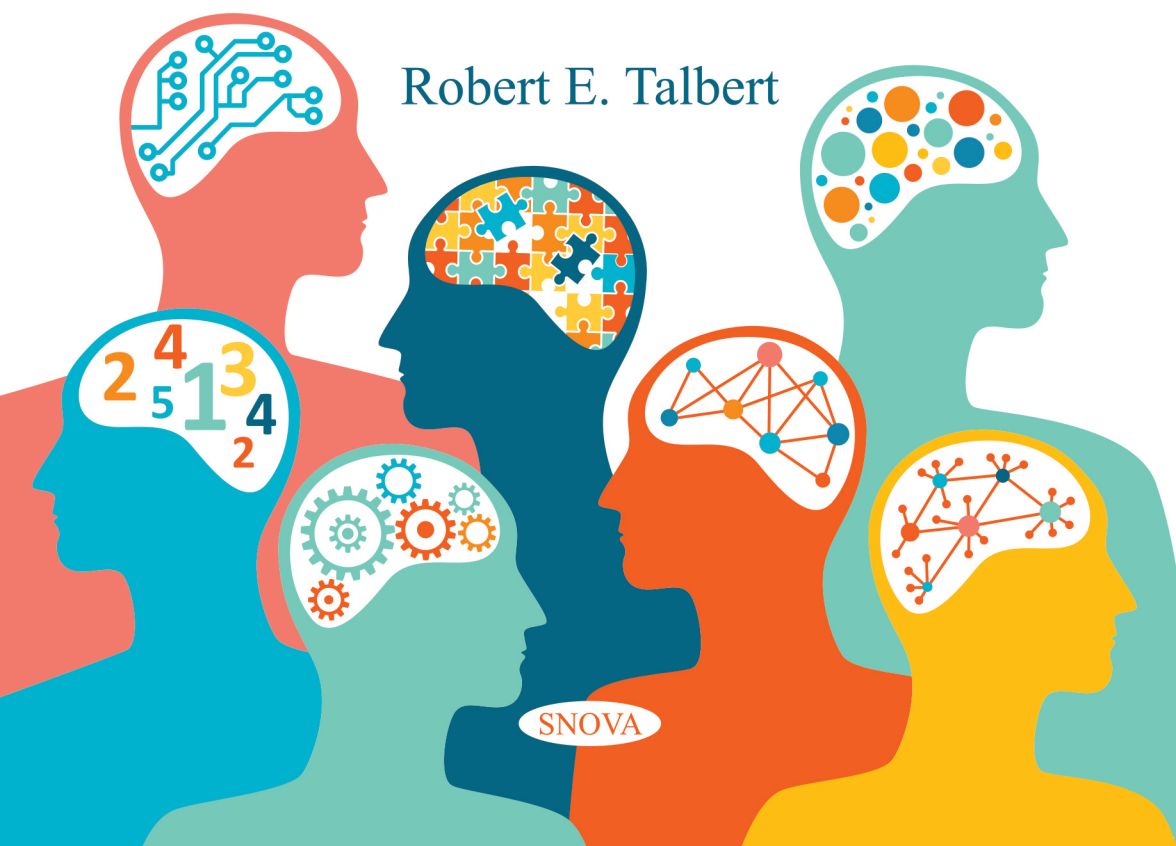


RESEARCH PROGRESS IN ALZHEIMER'S DISEASE AND DEMENTIA

ALZHEIMER'S DISEASE

New Biomedical Research,
Perspectives and Caregiving

Robert E. Talbert



Research Progress in Alzheimer's Disease and Dementia



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Robert E. Talbert

Editor

Alzheimer's Disease

**New Biomedical Research, Perspectives
and Caregiving**



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Preface

An estimated 5.8 million Americans are living with Alzheimer's Disease. Alzheimer's Disease is projected to claim the minds of nearly 14 million Americans and surpass \$1 trillion in costs by the year 2050. This book will explore new pathways that could lead to earlier detection and potential therapies, the hardships of Alzheimer's disease and other dementias, and the debilitating and progressive nature of this awful disease and the terrible toll it takes on family caregivers.

Chapter 1

Alzheimer's: New Directions in Biomedical Research and Caregiving*

Special Committee on Aging

Tuesday, April 2, 2019

U.S. Senate, Special Committee on Aging,
Washington, DC.

The Committee met, pursuant to notice, at 9:39 a.m., in Room 106, Dirksen Senate Office Building, Hon. Susan M. Collins, Chairman of the Committee, presiding.

Present: Senators Collins, Tim Scott, McSally, Hawley, Braun, Rick Scott, Casey, Blumenthal, Jones, Sinema, and Rosen.

Opening Statement of Senator Susan M. Collins, Chairman

The CHAIRMAN. The hearing will come to order.

Good morning, and welcome to all the individuals, families, and organizations from all across the country who have come to our Nation's Capital to advocate for better treatments and ultimately a means of prevention and a cure for Alzheimer's disease as well as for more support for caregivers.

In the fight against Alzheimer's, you are the champions. Your advocacy has ushered in an era of hope paired with action against this devastating

* This is an edited, reformatted and augmented version of Hearing before the Special Committee on Aging, United States Senate, One Hundred Sixteenth Congress, First Session, Serial No. 116-05, dated April 2, 2019.

In: Alzheimer's Disease

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disease. Since we gathered last June, through your diligent work, in a matter of months, we successfully pushed the landmark BOLD Infrastructure for Alzheimer's Act across the finish line.

Today this law marks a new public health approach for this disease. It will promote early diagnosis and improve treatment and care for millions for whom the disease is a reality day in and day out.

The statistics remain stark. A new CDC report shows that the rate of Americans dying from dementia has more than doubled in our country since the year 2000. An estimated 5.8 million Americans are living with Alzheimer's, costing our Nation \$290 billion a year, including \$195 billion in costs to Medicare and Medicaid.

If we continue along this trajectory, Alzheimer's is projected to claim the minds of nearly 14 million Americans and surpass \$1 trillion in costs by the year 2050.

While scientists and medical professionals are working hard on an effective treatment and cure, recent clinical trials have unfortunately ended in a string of failures.

Just last month, two more major trials targeting amyloid deposits in the brain were halted. For decades, many researchers have been targeting amyloid, the hallmark sign of Alzheimer's disease.

Today, due to advancements in brain imaging, we know that some people exhibit rampant amyloid plaques and yet never develop the disease. While amyloid remains an important part of ongoing research and I remain hopeful that the new trials starting earlier in the disease process will produce better news, the record funding that we have provided will allow our medical researchers to pursue so many other promising approaches.

I am delighted that last year, a bipartisan coalition, of which every member on this Committee is a part, worked hard to achieve a \$425 million increase in Federal funding for Alzheimer's research. That was the largest increase in our Nation's history, and I can see Dr. Hodes smiling broadly at that.

With our total investment at more than \$2 billion for Alzheimer's this year, we are on a strong path forward, and we are not going to turn back.

This year, as we have before, I expect Congress to once again reject the President's unwise request to cut the funding for the National Institutes of Health.

The robust funding that Congress has provided is enabling scientists to explore a myriad of new pathways that could lead to earlier detection and potential therapies. From the ocular and the cardiovascular to the genome and

the microbiome to the immune and the lymphatic system, researchers are leaving no system unexamined and no cell unturned.

While we continue to forge ahead to accelerate biomedical research, we face the reality that this disease is affecting millions of American families. BOLD, now signed into law, marks a milestone toward building the public health infrastructure we need to better support individuals, families, and communities.

Support can make all of the difference. Tom O'Connor, a caregiver from Portland, Maine, who is with us today, told us, "When we got the diagnosis, we were shocked and did not know where to start."

When he was referred to community partners, he received the information he needed and was able to put a plan in place to make the time ahead better for himself and for his wife, who is battling Alzheimer's.

Diagnosis is the first step that can empower individuals and families to understand changes in the brain, but developing a plan for care can make the journey so much better. Care plans can also help to reduce comorbidities, prevent hospitalizations, and improve life not only for those living with the disease, but also for their caregivers.

As the BOLD approach spreads to communities across America, we must continue to develop Federal policies to better support all Americans with Alzheimer's and their families.

Last year, I heard from constituents facing early onset Alzheimer's that it can be difficult to access necessary supports simply due to not meeting the age thresholds for various Federal programs.

This year, I am leading the reauthorization of the Older Americans Act along with my Ranking Member, Senator Casey.

Last week, I introduced a bill that would ensure that key services in the Older Americans Act, such as the National Family Caregiver Support Program, will also serve those with Alzheimer's who are younger than age 60.

Whenever I ask family caregivers, which included my own mother, about their greatest needs, the number one, request that I hear is for more respite care. Today, I am also introducing the Lifespan Respite Care Act with Senator Tammy Baldwin to help communities and States provide respite care for families.

From accelerating research to advancing care, every year that we gather as one sea of purple, we make waves, and by the way, I want to thank Michael Hartt for giving me a sash today to wear. Thank you, Michael.

From accelerating research to advancing care, we are making progress. While Alzheimer's robs our loved ones of precious memories, I stand with you to do everything we can to make Alzheimer's itself a memory 1 day.

Thank you. I am not delighted to turn to another fierce advocate for research for this disease, the Ranking Member, Senator Casey.

Opening Statement of Senator Robert P. Casey, Jr., Ranking Member

Senator CASEY. Thank you, Chairman Collins, for, of course, holding this hearing today, one of the highlights of the year in terms of hearings. I do not know of a hearing throughout the year that has this much energy and enthusiasm and this kind of a crowd and that kind of applause.

I also want to thank Chairman Collins for her enduring leadership in the fight to find a cure for Alzheimer's disease.

I want to extend our gratitude as well to all the advocates in the room today, all of the caregivers, family members who have traveled across the Country to be in this hearing room with us today.

Few American families are unaffected by this vicious disease. Indeed, over 5.8 million people over the age of 65 currently live with Alzheimer's disease. Approximately 280,000 of those people are Pennsylvanians, and those number are rising.

We know that the impact it has on the person diagnosed, but also the impact on their family can be devastating, and that is, of course, an understatement.

We must support efforts to find a cure.

I am pleased every year to be able to lead the appropriations letter in the Senate with Senator Burr to advocate for more research funding at the National Institutes of Health and to join Chairman Collins in ensuring robust funding for Alzheimer's disease research and in this case, of course, specifically in her work on the Appropriations Committee, and we commend her for that.

Until there is a cure, we must do everything in our power to make sure that people receive the best possible care, so we focus on both finding a cure, but also on ensuring quality care.

We know that this disease impacts different people differently, so our efforts must take into account people who are diagnosed at younger ages,

people with disabilities, people from diverse backgrounds, and people living in both urban and rural settings.

For example, people who are diagnosed at younger ages and are still working may have difficulty knowing where to turn for help because many essential supports are more commonly advertised to seniors. That is why I joined with Senator Collins, Senator Jones, who is with us today, Senator Capito in introducing the Younger-Onset Alzheimer's Disease Act to ensure that people younger than age 65 have access to counselors and support groups to help them navigate the health care system and plan for their long-term care needs.

A subset of the people diagnosed at these younger ages are of course people with disabilities. For example, nearly half—half—of all people with Down Syndrome will develop Alzheimer's disease in their lifetime; 30 percent of these Americans will be diagnosed before the age of 50.

Research and clinical trials must include people with disabilities to ensure their needs are met in the quest for treatment and a cure.

I would like to thank Senator Collins again for agreeing to work with me on policies that would address this specific disparity among people with disabilities.

We also know that African Americans are two times—two times more likely than their white counterparts to develop Alzheimer's disease, and the Hispanic and Latino populations of America are one and a half times more likely to develop Alzheimer's disease. We must understand why and what can be done about those issues.

People living in rural areas may not live near a major medical center or a research facility, which makes it harder for them to participate in research studies or clinical trials.

We must tackle this disease from every angle, from continuing our research for a cure to ensuring medical professionals and community organizations can provide the best care possible to every American with Alzheimer's disease.

I look forward to our witnesses' testimony today and the important conversations we will have. Thank you very much.

The CHAIRMAN. Thank you, Senator Casey.

Before we turn to our great panel of witnesses, we are going to start with a video so that we can hear directly from people around the country who are living with Alzheimer's.

I want to thank the Alzheimer's Association for providing us with their voices.

[Video played.] [Video may be viewed at aging.senate.gov/hearings]

Those thoughts about diagnosis and insights about the path forward will help to frame our discussion today.

Now I am pleased to turn to our witnesses. First, I am delighted to welcome from the great State of Maine, Mary Dysart Hartt and Michael Hartt, former business owners from Hampden, Maine.

Today Mary is the caregiver for her husband, Mike, who was diagnosed 4 years ago at the age of 62. Now, Mrs. Hartt is known across the State of Maine for her famous Pies for a Purpose, which are Purpleberry pies. Yes, they are baked and sold to raise awareness about Alzheimer's.

Mrs. Hartt has been honored as Restaurateur of the Year by the Maine Restaurant Association. She is also a photographer and a runner, and next month, she will run in the Boston Marathon and is fundraising for Alzheimer's research.

Next, I would like to turn to our Ranking Member to introduce our witness from the Commonwealth of Pennsylvania.

Senator CASEY. Thank you, Chairman Collins.

I am pleased to introduce Clay Jacobs. Clay is the Executive Director of the Greater Pennsylvania Chapter of the Alzheimer's Association. Clay is from North Abington Township, which happens to be Lackawanna County, where I live. It had nothing to do with his presence here today, but it certainly helped.

Clay's wife, Becky, is also with us today. We are grateful that Becky took the time to travel to Washington.

Clay is a graduate of a great Pennsylvania institution of higher education, Westchester University. He also told me earlier that he is a graduate of Abington Heights High School.

In his current position, Clay works to support people living with Alzheimer's disease and their families through direct services, support, and education programs.

I also want to welcome the large contingent of advocates who are in the audience today from Pennsylvania and across the country. Thank you for making the journey to be with us, and, Clay, thank you for being with us today. We look forward to your testimony.

The CHAIRMAN. Our next witness, Dr. Sharon Fekrat, is a professor of Ophthalmology and associate professor of Surgery at Duke University School of Medicine. She also serves at the Durham VA Medical Center. She has coauthored more than 130 publications in medical journals and 45 textbook chapters.

Finally, we will hear from Dr. Richard Hodes, the Director of the National Institute on Aging at the National Institutes of Health. Dr. Hodes will provide an overview of the advancements in Alzheimer's research across the NIH and discuss partnerships with industry to accelerate therapies. He will also share new NIH research on supporting caregivers.

I want to thank you all for joining us, and we will start with Mary Hartt.

Statement of Mary Dysart Hartt, Family Caregiver

Mrs. HARTT. Thank you, Chairman Collins.

The CHAIRMAN. We are going to have your mic turned on for you. Mrs. HARTT. I had a plan, and then I did not do it.

Chairman Collins, Ranking Member Casey, and members of the Committee, thank you for the opportunity to testify about my experiences as a caregiver for my late mother and now my husband, Mike, who is currently living with Alzheimer's disease.

Mike was diagnosed at age 62. My hope is that, in sharing our story, others who are impacted by this disease will feel less alone and understand that with proper supports, there is life after a diagnosis.

Mike was 58 when I started noticing that things did not seem quite right. After living on our family farm since 1977, daily tasks like running the tractor became a challenge. During that same time, I was part of a family care team caring for my mom who was living with dementia. She was a brave woman who started our family owned business, Dysart's, with my father 52 years ago, and for 52 years, our business has been open 24/7, so you can gather how brave she was to start that.

My two brothers and I are very proud to have carried on our parents dream into the third generation. I began to see similarities in the challenges both Mike was facing and decided to reach out to our family doctor who agreed to help me monitor Mike for changes. For 4 years, we continued on this path, with things coming to a head when Mike was 62 and agreed to be tested.

After incorrectly being diagnosed with frontotemporal dementia, or FTD, we received a diagnosis of younger-onset Alzheimer's from Mass General Memory Clinic in Boston. We are so thankful for the care we received at Mass General, and following the diagnosis, our lives changed significantly.

Mike had owned a business that manufactured log homes. He was our money manager. After the diagnosis, we sold our farm where we had lived for

nearly 40 years and simplified our life. The farm had a half-mile-long driveway, and it snows occasionally Maine.

At 63, Mike volunteered to give up driving, a freedom that he really loved.

Before Mike was diagnosed, we were not familiar with younger-onset Alzheimer's disease but had had some knowledge of Alzheimer's and dementia through the experience of caring for my mother.

One common assumption about this disease is that life completely stops. While we have faced unique challenges as we have tackled this disease, we continue to move forward with our lives as best we can.

In just 2 weeks, as Senator Collins says, I am going to be running the Boston Marathon with a charity number for the Alzheimer's Association to help rid the stigma of this disease. Too often, Alzheimer's is talked about in terms of cognition and memory, but it is much more.

In Mike, I see it affect his emotions and temperament. If someone is diagnosed with cancer, people automatically rally around to offer support and guidance. An Alzheimer's diagnosis is sadly not the same, but there is nothing to be ashamed about. We cannot hide behind a diagnosis if we want to make progress.

The staff at Mass General made clear that this disease is something that is meant to be taken day by day, to be approached with humor and a grasp of reality. Our doctor told us, "Do not worry about tomorrow. Enjoy today." That is how we have chosen to live our life.

Thanks to our providers and the support we received at the Alzheimer's Association, Maine Chapter, we have begun fulfilling wishes on our bucket list. Lucky for Mike, most of them have been fishing adventures. After more than 40 years of marriage, I took Fly Fishing 101, but I cannot out-fish him yet.

However, I know these adventures are not typical for everyone, especially those without a care plan. For us, this plan came in pieces and with the help of our team of care providers at Mass General.

Mike's diagnosis at 62 was a shock, but working with the team of care providers gave us time to talk through the reality of the situation and plan for the challenges that lie ahead.

We continue to have regular visits, and at our last appointment, we had the conversation about giving up power of attorney, something I would never have thought to seek but was part of our plan.

Thank you, Chairman Collins, for introducing the Improving Hope for Alzheimer's Act. It will make a difference in the lives of people living with Alzheimer's disease and other dementias and their families.

I think a lot about how lucky we have been in our life to be able to care for ourselves in this next phase. For many people with younger onset, that is not the reality. The services and supports——

[Mr. Hartt points to timer.]

I think he is giving me a time.

The CHAIRMAN. He is doing my job.

Mrs. HARTT. There you go.

The services and supports that are there for those 60 years and older are vast compared to those that are available to the population in the Alzheimer's and dementia community who have not yet reached that age.

Thank you, Chairman Collins, Ranking Member Casey, Senator Jones, and Senator Capito for leading the Younger-Onset Alzheimer's Disease Act, which would help those with younger-onset with supports and services.

Throughout the last few days, Mike and I have joined our Alzheimer's Association, Maine Chapter, along with 12,000 advocates from across the Nation to make a difference in our Nation's Capital.

I am here today because I am the wife, caregiver, friend, and daughter of Alzheimer's. We all are, and we must remain a strong and a resilient voice for those who have lost theirs.

Thank you very much.

The CHAIRMAN. Mary, you and Mike are truly an inspiration, and I thank you both for being here.

Mr. Jacobs.

Statement of Clay Jacobs, Executive Director, Greater Pennsylvania Area Chapter of the Alzheimer's Association, Wilkes-Barre, Pennsylvania

Mr. JACOBS. Chairman Collins, Ranking Member Casey, and members of the Committee, I am Clay Jacobs, and I am the Executive Director of the Greater Pennsylvania Chapter of the Alzheimer's Association.

Thank you for the opportunity to testify before the Committee on how we are working to support persons living with Alzheimer's disease, related dementias, and their families.

Currently, 5.8 million Americans are living with Alzheimer's, and without significant action, nearly 14 million may have the disease by 2050. More than 16 million unpaid caregivers are supporting and caring for these individuals at

a cost of \$234 billion. In my home State of Pennsylvania, 280,000 older individuals have Alzheimer's today, and in just a few years, 320,000 will likely be affected.

Among the millions of individuals living with Alzheimer's, we know that there are communities who are disproportionately affected but remain underserved. Older African Americans are approximately twice as likely to have Alzheimer's or other dementias as older whites, and older Hispanics are about one and one half times as likely to be affected.

Another population that is often under-recognized and underserved is the approximately 200,000 individuals under the age of 65 who have younger-onset Alzheimer's disease. The need to reach everyone affected will grow significantly in the coming years, and the Alzheimer's Association is working to reach as many of those people as possible.

Alzheimer's is also a local disease, and our nationwide network of chapters serve to respond to the specific needs in their communities.

To address the unique challenges of younger Pennsylvanians living with Alzheimer's, we offer early stage education and support groups throughout the Commonwealth to promote social engagement in local communities by partnering with museums, local tourism boards, libraries, and other organizations.

We also work with the Pennsylvania Department of Aging to train facilitators for memory cafes and a variety of other services.

In spite of these efforts to support this population, we know that they simply do not have access to many of the services they need.

The Alzheimer's Association is grateful to Chairman Collins, Ranking Member Casey, Senator Jones, and Senator Capito for introducing the Younger-Onset Alzheimer's Disease Act.

To reach other underserved populations in the Pennsylvania Chapter of the Alzheimer's Association, we conduct faith-based outreach and community education in partnership with a large African-American sorority, Alpha Kappa Alpha. We have recruited and deployed Spanish-speaking volunteers for health fairs, education programs, and support groups.

We have actually had the great pleasure of working with Ranking Member Casey's staff on a number of these efforts.

With our local area Agency on Aging, we work to reach Chinese, Korean, and Vietnamese organizations, attending their meetings and health fairs, working with interpreters when needed.

I would actually like to share an example of how important it is to reach the variety of communities impacted by Alzheimer's and why outreach matters.

Ruben Deoleo was born in the Dominican Republic. He moved to Pennsylvania in his 20's to serve as a minister, a drug and alcohol counselor, and a motivational speaker for the Dauphin County Prison. Memory problems, however, began to affect his life's calling. After losing several jobs, his wife, Rosayna, asked Ruben to see a doctor. For over 2 years, they grappled with what was happening and, just 4 months ago, he was diagnosed with Alzheimer's at the age of 58. They struggled with the diagnosis and, in particular, the fact that it was an untreatable illness.

However, when Ruben learned about an Early Stage Engagement group at Lancaster General Health-Penn Medicine and that other individuals living with the disease cope and can live well, he decided to fight back. Ruben has a sense of purpose as a member of the group. He is energized, and he wants to create the same opportunities for others. He is now a volunteer for the chapter, helping the Spanish-speaking community to understand Alzheimer's and the resources that are available. Ruben is getting valuable support while also reaching others.

A constant theme throughout all of our outreach is the importance of care planning after diagnosis. It is essential to learning about medical and non-medical treatments, clinical trials, and support services. These services result in fewer hospitalizations and emergency room visits and a higher quality of life.

This is also true for caregivers, who too often find themselves as the plan, with little support after diagnosis.

The association was grateful for the support of Members of Congress who sponsored or cosponsored the HOPE for Alzheimer's Act in the 114th Congress and to the Centers for Medicare and Medicaid Services for now covering care planning services. However, access to services remains an issue. That is why the association supports the Improving HOPE for Alzheimer's Act, which would help educate clinicians on Alzheimer's and dementia care planning services through Medicare.

We are grateful to Senator Collins for her leadership on the legislation.

Thank you for your time and for the invitation to be here with you today. I am happy to answer any questions.

The CHAIRMAN. Thank you for your testimony.

Dr. Fekrat.

**Statement of Sharon Fekrat, M.D., Professor of
Ophthalmology and Associate Professor of Surgery,
Duke School of Medicine, Durham, North Carolina**

Dr. FEKRAT. Thank you, Chairman Collins, Ranking Member Casey, and members of the Committee for the opportunity to testify and share some very exciting multidisciplinary and collaborative work on one of the most important health issues of our time, Alzheimer's disease, the societal and cost impact of which you are well aware.

My name is Dr. Sharon Fekrat, and I am a retina surgeon at the Duke University School of Medicine.

Alzheimer's disease is the leading cause of dementia worldwide, yet its early detection remains challenging. The high cost of MRI, the limited sensitivity and specificity of genetic and serum markers, and the invasiveness of PET imaging and spinal fluid sampling limit our ability to detect Alzheimer's early.

Alzheimer's has a 20-year relatively asymptomatic period of neuropathogenesis, there is growing interest in identifying Alzheimer's at asymptomatic stages for earlier clinical trial intervention to ultimately identify medications to delay the onset of, prevent, or even reverse Alzheimer's. We need rapid, easily accessible, inexpensive, noninvasive, yet accurate, diagnostic techniques to screen for Alzheimer's.

The task before us is not insurmountable. If a human being can walk on the moon or live in a Space Station, then we can find a means of diagnosing Alzheimer's earlier and subsequently identifying effective therapeutic interventions.

This requires collaborative teamwork across disciplines and institutions, innovative critical thinking, and going out on a limb where the fruits are.

Look at the eyes of the person next to you. You see the colored iris and dark circular pupil. Yet there is so much more there than meets the eye. Behind the pupil, there is the wallpaper lining the inside of the eyeball called the retina.

The retina wallpaper is the film of the camera. It is nerve tissue and a direct extension of our brain. The retina shares many structural and functional similarities with the brain. Spinal fluid biomarkers for Alzheimer's such as tau and amyloid have been found in the vitreous gel behind the pupil, and levels correlate with cognitive test scores. Amyloid has also been detected and imaged in the retina.

The neurodegenerative process in the brain also occurs in the retina with thinning of certain retinal layers. Changes in the retina and its small blood vessels may mirror, or even precede, detectable changes in the brain and its small blood vessels.

Imaging the retina in Alzheimer's, however, is not new. Color photographs of the retina in Alzheimer's show decreased retinal vein diameters, blood vessel branching complexity, and tortuosity. Recent imaging advances now allow us to evaluate the retinal microvasculature with unprecedented detail on the order of 5 microns, not even the width of a human hair, using new technology called OCTA which takes almost 70,000 scans per second to look at the very small retinal blood vessels.

With this FDA-approved imaging technology, we can now take pictures of the retina through an un-dilated pupil quickly, noninvasively, inexpensively, and reproducibly at high resolution.

Several research groups, including our group at Duke, are exploring how this technology along with other retinal imaging methods can be used to diagnose preclinical Alzheimer's.

We recently completed the largest prospective study using this technology, OCTA, of 70 eyes with Alzheimer's, 72 eyes with mild cognitive impairment, or MCI, and 254 eyes from cognitively healthy adults. We found decreased retinal blood vessel density and thickness in one of the retinal layers in Alzheimer's compared to MCI and compared to controls, even after adjusting for age, sex, and education.

A larger sample size may be needed to detect the difference between MCI and controls because of the varied spectrum of MCI.

Our study adds to the published literature and improves our understanding of the smallest blood vessels in Alzheimer's. Right now, these tests cannot be used to solely diagnose Alzheimer's, but this is the beginning of something big.

Before these tests are ready for prime time, the findings must be validated in larger and diverse populations. The goal is to obtain multimodal retinal images that would result in a suite of biomarkers that could predict the risk of Alzheimer's and stratify the stages of disease, similar to getting a cholesterol panel and being able to determine your risk of heart disease.

The potential impact on early detection and clinical trial results is motivating. We are building multidisciplinary and multi-institutional teams and forging relationships with industry to move forward. We are collecting longitudinal data to assess changes over time, imaging genetically predisposed

asymptomatic persons, using images for artificial intelligence, and collecting retinal images globally to store in a central registry for researchers to access.

Our eyes may indeed be windows to our brain health.

Thank you for your efforts to support those working to find the way forward, which in turn supports those with Alzheimer's disease and their families. Time is of the essence.

The CHAIRMAN. Thank you very much for sharing your research.

Dr. Hodes, welcome back. We are delighted to have you join us again this year.

**Statement of Richard J. Hodes, M.D., Director,
National Institute on Aging, National Institutes
of Health, Bethesda, Maryland**

Dr. HODES. Thank you, Chairman Collins and Ranking Member Casey and members of the Committee for the opportunity to be here and share the basis for the hope which we now have as a result of research through support that comes from you and looking forward toward research accomplishments, recent and future, and I will try to do justice to the scholarly introduction that Senator Collins provided of the research that is now ongoing.

If we look at the next slide, just to illustrate the magnitude of increase and support that has come from congressional appropriations of around \$600 million in 2016 through what you see is a total of \$1.9 million in 2018 and 2019, the current year, if we add the appropriations and estimate the total, this would be approximately 2.3-to \$2.4 billion, an extraordinary increase.

Importantly, it has energized and excited the research community. It has led to the recruitment of a large number of new investigators, people who are trying to tie the directions they would place their wisdom and their careers and now take it to the important cause of Alzheimer's research.

It has led to the current support by NIA of approximately 140 clinical studies and trials. Some of these are in the important area alluded to, trials to identify the most effective means of providing support, care, and services to those already affected. Others are a diverse set of trials looking at the strategies for prevention, cure, treatment of disease.

Some number of those are non-pharmacologic, looking at interventions such as exercise, diet, cognitive training, or combinations of them.

If we look at the next slide, an example of the number and diversity of pharmacologic studies undertaken, this illustrates here at various stages of drug discovery, drug development, then their implementation in early stage clinical trials, and finally, the more advanced stage III clinical trials, and the colors are intended here to show the number of trials attacking different categories of targets.

Alluded to, was amyloid, which remains an important area of research where failures have occurred in attempts to treat at later stage of disease by targeting amyloid, where hope remains, and additional trials are targeted at looking at early intervention.

Notably, as commented upon, the availability of biomarkers that now detect disease years to decades before symptoms means we can make a difference by targeting interventions not only of people who need them or had the disease but those for whom prevention is important before the onset of substantial damage to neurons and their connections within the brain.

In the next slide, you see a summary of what we have just shown in color to make it simply evident that the numbers of trials targeting amyloid, in gray, is far exceeded by those, the diversity of targets that you see here, so if some 32 trials are currently ongoing, only 13 are now targeted toward amyloid.

The diversity comes from a variety of basic studies, new methods for identifying genetic, molecular underpinnings of the processes that occur in Alzheimer's, amyloid and other, are translated into new targets for intervention.

Most recently, in public-private partnerships with pharma, biotech, academic institutions, in a new spirit of big data and open data, these findings, the large data, then computational analyses have led to the discovery of new potential targets recently published, a wall of targets, some 100 candidate, best-consensus candidates for future studies, which will now go into the pipeline in development for ultimate clinical trials, giving us hope and expectation with these multiple approaches that will do far better in making advances toward treatment, cure, and prevention.

In the next slide, this is just an illustration of the pace of advance in one of the areas of basic science. This is in genomics. If you look at the discovery of genes, which are associated with either a higher risk of Alzheimer's or a lower risk, that is, protective factors, you can see year by year, the increase in number of genes there.

Just to note, in 2018, that large list of genes is more than has been discovered, had been discovered in all the preceding years. They are color-coded here, hard to see, I know, but meant to illustrate that the genes are not