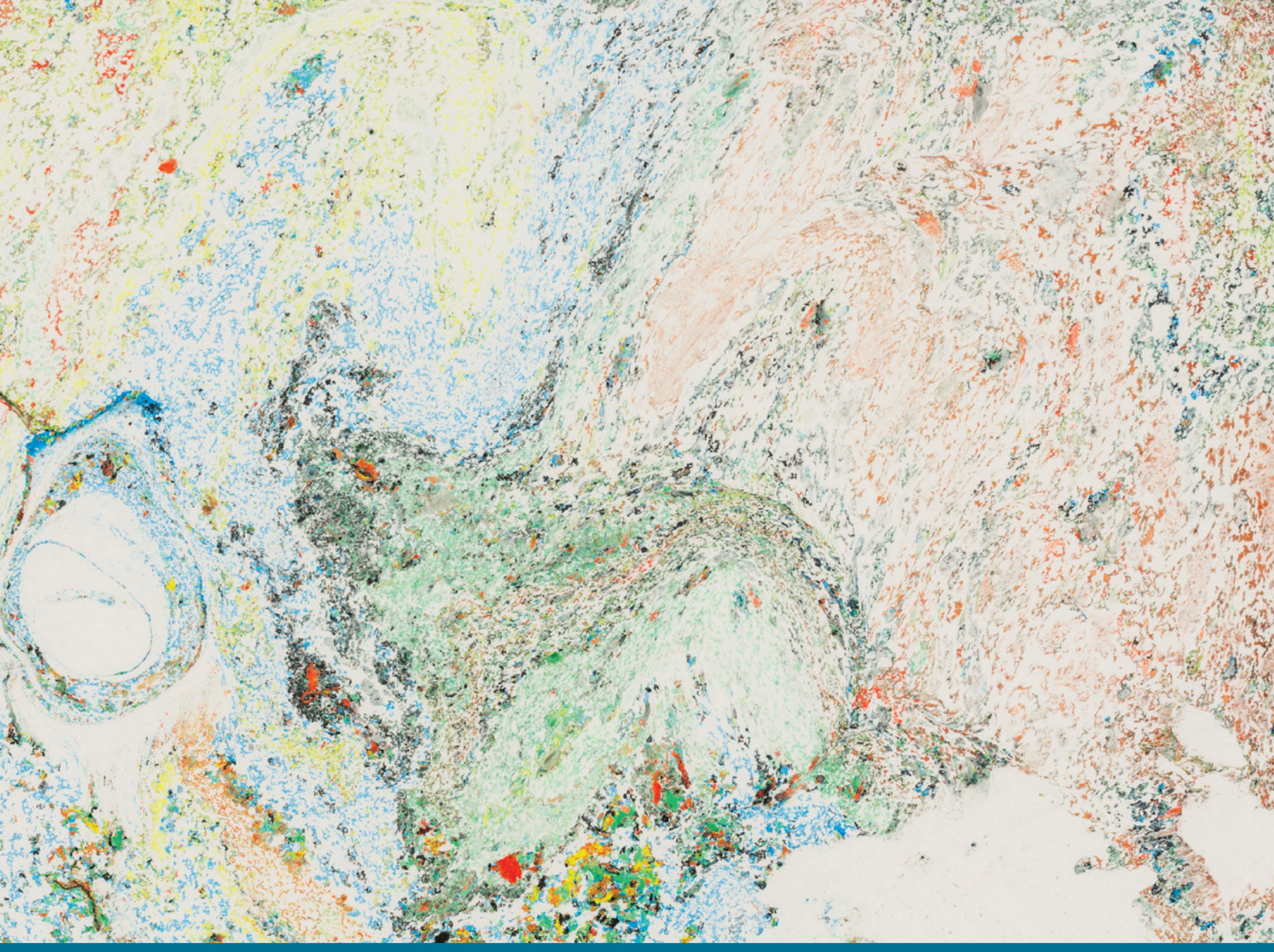


Waisman Center

2019 ANNUAL REPORT

The Waisman Center advances knowledge about human development, developmental disabilities, and neurodegenerative diseases. One of only 14 centers of its kind in the United States, the Waisman Center encompasses laboratories for biomedical, behavioral, and clinical translational research, a brain imaging center, and a biomanufacturing facility for the production of biopharmaceuticals for early stage human clinical trials. In addition to its research efforts, the Waisman Center provides an array of services to people with developmental disabilities, offers numerous clinical, educational, and outreach programs to children and their families, and trains scientists and clinicians who will serve our nation in the future.

Cover Artwork: *Untitled*, Unknown, Portugal

All artwork featured in the report is from the Harvey A. Stevens International Collection of Art by People with Developmental Disabilities. The collection is maintained and sponsored by the Friends of the Waisman Center.

Director's Message

As we draw near to the end of 2019, I am pleased to share with you our annual report that highlights several of our recent accomplishments at the Waisman Center. As you turn the pages, you will learn about some of our research discoveries and the new ways we are helping individuals and families affected by developmental disabilities and neurodegenerative diseases. We are confident that these efforts will continue to bring benefits to the community we serve in the years to come.

Equipped with innovative tools and novel ideas, Waisman Center investigators and clinicians see many exciting opportunities to push forward scientific discovery, expand and enhance our clinical services, as well as integrate our research, training, and outreach. I encourage you to participate in all of our activities and am always open to your ideas and comments on how we can better engage you. We cannot accomplish our mission alone!

Toward the end of this annual report you will find the names of our many generous donors — invaluable partners in our progress. It is truly a privilege to have you on our team.

Thank you for your support of the Waisman Center!

Qiang Chang, PhD
Director, Waisman Center
Professor, Medical Genetics & Neurology

Whole Exome Sequencing Illuminates Genetic Condition

If you ask David Seamans what his favorite thing to do is, he'll pause thoughtfully for a moment before responding, "Everything."

He really does mean everything. In May of 2019, he traveled with his brother to Saipan to aid in hurricane relief. He spent two weeks in over 100-degree weather replacing roofs. "It was the coolest thing I've ever been involved with other than getting married and watching my two daughters be born," he says. "The way the people reacted was just absolutely incredible."

This experience wouldn't have been possible for Seamans just over a year ago; he had what was, at the time, an undiagnosed and progressively debilitating and blinding disorder that would have prevented it. One test later and Seamans' life has completely changed. Today, he has regained his strength and his health and is only too happy to give back. "I got my miracle," he says. "Let's go hand it on and help somebody else out."

About 10 years ago, Seamans began having unexplained neurological symptoms.

It began with his vision. Once an avid reader, he began struggling to see the words on the page: "I would read for 10-15 minutes and I couldn't focus on anything."

Soon after, he developed neuropathy in his limbs. "My hands and feet were going numb all the time," he says. "I couldn't walk 20 feet without canes or a walker. I was dragging my feet, I was dropping stuff all the time and I couldn't see squat."

Seamans was in regular consultation with multiple specialists, but they couldn't determine the cause for his worsening condition. It was suspected that his symptoms were possibly the onset of multiple sclerosis (MS). However, his results came back negative when he was tested for the disease.

As his eyesight diminished and the physical challenges of daily life increased, Seamans' world was becoming smaller and smaller. He was no longer able to drive. "I figured I was a goner. Everything was breaking down so bad," he says. Not knowing what was causing his progression was especially hard. "To say it was depressing would be an understatement. I wanted to know. If I know why I'm blind, I can accept that."

In a fortuitous turn of events, Seamans' primary care doctor was discussing his case with a colleague who suggested a genetic consult. He was eventually referred to the Waisman Center Medical Genetics Clinic where he met with Elizabeth Kellom, MS, CGC, a genetic counselor.

The Waisman Center Medical Genetics Clinic is an interdisciplinary clinic for people who have suspected or known hereditary conditions. It is one of 10 specialty clinics at the center that serve individuals and families with a broad range of intellectual and developmental disabilities. In the Medical Genetics Clinic, genetic counselors provide diagnostic and confirmatory services, care coordination, and counseling.

"We talked about all of the testing options," Kellom says of her hour-long meeting with Seamans. "We talked about broad-based genetic testing to get a pretty good look at the vast majority of Mendelian disorders versus single gene tests for the most common genetic causes of optic atrophy," says Kellom. Mendelian disorders are caused by a mutation in a single gene and include disorders such as cystic fibrosis, phenylketonuria (commonly referred to as PKU), and Rett syndrome.

Given the options, Seamans decided to undergo whole exome sequencing, which is a broad-based test. This method allows for sequencing the patient's exome — the sections of an individual's DNA that provide the core

"We talked about broad-based genetic testing to get a pretty good look at the vast majority of Mendelian disorders."

Elizabeth Kellom, MS, CGC
Waisman Center Genetic Counselor

"Without the recycled biotin, you end up with biotinidase deficiency — a condition that would typically present in childhood with neurological features such as seizures, developmental delay, alopecia, dry skin, and hearing loss."

– Elizabeth Kellom

instructions for making proteins — and identifies variants in many genes at once. The cost for whole exome sequencing can be from $1,200 to $3,000 and is not covered by many insurance companies in Wisconsin. However for Seamans, it was a price he was willing to pay in the hope of finding some answers. According to Kellom, "It ultimately turned out to be the correct thing to do."

For the whole exome sequencing, Seamans performed a buccal swab in which his DNA was collected from the inside of his cheek. The swab was sent off to PerkinElmer Laboratories in Illinois to be analyzed. He spent the next five weeks, he says, "stressing and just hoping they found something."

Seamans' genetic test report showed several mutations in a gene called BTD. This gene provides instructions for biotinidase, an enzyme that recycles biotin — a B vitamin that is essential to properly functioning metabolism. "Without the recycled biotin," Kellom explains, "you end up with biotinidase deficiency — a condition that would typically present in childhood with neurological features such as seizures, developmental delay, alopecia, dry skin, and hearing loss."

After the genetic test, enzyme testing confirmed the diagnosis in David. Had he been born 25 years later, this would have been done at birth. Screening for biotinidase deficiency is currently done as part of the Wisconsin newborn screening panel, but it wasn't included on the panel until 1991. "What we're finding is that there's a wide range of presentations of this particular condition and Dave's represents the extreme of that," she says. "At 51, he is the oldest known person to develop symptoms of biotinidase deficiency."

With Seamans' condition confirmed, Kellom gave him a call. "She was like, 'We found it!'" Seamans recalls. "'And I hope you're sitting down because it's treatable!'"

Kellom told Seamans that the solution was simple enough: go to a local drug store and buy some biotin supplements. Seamans returned to the Waisman Center and met with Greg Rice, MD, a biochemical clinical geneticist in the Waisman Center Biochemical Genetics Clinic, to set up a treatment plan.

"It's rare to find a condition that has a treatment as clear as what Dave received, but that doesn't mean there isn't value," Kellom says. "To even have some sort of a roadmap, for some families, is so beneficial to not have to wonder about the cause," she says. "I wish insurance companies valued that more. One day, I'm really hopeful that it will be consistent across insurance companies that this is a valuable test and that it's cost effective."

Nowadays, you can usually find Seamans outdoors.

"Most people think of cutting firewood as a chore," he says, "but that's something I've always liked doing. I've always loved watching the stars at night, but it had gotten to where if I was lucky and I looked just right, I could only see one star at a time."

Then on July 2, 2018, only two weeks after starting biotin supplements, he noticed a big change. "I went outside and looked up and saw the Big Dipper — the whole thing — and I cried," he says.

While Seamans has made vast improvements in his health and vision, it is still a long and uncertain road to recovery. His vision remains slightly impaired and he continues to get physical therapy. He has regular follow-up appointments with his primary care doctor and ophthalmologist.

Seamans greatly appreciates the services he received at the Waisman Center Medical Genetics and Biochemical Genetics Clinics. The sentiment is mutual. "I'm really lucky to have met Dave and walked through this process with him. To see what he's now able to see and to know that I played a role in that is incredibly rewarding," Kellom says. "On those days that we have patients where we are still dealing with that unknown — which still happens even with whole exome sequencing — it helps to know you helped at least one person really reach that quality of life that he was missing. It doesn't get better than helping somebody see."

Seamans has advice for anyone who has symptoms similar to his or of unknown origin: "Get the test" he says of whole exome sequencing. "Best money I ever spent. I'm just hoping that what I've gone through can shed light on it so somebody else can get help."

Wiring the Genome:

New Researcher Uses Machine Learning to Decode Genomic Information

Recent advances in genome sciences — the study of an organism's complete set of DNA — present a golden opportunity to identify the genetic causes and underlying mechanisms of intellectual and developmental disabilities. These discoveries will also improve diagnosis and potential treatments for these conditions.

To advance science in this innovative field, the Waisman Center successfully competed in a campus-wide initiative and won an opportunity to hire three new tenure-track faculty members for a Functional Genetics/Genomics of Neurodevelopmental and Neurodegenerative Diseases Cluster. The interdisciplinary team will include a biostatistician, a neuroscientist, and a geneticist. The cluster will serve as a nucleus to integrate research, training, and clinical services in this up-and-coming research area at the Waisman Center.

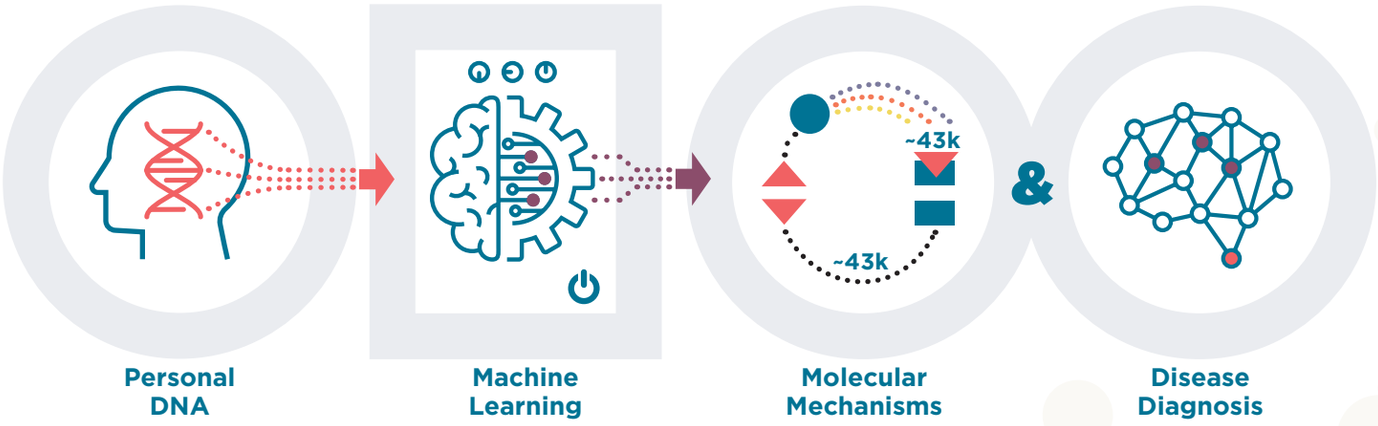
Daifeng Wang, PhD, a bioinformatician, was the first hire and fulfills the biostatistician role in the cluster. He began working at the Waisman Center in July 2019. His research focuses on the use of machine learning to analyze large scale genomic data to better understand gene regulation and functions in the brain.

Machine learning is a form of artificial intelligence (AI) that uses computer programs to analyze data quickly and efficiently. "It's really difficult to process so much complex data manually, so we have to use computer programs to analyze the data and generate predictions that could relate to a disease," Wang says. He hopes to apply these machine learning tools to a broad range of Waisman research focused on intellectual and developmental disabilities and neurodegenerative diseases. "The ultimate goal is

"It's really difficult to process so much complex data manually, so we have to use computer programs to analyze the data and generate predictions that could relate to a disease."

Daifeng Wang, PhD
Assistant Professor of Biostatistics and Medical Informatics and Waisman Center Investigator

Decoding Genomic Information to Better Understand Molecular Mechanisms and Improve Disease Diagnosis



to achieve some kind of precision medicine," he says. 'Precision medicine' is a term used to describe any kind of personalized treatment that is produced for a very targeted group of patients — or even one specific patient.

To achieve this, Wang employs deep neural network, a newer method of machine learning that uses computer programming to recognize patterns in large amounts of data. Wang describes what he's doing as "decoding a black box," referring to an electronic device that wires a series of inputs (in this case, DNA mutations) and outputs (diseases). "Everything connects to everything in a layered structure in the black box," he says. "We try to make the black box biologically interpretable by using prior biological knowledge to reveal the 'genetic' wires within the layered structure."

The focus of Wang's current research is how genomic variants, like DNA mutations, affect gene expression and regulation. "Gene regulation is a very important mechanism," he says. "Genes don't act alone. To ensure proper biological function, they need to interact with each other."

Wang uses available genomic data to test whether certain traits or a combination of traits will lead to a specific disease. If enough of the same traits produce the same diseases, then he can make meaningful connections to pathology. He says there is currently so much genomic data available — which could be used to predict neurodegenerative, developmental, and psychiatric disorders — that integrating all of this data can be a challenge. Wang's innovative use of machine learning makes that integration possible.

Wang has a PhD in electrical and computer engineering from the University of Texas at Austin and did his postdoctoral training at Yale University. He was drawn to the cluster hire position because of the Waisman Center's emphasis on interdisciplinary translational research. He looks forward to collaborating with others on IDD genomics.

In 2019, the Waisman Center established the *Mailick and Messing Interdisciplinary Research Fund* to support the cluster hire initiative and research in IDD genomics. The fund honors the career-long service of former Waisman Center directors Marsha Mailick, PhD, and Albee Messing, VMD, PhD. More than $500,000 was raised to help with the purchase of laboratory equipment and supplies, and to support students and postdoctoral researchers. For more information about the fund or to donate, please visit: www.waisman.wisc.edu/giving/

Electronic Records Pin Broad Set of Health Risks on Genetic Premutation

It was long believed the FMR1 premutation — an excessive number of trinucleotide repeats in the FMR1 gene — had no direct effect on the people who carry it. Until recently, the only recognized effect on the carriers of the flawed gene was the risk of having offspring with fragile X syndrome, a rare but serious form of developmental disability.

In recent years, however, at least two clinical conditions have been well documented in the carriers themselves: an age-dependent neurodegenerative disorder and early menopause.

Now, a team of researchers from the Waisman Center and the Marshfield Clinic has found that there may be a much broader health risk to carriers, with potentially dozens of clinical conditions that can be ascribed directly to carrying the premutation. The researchers employed machine learning, a form of artificial intelligence, to mine decades of electronic health records of nearly 20,000 individuals.

In a recent study published in Science Advances, a team led by Marsha Mailick, a Waisman investigator, and graduate student Arezoo Movaghar provide a better understanding of the previously disputed relationship between this well-known genetic premutation and a wide range of clinical conditions. At the same time, the interdisciplinary study richly illustrates the power of data-driven discovery.

In the study, carriers were found to experience a much higher prevalence and severity of such conditions as depression, anxiety, mood disorders, sleep apnea, respiratory and stomach problems, bone fractures, incontinence, and a host of other conditions.

"Our extensive phenotyping shows that premutation carriers experience a clinical profile that is significantly different from controls, and that is evident throughout adulthood," the study's authors write.

Important Implications

"The research was especially challenging as not all carriers are affected and the specific conditions each may experience varies," explains Mailick. "Yet the overall pattern revealed in the electronic health record was striking."

"The research was especially challenging as not all carriers are affected and the specific conditions each may experience varies."

Marsha Mailick, PhD
Emeritus Vice Chancellor for Research and Graduate Education and Waisman Center Investigator

The findings have important implications for the estimated 1 million people in the United States and many more in the rest of the world who carry premutations of the FMR1 gene. People are generally unaware they carry the altered gene unless a family member is found to have fragile X syndrome, which is rare.

The new study depended on the electronic health records of 19,996 adults collected over 40 years by the Marshfield Clinic, a health system in central Wisconsin that was among the first in the nation to adopt electronic record keeping. In addition to their extensive, searchable medical histories, study subjects also contributed their DNA through the clinic's Personalized Medicine Research Project, enabling the study's authors to identify 98 patients who carry the FMR1 premutation.

A primary goal of the new study, according to Mailick, was to use electronic health records to set up a double-blind methodology — where both clinicians and patients were blind to genotype — to assess whether premutation carriers differed in their patterns of clinical diagnoses from those lacking the premutation.

The question is an important one as some clinical reports have suggested that premutation carriers were at greater risk for a wide range of health conditions, including autoimmune diseases, migraines, neuropathy, depression, infertility, fibromyalgia, anxiety and cognitive deficits, all with varying frequencies and emerging at different stages of life.

Such correlations, notes Mailick, are the stuff of biomedical controversy as nearly all of the studies associating those conditions with the premutation were the result of a family member being diagnosed with fragile X. Following diagnosis of fragile X, family members are offered genetic testing leading to the identification of relatives who carry the premutation. Awareness of that genetic status by patients and clinicians can confound prevalence estimates of symptoms. Frequently, carriers' medical conditions are blamed on the stress of care giving and having a family member with fragile X syndrome.

Unbiased Data

"This is a controversy," says Mailick, who has spent a career studying the life course trajectories of people with developmental disabilities as well as their families through UW–Madison's Waisman Center. "There wasn't unbiased data available before this study to inform the controversy. This study does so in a powerful way. The data validate the clinical experience."

Arezoo Movaghar, graduate student

For men, clinical diagnoses commonly found in health records of FMR1 carriers include depression, diseases of the respiratory system, and urinary incontinence, as well as half a dozen other afflictions.

Movaghar and Mailick say some of the conditions associated with FMR1 carriers have long been suspected, but the number and range of health effects they found was a surprise: "We see conditions nobody ever associated with the premutation," Movaghar says.

To be included in the study data, subjects had to experience the diagnosis in at least two separate visits, helping weed out misdiagnoses or recording errors.

The approach used in this study, the Wisconsin researchers say, could also be applied to other genetic variants similarly believed to be innocuous but that potentially may have health effects.

Co-investigators include Arezoo Movaghar, David Page, Murray Brilliant, Mei Wang Baker, Jan Greenberg, Jinkuk Hong, Leann Smith DaWalt, Krishanu Saha, Finn Kuusisto, Ron Stewart, Elizabeth Berry-Kravis and Marsha R. Mailick.

This study was supported by grants from the National Institute of Child Health and Human Development (Grant numbers R01 HD082110 and U54 HD090256). Additional support provided through the National Human Genome Research Institute (Grant number UO1HG8701), the National Center for Advancing Translational Sciences (Grant number UL1TR000427), from the Wisconsin Alumni Research Foundation (WARF) and Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD) under Cooperative Agreement U01DD000231 to the Association of University Centers on Disabilities (AUCD).

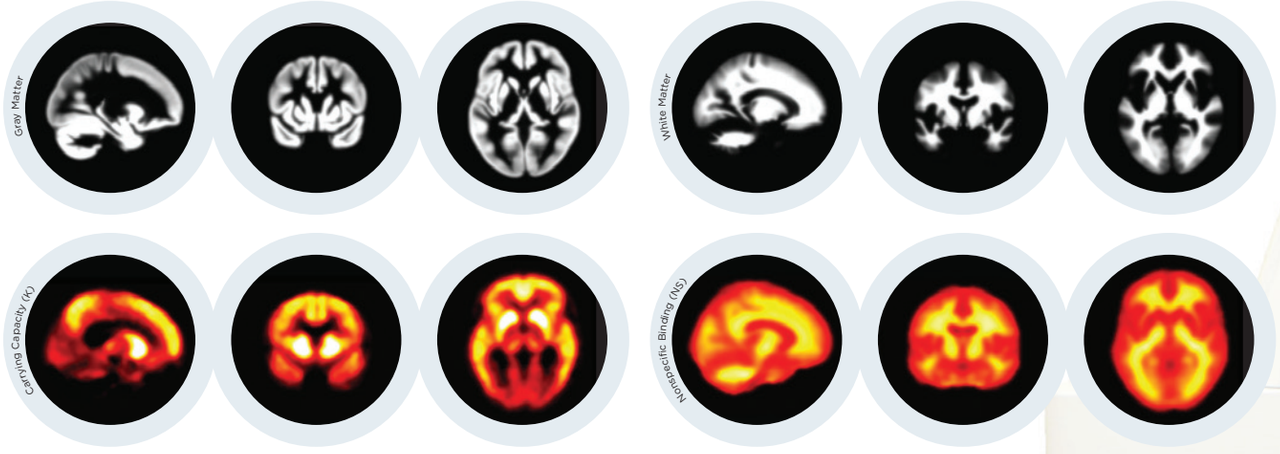
Future Focused:

Mancheski Foundation Funds Next-Gen Research on Down Syndrome and Alzheimer's

A gift from the Mancheski Foundation continues to provide integral support to doctoral student Matthew Zammit as he furthers his research on the progression of Alzheimer's disease in individuals with Down syndrome.

Zammit is beginning his fourth year as a doctoral student working in the laboratory of Bradley Christian, PhD, a Waisman investigator and professor of medical physics and psychiatry at the University of Wisconsin-Madison. The support from the Mancheski Foundation has allowed Zammit to continue his research focused on understanding the progression of Alzheimer's disease in individuals with Down syndrome. Adults with Down syndrome are at very high risk of developing Alzheimer's disease, with a 75% prevalence of dementia by age 65. As a result, there is strong motivation to get this population involved in clinical trials aimed at prevention of the disease. One promising intervention is an anti-amyloid therapy, in which an agent is administered that is designed to clear beta-amyloid plaques in the brain. Beta-amyloid plaques are thought to be the earliest marker of Alzheimer's progression, and removal of these plaques may slow the rate of cognitive decline. While such therapies have shown to be unsuccessful at reversing cognitive decline in individuals already diagnosed with Alzheimer's dementia, there is speculation that administration of this therapy before symptoms are present may prove effective. With this in mind, Zammit is using neuroimaging and neuropsychiatric data to find the ideal time point of Alzheimer's disease progression in individuals with Down syndrome in order to recruit for clinical trials aimed at monitoring the effectiveness of prevention strategies. Zammit is also currently working on publishing a manuscript focused on using PET imaging to measure to measure beta-amyloid change over time in Down syndrome, highlighting a new analysis method called Amyloid Load. This metric is very sensitive to detect changes in beta-amyloid and will be feasible for use in clinical trials.

2019 Society of Nuclear Medicine and Molecular Imaging's 'Image of the Year Award' Finalist



Down syndrome-specific [C-11]PiB PET template images of Aβ carrying capacity and radiotracer nonspecific binding derived from PET images of 169 individuals. Tissue maps of gray and white matter are displayed for a visual reference. The Aβ plaques are restricted to gray matter regions while the radiotracer nonspecific binding signal is confined to white matter. The image of carrying capacity is representative of the theoretical limit for the Down syndrome brain to carry Aβ, while highlighting the striatum as a region very susceptible to Aβ accumulation.

In 2019, Matthew was honored as a recipient of the Young Investigator Award at the third international conference of the Trisomy 21 Research Society (T21RS) in Barcelona, Spain. This is the only conference in the world that is fully dedicated to studying all aspects of Down syndrome. Support from the Mancheski Foundation enabled Matthew to present at the conference providing a great opportunity for him to engage and network with other researchers in the field and for his work to gain recognition from the international scientific community.

With support from the Mancheski Foundation during the 2018-2019 academic year, Matthew Zammit:

Presented at

8

Academic Conferences

Contributed to

3

Research Publications

Matthew Zammit and Bradley Christian, PhD

New Funding for Down Syndrome Research and Biobank

The Waisman Center is one of 25 recipients to receive funding through a National Institutes of Health (NIH) grant that focuses on advancing research on Down syndrome. The grant is part of the NIH Investigation of Co-occurring Conditions Across the Lifespan to Understand Down Syndrome (INCLUDE) project.

INCLUDE is a trans-NIH effort that will fund research investigating critical health and quality-of-life needs for individuals with Down syndrome, while simultaneously investigating the risk and resilience factors for co-occurring conditions shared with individuals who do not have Down syndrome. The project was launched in 2018 with $22.2 million dedicated for research by NIH.

"Individuals with Down syndrome are both affected by and protected against many of the conditions that afflict the general population," said NIH Director Francis S. Collins, MD, PhD. "By improving our understanding of the basic biological mechanisms of Down syndrome, and making clinical trials more accessible and specifically tailored to individuals with Down syndrome, we expect that research from the INCLUDE project will benefit everyone."

The Waisman Center project will build a cohort of children and youth with Down syndrome that will include a database and biobank that can be used for comprehensive clinical research and future clinical trials. No such cohort focused on individuals under the age of 18 currently exists. The project builds upon the center's Down Syndrome Clinic, nationally recognized Down syndrome research, and the Clinical Translational Core (supported by the NICHD-funded Waisman Intellectual and Developmental Disabilities Research Center grant). Establishing this cohort will help researchers integrate demographic, clinical, genomic, and neurobehavioral data to better understand the development and function of individuals with Down syndrome and provide critical measures and information for future clinical trials.

Qiang Chang, PhD; Maria Stanley, MD; Sigan Hartley, PhD; and Daifeng Wang, PhD, will lead the Waisman Center project with support from the Down Syndrome Clinic and the Clinical Translational Core.

"By improving our understanding of the basic biological mechanisms of Down syndrome, and making clinical trials more accessible and specifically tailored to individuals with Down syndrome, we expect that research from the INCLUDE project will benefit everyone."

— Francis S. Collins, MD, PhD, Director, NIH

CMT Advocate Will Not Be Sidelined

According to Deb Weber, life is not a spectator sport. "You can sit on the sidelines and watch or you can participate," she says.

Weber has chosen to participate. She has dealt most of her life with a progressive neurological disease called Charcot-Marie-Tooth disease, or CMT. Though relatively unknown, CMT affects one in every 2,500 people worldwide — that's more people than multiple sclerosis (MS). "Although if you say MS to people, they recognize it more," says Weber.

CMT is a disease in which the protective myelin sheath of one's nerve cells is deteriorating, which makes it difficult for the nerves to properly function. "The myelin is what keeps the band of nerves working," Weber says. "So if you think of your nerves as an electrical cord, the orange casing on the outside is the myelin sheath, and if it were fraying away, then the inside wire would short out. It wouldn't work as well."

CMT is equally common among all ages, genders, and races and is one of the most common heritable neurological impairments. The symptoms present as neuropathy, foot drop, poor balance, difficulty with dexterity, or abnormal sensation — just to name a few.

For Weber, it presented as weakness in her limbs.

"I was always looking at the ground to make sure that I didn't step on a pebble because I would be the one who would sprain my ankle," she says. "At some point I had trouble walking on the grass. It was hard for me to go to a soccer game without holding on to somebody."

Weber discovered she had CMT in the early 90s. While unpacking a new home in Panama where her then-husband was stationed, her hands began to hurt.

"I actually thought I had carpel tunnel," she says now, reflecting on a time that changed her life.

Weber underwent an extremely painful nerve conduction test. During a follow-up appointment was the first time she'd heard of Charcot-Marie-Tooth disease, which, at the time, had not been researched extensively. "The doctor basically patted me on my shoulder and said, 'Best of luck to you. It could be nothing or you could be in a wheelchair. We don't know much,'" Weber recalls.

Since the days when Weber received her diagnosis, "I think we have filled in some of the gaps on how CMT works," says John Svaren, a professor of comparative biosciences and Waisman Center investigator. Svaren researches CMT1A, the most common form of CMT. Weber has CMT1A, which results from a duplication or deletion in the gene PMP22. "So for example, my mom gave me two copies, my dad gave me one, and I have three copies," explains Weber whose mother and son also have the condition.

Weber became connected to Svaren by chance at a CMT Association (CMTA) conference in Tampa, Florida. "John was actually there and I heard him say that he was from the Waisman Center," Weber says. "Who else has something like that in their backyard? The CMTA is up to 120 branches but not everyone has an expert living in their city."

Svaren is chair of the CMTA scientific advisory board and he visits Weber's branch annually to update them on important research.

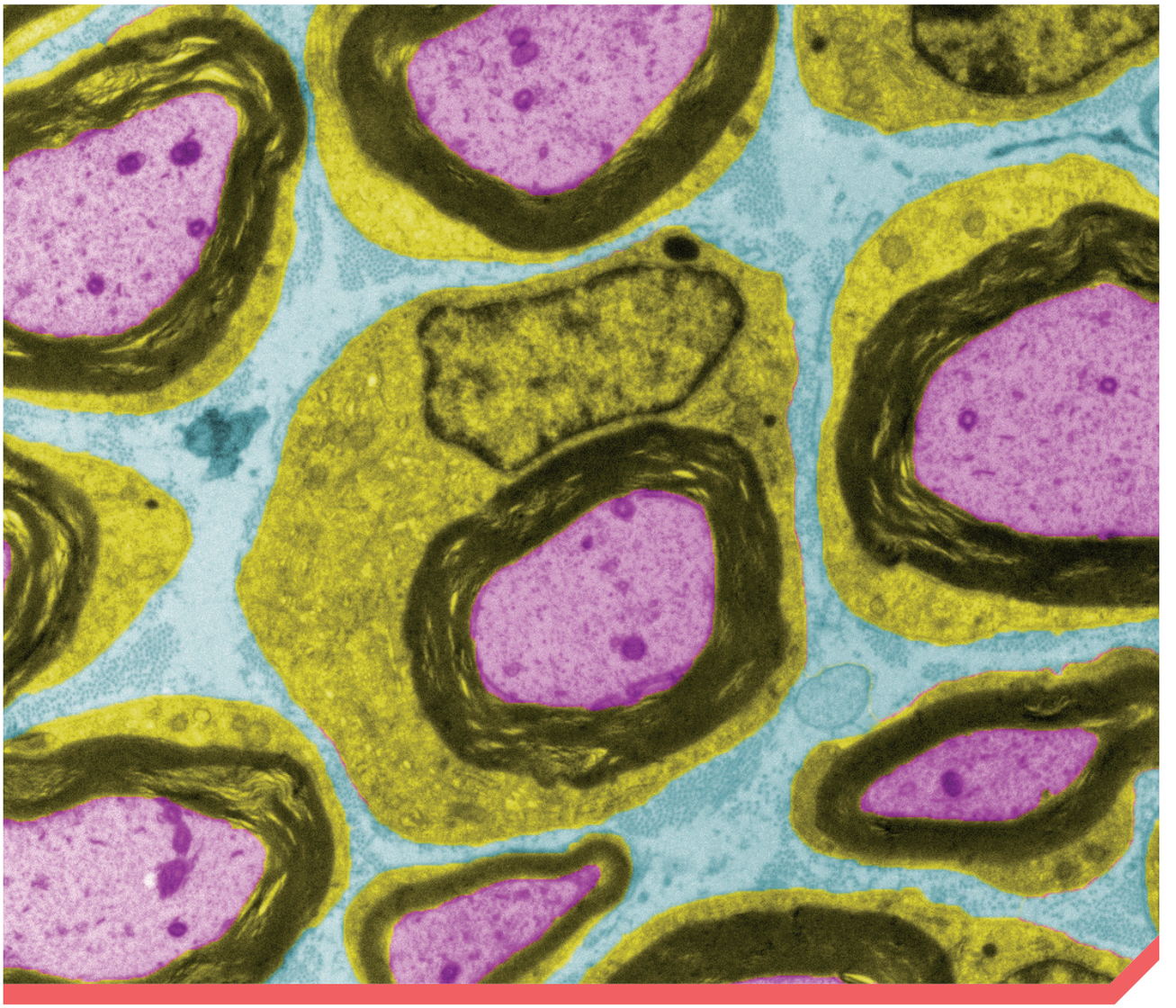
Understanding the progression of the disease is a key goal in Svaren's research. The mission for researchers now, says Svaren, is turning attention toward finding new targets for therapies. Svaren and his team at the Waisman Center are studying massive libraries of chemical compounds at the National Institutes of Health in order to identify drugs that could regulate the levels of PMP22 in individuals with CMT.

In order to control how PMP22 is expressed, Svaren is hoping to leverage a new technology called antisense oligonucleotides therapies, or ASO, in collaboration with a company called Ionis which has developed similar therapies for other diseases like spinal muscular atrophy.

"This is a new kind of drug, where it's actually targeted at the gene itself rather than the protein that is coded by the gene," explains Svaren. ASO therapies target the RNA

"This is a new kind of drug, where it's actually targeted at the gene itself rather than the protein that is coded by the gene."

John Svaren, PhD
Professor of Comparative Biosciences and Waisman Center investigator



Colorized electron microscopy image of peripheral nerves with Schwann cells in green. Image from Svaren Lab.

produced by the overexpressed PMP22, and reduce the amount of the protein in the nerves.

But in order to see if an ASO therapy would succeed, Svaren needed to find a target, or biomarker, which could tell researchers whether or not the levels of PMP22 are being reduced. "We've worked with other scientists to try to develop new biomarkers that can be sensitive to treatment, so you would know early on in a clinical trial if things are working," Svaren says.

The biomarker that Svaren is most interested in is located in the myelin of tiny nerves that are part of skin. Identifying gene changes in these nerves could offer clues into treatment effectiveness. "It's quite exciting, because before we really didn't have any methods to know whether a therapy like an ASO was working," Svaren says.

Locating and measuring PMP22 and other genes in these nerves involves a small skin punch, used to lift the nerve cells in the skin so they can be studied using a new technology called Nanostring.

"In collaboration with one of the leading CMT neurologists, Michael Shy, MD, at the University of Iowa, we have now shown that we can precisely measure PMP22 and other genes in skin biopsies for CMT1A," says Svaren. The recent publication of this test in Annals of Neurology, along with other emerging biomarkers, should facilitate future clinical trials since it will be easier

"I guess I'm surprised to find myself in this role because I spent many years in denial. Now, I'm in a place where I can spread awareness about CMT rather than be embarrassed by my condition."
– Deb Weber

to detect early effectiveness of ASO's and other treatments. Weber recently had a skin punch done while visiting the Charcot Marie Tooth Association-sponsored Center of Excellence at the University of Iowa, in Iowa City. "You go year after year, so they can measure the progression," says Weber.

Deb's husband, Tom, gave his own skin and blood samples to use as a control for future tests. Svaren also has tiny scars on his wrist from the samples he has given. "Over time, through the efforts of many other people in addition to myself, there's been a lot more of a shift to developing new therapies," says Svaren.

Public Awareness Is Another Hurdle CMT Research Faces

Svaren is a public-facing researcher, doing outreach for his work writing news articles and meeting patients. "I think just meeting people helps you realize how much CMT affects them," Svaren says. "I remember this woman who put on some custom braces and she just started crying because all of a sudden she had balance. Before the braces she had to keep a hand on the wall or a chair to stay balanced. She was just overwhelmed."

"Those are the kinds of things you don't really know until you get to meet people," Svaren says. "It's still a relatively small field. So even some neurologists are relatively unfamiliar with the disease." Weber agrees. "When I was initially looking for a neurologist, I would call around and ask if they had experience treating patients with Charcot-Marie-Tooth disease. The person on the line was like, 'This is not the dentist's office,'" says Weber.

Weber has been a tireless advocate working to raise CMT awareness and support for research. She is currently the leader of her local CMTA chapter in Madison that has more than 20 members. She also writes an email newsletter with a distribution of more than 120 people.

Last year, the Madison CMTA held their first fundraiser, called "Uncorked for a Cure." The group set an initial goal of raising $20,000, but decided to be more realistic and lowered the goal. "We thought if we raised $10,000, we were blowing the roof off the place." They raised $27,500.

"All of that goes to research," she says. The CMTA recently awarded a $154,000 grant to Svaren and other collaborators to support their CMT research focused on gene therapies.

Weber's journey has been a difficult one, but she has not been sidelined. She's happy that she gets to help others and show them that they're not alone. And even if there is no treatment yet for CMT, there is promising research on the horizon and great support systems in place for those with the condition.

"I guess I'm surprised to find myself in this role because I spent many years in denial. Now, I'm in a place where I can spread awareness about CMT rather than be embarrassed by my condition," says Weber. "I think it's a super exciting time to be an advocate. We have research happening here and trials going on in different parts of the country. You also no longer leave a doctor's office and hear them say, 'Well, best of luck to you.' Fortunately, that's not how things are anymore."

Meet Our New Directors

Leann Smith DaWalt, PhD, a longtime Waisman Center investigator, began her appointment as the director of the University Center for Excellence in Developmental Disabilities (UCEDD) on Oct. 14.

She succeeds Bill MacLean, PhD, who retired in early October.

The UCEDD supports the full inclusion and self-determination of people with developmental disabilities and their families through a broad range of service, training, and outreach programs including the Waisman Center Clinics, the Waisman Early Childhood Program, and the Leadership Education in Neurodevelopmental Disabilities (LEND) training program.

"In my time at the Waisman Center, I've had the opportunity to become increasingly involved in the activities of the UCEDD," DaWalt says. "I am inspired and excited by the UCEDD's mission and the many opportunities to serve our state through the work of the UCEDD."

DaWalt joined the Waisman Center in 2006 as a postdoctoral fellow under the mentorship of Marsha Mailick, PhD, and Jan Greenberg, PhD. After completing her fellowship in 2008 she became a Waisman Center investigator and co-PI of the Lifespan Family Research Program. DaWalt's research focuses on the impact of intellectual and developmental disability on the family system and the role of the family and community in supporting development for individuals with disabilities across the lifespan. She is also the PI of several intervention studies focused on teens and adults with autism spectrum disorder (ASD).

Her interest in supporting individuals with disabilities and their families began during college when she worked as an in-home therapist for a child with ASD.

DaWalt has a bachelor's degree in psychology from Lambuth University in Jackson, Tennessee, and a master's degree and PhD in developmental psychology from the University of Notre Dame.

As director, she aims to continue the expansion of UCEDD's reach throughout the state. "I look forward to being able to support our teams in carrying out their work," she says. "As technology continues to improve, I see the UCEDD providing more training, technical assistance, and direct service throughout Wisconsin."

DaWalt is also focused on further cultivating collaborations internally. "I am eager to support the ongoing integration across programs within the Waisman Center," she says. "I hope these efforts will directly benefit translational research and improve the lives of individuals with disabilities and their families."

"I hope these efforts will directly benefit translational research and improve the lives of individuals with disabilities and their families."

Leann Smith DaWalt, PhD
UCEDD Director

On September 23, the Waisman Center welcomed Ann Marie Lauritzen, MMSW, M.Ed, as the new director of the Waisman Early Childhood Program.

She succeeds Joan Ershler, PhD, who retired at the beginning of September after 27 years of service.

"I am excited to work with such a positive, caring and devoted staff," Lauritzen says. "Supporting and serving children and families is my life's passion and to be able to be a part of the Waisman Center is an honor."

Lauritzen's new position is the latest in a 25-year career dedicated to children and education and she also brings a wealth of administrative experience with her. In that time, she has been a social worker, a daycare owner, a special education liaison, a behavioral specialist, an equity coach, a trauma-informed care specialist, a principal for alternative education, and a coordinator of student services staff.

Lauritzen has a master's degree in social work and a bachelor's in psychology and Spanish from UW–Madison. She also has a master's in special education administration and principalship from Edgewood College.

Her work in graduate school interested her in this position. She interned at the Waisman Center while studying for her master's.

"My experience serving families at the Waisman Center changed my life and inspired me to support and advocate for all families in our communities," she says.

Lauritzen says one of her primary goals is to maintain an environment in which all families and staff feel unconditionally welcomed. "Collaborating with the staff, I hope that we create a shared vision that ensures the highest level of care, compassion and innovation for our youngest learners, a vision which upholds inclusion and equity."

"My experience serving families at the Waisman Center changed my life and inspired me to support and advocate for all families in our communities."

Ann Marie Lauritzen, MMSW, M.Ed
WECP Director

Navigating a Brighter Future for Youth with Disabilities and Their Families

Helping youth with disabilities pursue post-high school employment and education opportunities can mean piecing together services from a broad range of agencies and organizations. This can be a challenge for anyone, but for low-income families, day-to-day survival may create additional barriers to accessing services and supports needed to launch youth with disabilities into adult life. For example, a family member might not have the transportation needed to access those services or may miss phone calls from a service provider because they ran out of phone minutes for that month.

The Waisman Center was a key partner on a statewide program to help families of children with disabilities overcome some of these barriers. Wisconsin Promise, a 5-year initiative assisted more than 1,000 youth social security income (SSI) recipients and their families. The program was implemented by the Division of Vocational Rehabilitation (DVR) in collaboration with other state and service agencies, including the University Center for Excellence in Developmental Disabilities (UCEDD) at the Waisman Center.

The goal of the Promise program was to help youth with disabilities and their families achieve better outcomes in education, employment, and financial self-sufficiency through transition services and supports including training and guided support in the form of one-on-one family navigators or advocates.

The Waisman UCEDD has a long history of incorporating family navigation into its programs and clinical services. "The Waisman UCEDD's emphasis and programs on family support and leadership made hiring family advocates through the Waisman Center a good fit," says Ellie Hartman, PhD. Hartman was the project manager of Wisconsin Promise.

"We found through experience that one-on-one services from someone in the community with similar lived experiences really helps build trust, especially when that individual meets the youth and families wherever they are," Hartman says. "Helping navigate today's concern built trust, so family advocates could start to talk about transition and future planning with the youth and family."

Fatima Becerra was one such family advocate. She knows the importance of self-advocacy for families affected by disabilities. Growing up, her family struggled to get services for her brother who has Down syndrome. At 9 years old, she often had to translate between English-speaking service providers and her Spanish-speaking parents.

"I was able to adapt and learn a lot of things," the Milwaukee resident says. "It was a roller coaster of emotion because services wouldn't follow through. I think it's more frustrating for people who can't speak the language to express themselves."

The Waisman Center hired and trained the Promise advocates who then worked with families throughout the state. Advocates were hired not for their educational background, but for their firsthand experiences. The advocates were required to have been impacted in some way by a disability. This way, they were more able to relate to the families they served as a peer.

Wisconsin Promise is an example of the types of programs and partnerships that underscore the UCEDD's mission to support the full inclusion and self-determination of people with developmental disabilities and their families.

Wisconsin was one of six states participating in the national Promise initiative. It was a joint effort of the U.S. Department of Education, the U.S. Social Security Administration, the U.S. Department of Health and Human Services, and the U.S. Department of Labor.

Each state approached the Promise program differently. Wisconsin's family-centered approach differed in two ways. First, Wisconsin not only provided Promise and vocational rehabilitation services to youth, but to their families as well. The second, and most integral difference, was that Wisconsin was the only state to include family advocates. Other states had similar group training opportunities, but only Wisconsin evolved this service into individual family advocates with lived experience and one-on-one coaching and mentoring. The family navigators were an important and essential component to the success of Wisconsin Promise.

Bercerra and others helped reconnect teens and their families to Promise services provided through DVR. These services included career exploration and planning, job development and placement, financial coaching, and counseling on how to increase overall income through work and maintain access to needed supports including healthcare. She also provided on-the-job support.

The advocates in Wisconsin were hired to increase expectations and help youth and families connect to needed resources and supports. Families were struggling with moving forward with some Promise services due to barriers such as lack of housing or transportation, healthcare, substance abuse, or poverty. In addition to the career services typically provided by DVR, Promise advocates provided guidance in education, nutrition, financial wellness, and self-advocacy, and connected them to available services. While DVR may connect people to employers, sometimes that is not enough to keep one's head above water. The Promise family advocates, however, created a more manageable path to engage in employment services and supports.

"It's great to find a job," says Beth Moss, the Promise youth transition coordinator at the Waisman Center who supervised the family advocates. "But if you don't have a place to live, then it's really hard to have a job because you don't know where you're going to be, you don't have clothing, you don't have transportation."

Wisconsin Promise included extensive family and self-advocacy training. Once advocates were connected with their families, they could stay connected with them beyond the DVR's typical business hours and in more

"But if you don't have a place to live, then it's really hard to have a job because you don't know where you're going to be, you don't have clothing, you don't have transportation."
– Beth Moss

accessible and convenient environments. Advocates texted on evenings and weekends or met up with families at restaurants or in their homes.

Becerra speaks candidly and passionately about the work she did as an advocate.

She tells the story of one family in Milwaukee whom she was able to help. The family was not connected to any employment or education services. They "had been let down many times" and "had a very, very bad relationship with the school" that the youth attended. "It was challenging at times when they were going through hardships to support them through that process," she says.

Having Becerra by their side during intense meetings, such as organizing an individualized education program (IEP) for their son, the family was able to reconnect with the school and strengthen their relationship.

"We talked to the staff and made a plan about what everybody was going to do," Becerra says. "They want to help their child, but they don't know how. They want things to be explained in a way that they can understand."

But her help was not just limited to the youth. She was also able to help the father get a job that he was happy with. Shortly after, he also started learning more English and volunteering at the school.

"It's beautiful having a relationship with the school because it's supportive for the youth," Becerra says.

Wisconsin Promise wrapped up operations in September 2019, but its results will have a lasting impact on communities throughout the state.

Family advocates "were super successful at engaging families," Moss says. "The number of jobs that the youth and families got vastly increased when they worked with a family advocate."

Sixty-seven percent of Wisconsin Promise youth have been employed since enrolling in the program compared to 2% who were employed before the program started. This increase is 10 percentage points higher than observed in the control group. Youth that met with family navigators had twice the number of jobs since enrollment than youth who had not met with a family navigator. Further, and most importantly, those youth helped by family navigators had twice the weekly earning amount.

A 2019 study of Wisconsin Promise published in the Journal of Vocation Rehabilitation concludes: "Youth with disabilities continue to show their skills, strengths, and potential can help build a better workforce in all local communities. Models that empower youth and their families while at the same time provide the needed disability-related supports and connection to paid work can increase employment outcomes and self-sufficiency."

Fatima Becerra

While Promise was a trial initiative, the success of the family navigator component specifically has led to two bills in the Wisconsin State Senate (344) and Assembly (375) that, if passed, would fund permanent family navigator positions within the Department of Workforce Development.

When asked how she personally feels about her experiences with Wisconsin Promise, "I have no words," Bercerra says. But then she continues, "I think I was just made for this — to help people and guide them through and connect them with services."

She recounts growing up in her own family — relying on disability and vocational services that never came through — and relates those experiences to those of the families she has helped.

"My mission was to help every family to the very end," she says. "To build those bridges and for them to approach services and to advocate for themselves. To be firm, but also have those relationships. I love this project, I love the mission. If I could do this for the rest of my life, I would."

Waisman Whirl Run, Walk & Roll for All Abilities

The fifth annual Waisman Whirl 10k/5k/1 mile run, walk, and roll took place on Sunday, October 4. More than 250 people participated along with 100 volunteers and 200 supporters. The event is hosted by the Friends of the Waisman Center–a non-profit, 501(c)(3) organization –and raises awareness and funds for the Waisman Center. In addition to the Whirl, the Friends also host a spring gala and summer golf outing. The proceeds from these events support many programs that directly benefit individuals and families impacted by developmental disabilities and neurodegenerative diseases, including the Waisman Center Clinics, the Waisman Early Childhood Program Scholarship Fund, the Waisman Center Day with the Experts series, and the Harvey Stevens International Collection of Art by People with Developmental Disabilities.

For more information, please visit waisman.wisc.edu/event/run-2019/

Major Lifetime Gift Establishes Scholarly Society

Richard Morse, MD, and Lawrence Connor, MSW near their home in New Orleans.

It's been seven years since Dick Morse, MD, a UW alum and retired child psychiatrist, and his lifelong partner, Lawrence M. Connor, MSW, a retired social worker, established an $11 million (now worth an estimated $17 million) planned estate gift for the Morse Society — a multidisciplinary graduate fellowship program at the Waisman Center. However, shortly thereafter, the New Orleans residents generously decided to launch the society during their lifetime so they could be involved with the program and witness the impact of their gift.

Since 2012, Morse and Connor contribute annually to the center to provide a partial stipend and tuition for a select group of graduate and postdoctoral students doing research in the areas of childhood mental illness, well-being, and developmental disabilities. They recently announced they are increasing their current support of the Morse Scholars by more than $800,000.

The focus of the Morse Society is to generate conversation across multiple disciplines. "When looking at the whole matrix of development, I think it's very narrow to look at it just from child psychiatry," Morse says. "Everything from motor functions and intelligence through mental health and social adaptation — unless these are integrated, you don't have a functioning child growing into a functioning adult. It's the same brain regulating all of it."

Morse says the ideal place for this program had to be a community that was small enough for scholars to see each other every week and large enough to represent a diverse breadth of research. He was particularly drawn to the multidisciplinary nature of the Waisman Center.

In addition to encouraging further research in each scholar's respective area, the program is designed to foster collaborations and build community. Morse believes that frequently socializing with other members of an academic

cohort is integral. "For me, it's where half of my education was," he says. With this in mind, a portion of the funds have been allocated to provide a monthly dinner for scholars to get together, talk about research, and listen to presentations.

"As a scholar, the dinners were an opportunity to build a research community around childhood mental health and developmental conditions," says Brittany Travers, PhD, a former Morse scholar. Travers is an assistant professor of kinesiology at UW–Madison and Waisman Center investigator who researches motor and brain development in individuals with autism spectrum disorder. She co-directs the Morse Scholars program with Seth Pollak, PhD, a professor of psychology and Waisman Center investigator. "The dinners were the perfect opportunity to learn from and debate with my peers," Travers says. "I learned how to present my research to interdisciplinary audiences, a skill which I very much value in my current position."

Morse wanted to dedicate this money to child development and psychiatry research because it is often underfunded. By supporting the next generation of researchers, this fellowship will hopefully raise awareness and a better understanding of children's needs and rights and improve overall health and well-being.

Morse is a 1967 graduate of the UW School of Medicine and Public Health. What surprised him the most during his time at the UW was the sense of community among the students. This was different from his experiences at other universities. "When I got to Wisconsin, I was amazed to see the quality of interpersonal connection there, and I was astounded to see a university that was so dialectical," he says.

Morse's parents also graduated from the UW — his father in 1925 and his mother in 1926. A lawyer and social worker respectively, they dedicated their careers to improving outcomes for children. Therefore, this additional gift to the Morse Scholars is to honor them and to celebrate the 100th anniversary of his family's involvement with the UW. The additional money, Morse says, will ensure continued partial funding of at least four doctoral students every year, and supported monthly dinners that include two postdoctoral researchers, and a junior and senior faculty member in addition to the doctoral students.

"Larry and I were extremely impressed with the quality of communication and camaraderie among the Morse scholars," Morse says of the scholars present at the 2018 Morse Society alumni dinner. "They had a tremendously good knowledge of each other and each other's work."

Since the program was initiated, it has funded 11 scholars, including four current students.

Seth Pollak, PhD, a co-director of the Morse Society since its inception, describes Morse as an extremely erudite and thoughtful person. "He really had a grand vision of what young trainees needed to advance knowledge about developmental issues," he says. "The whole idea is that maybe new knowledge will emerge if you can start integrating ideas or methods from other fields. Every year, there's a new class of Morse fellows and they're just the most marvelous young people to work with."

Ways To Give

Gifts provide integral support for groundbreaking research, comprehensive clinical services, and outreach programs that enhance the lives of individuals and families affected by developmental disabilities and neurodegenerative diseases. A planned gift is one of the many ways to support the Waisman Center that include:

- Sign-up to make automatic monthly donations
- Give in memory or tribute of a loved one
- Make a gift of appreciated securities, including stocks and bonds
- Include the Waisman Center in your will or estate plan
- Make a gift of your retirement assets or life insurance policy
- Contribute through a donor advised fund, community foundation, or grant
- Underwrite a scientific talk
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- Participate in a Friends of the Waisman Center fundraising event

For more information on giving or to give online, please visit: waisman.wisc.edu/giving/

or contact

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The Waisman Board of Visitors was established in 1996 to provide perspective and important linkages with the general public, business community, and public policy makers; to assist the Waisman Center in strengthening partnerships with the private sector; to provide an advocacy network; and to guide major fundraising efforts.

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Founded in 1975, the Friends of the Waisman Center is a nonprofit 501(c)(3) organization that supports the Waisman Center through fundraising, volunteer efforts, and community outreach. The Friends raise awareness and support for the center through three community fundraisers: a benefit concert, a golf outing, and the Waisman Whirl Run, Walk & Roll for All Abilities.

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Thank you to those who gave to the Waisman Center through the Friends of the Waisman Center for the period of September 1, 2018 - August 30, 2019 and the University of Wisconsin Foundation for the period of July 1, 2018 - June 30, 2019.

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The Waisman Center is supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U54 HD090256), the Administration for Community Living (90DD0804), and the Maternal and Child Health Bureau's Leadership Education in Neurodevelopmental Disabilities (T73MC00044) program.

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