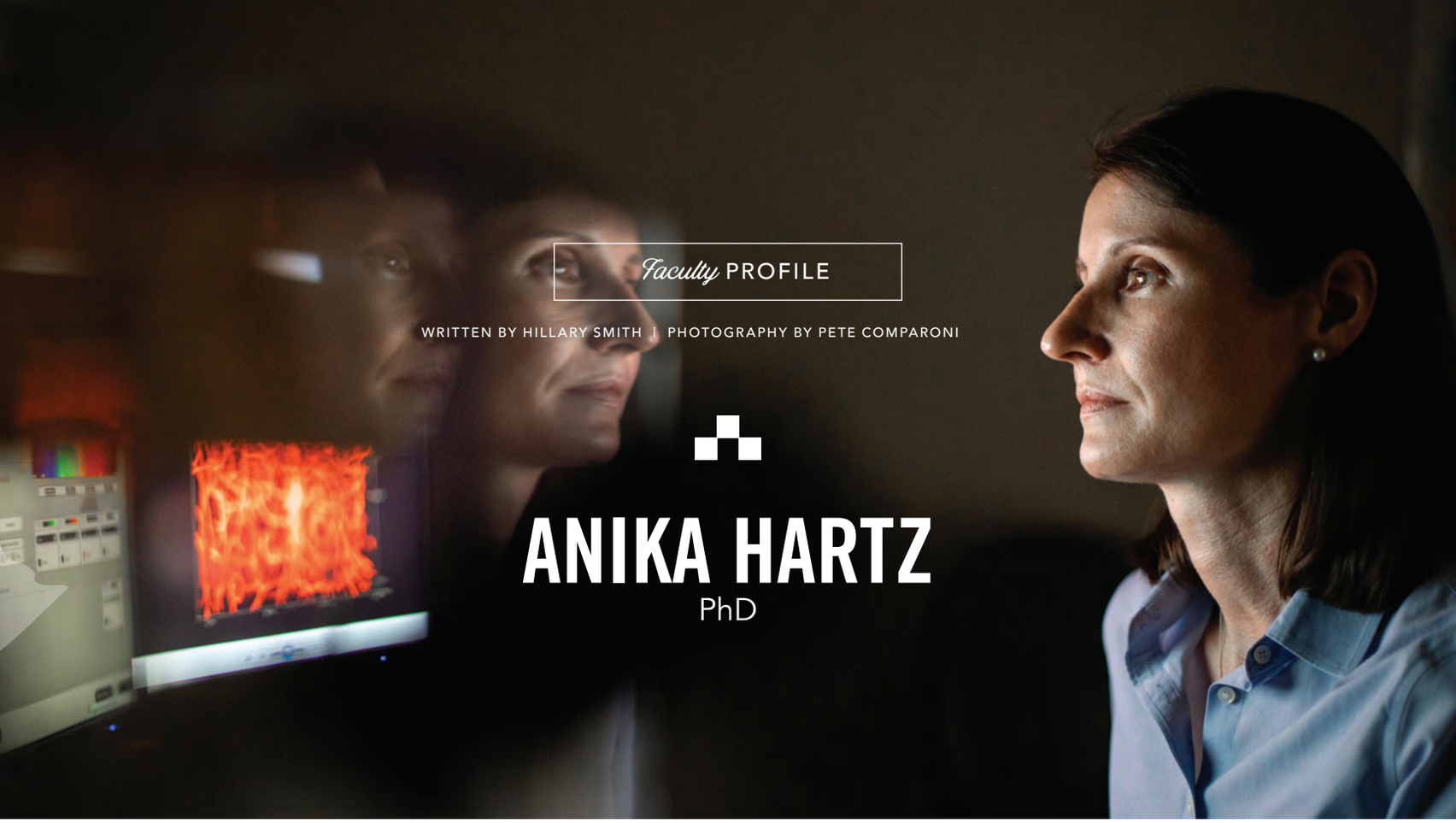
**1,684**
DEATHS FROM ALZHEIMER'S DISEASE (2019)

**921** **more deaths than expected** from dementia during the Covid-19 pandemic

**$3.84 BILLION** IS THE VALUE OF THE UNPAID CARE

**265** *million*
**HOURS OF UNPAID CARE**
provided by Alzheimer's caregivers

Alzheimer's Association Facts and Figures 2021



*Faculty* PROFILE

WRITTEN BY HILLARY SMITH | PHOTOGRAPHY BY PETE COMPARONI

# ANIKA HARTZ
PhD

**Anika Hartz, PhD never planned on becoming a scientist. She is a pharmacist by trade, who moved to the United States from her home of Germany in 2002 to begin her PhD. at the National Institutes of Health. At the time she had no intention of going into science. "Coming to the U.S. in 2002, changed my mind". explains Dr. Hartz.**

Her time at the National Institutes of Health was unique and marked a turning point for her career plans. "They typically only take post-doctoral researchers, but they made an exception and took me on as an unpaid guest researcher." Dr. Hartz was able to complete her thesis working in a top-notch scientific environment.

> "I fell in love with science," says Dr. Hartz. "I could join a pharmaceutical company today and probably make twice as much, but it is the love for science that really motivates me."

Since 2014, she has been using that love of science to help further research at the University of Kentucky's Sanders-Brown Center on Aging and College of Medicine's Department of Pharmacology & Nutritional Sciences. Dr. Hartz joined UK together with her husband Bjoern Bauer, PhD who is professor in the College of Pharmacy's Department of Pharmaceutical Sciences.

"UK and Lexington are a good fit because we are a husband-and-wife research team and came as a package." In addition to their roles as researchers, Drs. Hartz and Bauer are the parents of three daughters.

Dr. Hartz says the focus of her research is pretty simple. "I look at the blood vessels in the brain—the so-called blood-brain barrier—and how they change in Alzheimer's disease." With her background in pharmacy Dr. Hartz looks at drugs and therapies that might repair damaged blood vessels in Alzheimer's disease.

"I am not an Alzheimer's disease expert," explains Dr. Hartz, and because of that she says she is extremely grateful to work at a place like the University of Kentucky and Sanders-Brown Center on Aging. Hartz says having numerous colleagues with complementary expertise has been critical for her research as well as the ability to collaborate with colleagues from different fields. "My research field is fairly small with about 300 core blood-brain barrier experts worldwide. So, working in a small field it is very helpful to have Alzheimer's disease experts around me."

Dr. Hartz says the goal is to eventually translate strategies developed in her lab into clinical trials to help patients, "We are hopeful that our work will eventually have an impact on a person's health."

LOOKING TO *the Future*

WRITTEN BY JENNIFER KEMNITZ

# MOVING SANDERS-BROWN INTO THE NEXT DECADE

Over the next 10 years, every Baby Boomer will reach retirement age. By 2030, one out of five U.S. citizens will be 65 or older—the first time in U.S. history that older people outnumber children. And as life expectancy increases, many will live well past 65.

Not only does an aging population mean more individuals at risk for age-related dementia, but it also means more families must be prepared to care for them, which can take a tremendous emotional toll as well as a financial one.

"We're seeing a new generation of caregivers who are sandwiched between taking care of their children and taking care of their elderly parents," says Linda Van Eldik, PhD, director of the Sanders-Brown Center on Aging and the Alzheimer's Disease Research Center.

"Some people refer to it as the Silver Tsunami," says Donna Wilcock, PhD, associate director of SBCoA and head of the Steering Committee charged with defining the Center's strategic goals for the next decade. "As this large population ages, obviously we will see a proportional increase in dementia cases." Dr. Wilcock, who specializes in vascular dementia, also points out that Kentucky sits in the heart of the Stroke Belt, putting the state's older population at greater risk for Alzheimer's disease.

Dr. Van Eldik agrees. "It's a huge problem. And if we don't come up with something effective, the numbers of people with Alzheimer's and other age-related brain disorders will probably double by 2050."

Over the past four decades, SBCoA has made critical breakthroughs in treatments, lifestyle correlations and health equity that have changed the course of people's lives in Kentucky and around the world. Unlike many other Alzheimer's disease centers, SBCoA spans a continuum from basic science research to clinical research to family support and community engagement.

## JOIN OUR VISION FOR THE FUTURE

visit **sbcoa.med.uky.edu/donor-opportunities** or contact us at **859-562-2225.**

"It's this integration of research and clinical experience that makes us unique," says Dr. Van Eldik. "We've really been the leader in understanding what's happening in the brain and how that corresponds with different types of dementias. We're identifying biomarkers that will allow us to use precision medicine to target specific types of dementia. It's similar to what the cancer field has achieved over the last 20 years."

Dr. Wilcock adds, "Hopefully, it won't take us that long."

## TURNING A VISION INTO REALITY

To meet the growing need, SBCoA is building a state-of-the-art memory clinic more than twice the size of the existing facility. The new clinic will provide a seamless experience for patients and their families, with co-located services including cognitive testing, EEG/EMG testing, gait analysis and a dedicated space for caregiver consultations. "It will be a one-stop shop for memory care and support," says Lisa Deaton Greer, Senior Director of Philanthropy for UK HealthCare.

"Sanders-Brown currently sees upwards of 1,500 patients a year," Greer continues. "We'll be able to see so many more patients. For the 75,000 Kentuckians already living with Alzheimer's and the countless family members and caregivers who are also affected, the timing couldn't be more critical."

In addition to the many on-site services SBCoA will offer, the new clinic also provides space for expanded telemedicine services. "Maybe the advancement of telehealth is one silver lining from Covid," Greer says. "Doctors will be able to see patients all over the state, providing greater access to many more individuals in need."

But a bigger clinic alone won't find a cure for Alzheimer's disease. With a goal to raise $10 million over the next 10 years, SBCoA is looking toward the future. To lead the charge against age-related neurodegenerative disorders, SBCoA plans to build on its strengths—talent, research and outreach.

"We already have the hardest thing, which is talent," Dr. Wilcock says. "But we want to attract new expertise and provide them the resources to do their best work."

Research has been the backbone of SBCoA since its founding more than 40 years ago. And while the Center has received significant funding from the National Institutes of Health (NIH), "It's hard to really get any substantial funding for a research project without at least showing that what you're proposing is feasible," Dr. Wilcock explains. When faculty want to explore a new research area, they typically start with pilot studies. "For a relatively small dollar amount, they can collect the data they need and often turn that study into a larger grant."

One ongoing challenge in the battle against dementia is the misconception that it is simply a memory or thinking problem. "These dementias come with so many more debilitating symptoms," Dr. Wilcock says. "Lewy Body Dementia, for example, is usually associated with some terrible psychiatric problems that can result in tragic accidents."

Through its outreach and education programs, SBCoA helps individuals and their families understand age-related brain illnesses and find the community resources they need. The Center is particularly focused on expanding outreach to underrepresented populations.

"We're really trying to reach people in our African American communities," says Dr. Van Eldik. "We're partnering with The Balm in Gilead and organizing special events to emphasize brain health in churches in Lexington and Louisville. There are disparities throughout Kentucky, especially among African Americans and people living in Appalachia."

Even with the Silver Tsunami looming, Drs. Van Eldik and Wilcock agree that the next 10 years hold exciting promise.

"Everything is moving faster than it ever used to," Dr. Wilcock says. "If you'd asked me three years ago if I thought we were going to have a blood test for Alzheimer's disease, I would have said, well, maybe on the horizon. Now we have one approved for screening, and that's incredibly fast."

Dr. Van Eldik points out quickly: "We have to move fast. So, we're trying to spread the word about the disease and related dementias and their devastating effects. If enough people see that it's an important enough problem, then huge discoveries can be made very rapidly." ■

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“We realized that in order to provide optimal care, we have to not just treat the patient, but we have to educate and care for the caregiver as well.”

—GREGORY JICHA, MD, PHD

*Mind Matters* is an annual publication from the University of Kentucky Sanders-Brown Center on Aging.