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THE ALZHEIMER'S CRISIS: EXAMINING TESTING AND TREATMENT PIPELINES AND FISCAL IMPLICATIONS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH CARE

OF THE

COMMITTEE ON FINANCE

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THE ALZHEIMER'S CRISIS: EXAMINING TESTING AND TREATMENT PIPELINES AND FISCAL IMPLICATIONS

WEDNESDAY, DECEMBER 16, 2020

U.S. SENATE,
SUBCOMMITTEE ON HEALTH CARE,
COMMITTEE ON FINANCE,
Washington, DC.

The WebEx hearing was convened, pursuant to notice, at 2:31 p.m., Dirksen Senate Office Building, Hon. Patrick J. Toomey (chairman of the subcommittee) presiding.

Present: Senators Grassley, Thune, Portman, Cassidy, Young, Stabenow, Cantwell, Menendez, Carper, Brown, Casey, Warner, Hassan, and Cortez Masto.

Also present: Republican staff: Alyssa Palisi, Staff Director for Senator Toomey. Democratic staff: Alex Graf, Legislative Aide for Senator Stabenow.

OPENING STATEMENT OF HON. PATRICK J. TOOMEY, A U.S. SENATOR FROM PENNSYLVANIA, CHAIRMAN, SUBCOMMITTEE ON HEALTH CARE, COMMITTEE ON FINANCE

Senator TOOMEY. Okay; thank you all very much for joining us. The attendance at this hearing looks to be terrific, and I am very pleased with that fact. I am very grateful to my partner on this really, really important topic, Senator Stabenow, for all of her dedication to this cause.

So, welcome to the Senate Finance Subcommittee on Health Care hearing "The Alzheimer's Crisis: Examining Testing and Treatment Pipelines and Fiscal Implications."

As chair of the subcommittee, it has been a priority of mine to highlight the really extraordinary public policy challenges that Alzheimer's disease presents. To start with, as we all know, Alzheimer's disease is 100-percent fatal. There is no therapeutic intervention that can reverse, stop, or even slow its progression.

We do not really understand the mechanism by which it carries out its lethal work, but almost 6 million Americans are estimated to be living with the disease today—though as our witnesses highlight in their testimony, it is very likely that that is an understatement. Nevertheless, it is a figure that is expected to balloon to nearly 14 million by 2050. Alzheimer's is already the sixth leading cause of death for Americans, and the morality rate is increasing at an alarming rate.

Lastly, it is a growing financial burden on our Federal health-care programs. According to a study by the National Institutes on Aging, the annual cost of dementia in the United States is projected to reach between $379 billion and $511 billion—that is annual—by 2040.

These problems are compounded by the inequities in the Federal funding of Alzheimer's disease, which still does not receive its fair share of the NIH investment that is commensurate with its outsized impact on patients, families, and Federal health-care programs.

And further, despite knowing that amyloid plaques and tau proteins can begin to quietly develop in a patient's brain years before a patient ever experiences symptoms, we still do not have a non-invasive, affordable, and rapid diagnostic available to the public. The ability to detect the disease before neurological decay begins could provide an important opportunity for innovative drug makers to develop a treatment or a cure.

On January 4, 2011, the National Alzheimer's Project Act was signed into law after being passed unanimously by both chambers of Congress. This set forth an ambitious goal to find the cure for Alzheimer's disease by 2025. As we enter the last 5-year stretch toward this deadline, it is time for Congress and the public to take a detailed look at the state of Alzheimer's disease research, as well as analyze current barriers to the potential discovery of effective therapies and diagnostics.

In some ways, this could not be a more timely discussion. The race for cures and vaccines for COVID–19 has given Americans insight into the capabilities of the pharmaceutical and diagnostic industries. When incentives align and public policy is made with an eye towards innovation, academic and commercial researchers in the United States have proven that they are capable of nimbly solving some of our Nation's most urgent public health problems.

Without effective treatments, the social and emotional toll of this insidious disease will continue to bear down upon patients and their families. With Senator Stabenow's partnership, for which I thank her again, this marks our third hearing to examine the many difficulties that Alzheimer's disease creates for patients, families, and policy-makers.

In addition, we have sought public input to help inform the development of potential future legislation and areas for regulatory reform. In October, we recommended 15 regulatory actions that the Department of Health and Human Services, including the Centers for Medicare and Medicaid Services and the National Institutes of Health, can take to improve the lives of Alzheimer's patients.

It is my hope that the incoming administration will swiftly pick up where they left off. Unfortunately, legislative work does not fix the biggest issue facing Alzheimer's patients and their families: the lack of a cure, or even a treatment for the disease.

So today we will hear from key leaders in the field of Alzheimer's disease research. We will learn about where researchers are in the race for a cure and what more can be done to help them get there. I am really looking forward to hearing from each of them.

But before we do that, I will yield to Ranking Member Stabenow for the purpose of her opening statement.

OPENING STATEMENT OF HON. DEBBIE STABENOW, A U.S. SENATOR FROM MICHIGAN

Senator STABENOW. It is my pleasure to join you in hosting this subcommittee hearing, and I know how passionate we both are on this issue. And I really appreciate the work that we have been doing together on the subcommittee, and appreciate all of our colleagues joining us today.

Also, thank you to our witnesses for all you are doing, and for being here virtually today as we discuss this incredibly important topic.

Five-point-eight million Americans are living with Alzheimer's today, and that includes 190,000 people in my home State of Michigan. In just the next 30 years, that number is expected to more than double to 14 million Americans. And we know that the pandemic has hit dementia patients especially hard, with well over 13,000 excess deaths attributed to Alzheimer's since March.

Behind these numbers, though, are what is most important, and that is grandparents, and parents, and aunts and uncles, and friends, moms and dads, who have all faced this horrific diagnosis and limited treatment actions right now.

Today, we will learn the latest developments on Alzheimer's treatments and testing. There is still no drug, as the chairman said, to cure Alzheimer's disease or slow its progression. But there is hope.

I am pleased that the Federal funding for Alzheimer's research is five times higher now than it was just 9 years ago, and I agree that we need to do much more. With this funding, many researchers have been able to make strides toward new treatments. I know in my home State, there is tremendous work being done.

We need to continue to support their groundbreaking work, and to expand on it. We also need better testing so we can identify the disease early and help families plan and get people enrolled in clinical trials. And when we have a treatment, early and affordable testing and diagnosis will make sure that people who need it get it.

I introduced legislation with Senators Capito, Menendez, and 19 others called The CHANGE Act, which will encourage timely and accurate detection and diagnosis using evidence-based tools.

Finally, while working toward a cure, we must not forget the people who care for their loved ones with the disease. And we all know that Alzheimer's really is a family disease. I am so glad that the Improving HOPE for Alzheimer's Act was implemented on a bipartisan basis, and now newly diagnosed Alzheimer's patients can access a doctor's visit to create an individual care plan.

However, not everybody knows of this benefit, and not everyone is using it. So our Improving HOPE for Alzheimer's Act, cosponsored by 47 members, many on this subcommittee, requires HHS to conduct a nationwide campaign to increase awareness of this care planning visit and the importance of supporting families.

We also must ensure that once patients and their caregivers have a plan, they can actually implement the plan. That is why I will be introducing legislation next year—and I welcome my colleagues to be a part of this—directing the Department of Health and Human Services to test a payment model to support coordi-

nated care for dementia patients, as well as support for caregivers. By coordinating care, we can reduce complications and we can ensure that families have resources to help care for their loved ones.

So I am very proud of the progress we have made in the work we are doing together on a bipartisan basis. There is so much more to do, and I look forward not only to today's discussion, but also for ways that we can continue to work together on diagnosis, treatment, and ultimately what we all want, which is a cure for Alzheimer's.

Thank you, Mr. Chairman.

[The prepared statement of Senator Stabenow appears in the appendix.]

Senator TOOMEY. Thank you very much, Ranking Member Stabenow.

First of all, without any objection, any other members' opening statements will be made part of the record. My understanding is a vote is going to be called within the next few minutes, and, Senator Stabenow, if I understand correctly, you were thinking of maybe voting early, and I will continue with the hearing; and when you get back, maybe you could take over while I run and vote, if that is okay with you.

Great. Thank you.

Well, we have a really remarkable panel today. Their contributions to Alzheimer's research and the community of researchers has been extraordinary, and I appreciate very much each of them taking the time out of their day to join us and to educate us on their work.

First, we will hear from Dr. Nikolay Dokholyan. Dr. Dokholyan is a researcher from the Penn State College of Medicine. I hope I am pronouncing your name at least approximately right, Doctor.

The mission of his laboratory is to research and develop therapeutics that fight against neurodegenerative diseases like Alzheimer's. He has been recognized on numerous occasions for his contributions to the field of computational biology and biophysics.

Dr. Dokholyan, it is great that you could join us today. Thank you for being with us. And let me point out that the Commonwealth of Pennsylvania is very proud of your work.

Next we will hear from Dr. Randall Bateman, a physician researcher from the Washington University School of Medicine. His laboratory focuses on the causes, diagnosis, and future treatments of Alzheimer's disease. Earlier this year, his research findings gave the public hope that a rapid and inexpensive blood screening test to identify people at high risk of developing the disease may be within reach.

Then we will hear from Dr. Richard Mohs, the chief science officer at the Global Alzheimer's Platform Foundation. Dr. Mohs has authored or co-authored over 350 scientific papers. Most notably, his work describes clinical trials that led to the approval of some of the most commonly prescribed treatments for Alzheimer's disease today.

He retired in 2015 after serving in several leadership positions at Eli Lilly and spending 23 years with the Mount Sinai School of Medicine.

Last but not least, we will hear from Dr. Maria Carrillo, the chief science officer at the Alzheimer's Association. Dr. Carrillo oversees the Association's portfolio of research initiatives, working with both the national and international scientific communities to overcome barriers to research and development.

As a reminder, each witness will have 5 minutes to present their oral testimony, which will be followed by questions.

We will begin with our first witness, Dr. Dokholyan.

STATEMENT OF NIKOLAY DOKHOLYAN, Ph.D., M.S., G. THOMAS PASSANANTI PROFESSOR AND VICE CHAIR FOR RESEARCH, PENNSYLVANIA STATE COLLEGE OF MEDICINE, HERSHEY, PA

Dr. DOKHOLYAN. Thanks, Senators Toomey and Stabenow, for your invitation. I am a scientist whose research is focused on fundamental and translational research in neurodegenerative diseases at Penn State University College of Medicine.

I have been studying neurodegenerative disorders for over 20 years, focusing on fundamental processes that lead to the pathological behavior of proteins in human diseases. Besides a scientific desire to understand the processes leading to neuronal degeneration, it is personal to me. Like many Americans, I have family members who have suffered from Alzheimer's disease, so I know well the emotional and financial toll it takes on families.

Alzheimer's disease is a progressive, irreversible, and degenerative brain disease. Currently, close to 8 million Americans are living with this illness, and this number is likely a significant underestimate due to the lack of diagnostic tools, early diagnostic tools, and access to health care, especially in rural areas, causing many individuals in early stages of the disease to remain undiagnosed.

Age is the most critical factor. And as the U.S. population ages, the number of Americans living with Alzheimer's is projected to double by 2050. And among the top 10 leading causes of death, Alzheimer's is the only one that cannot be even slowed.

The national cost of care for patients is also a staggering $300 billion, and that is not including the $240-billion cost of unpaid labor from caregivers, families, and friends. And these numbers make Alzheimer's disease the most expensive disease in the United States. The projected cost of Alzheimer's by 2050 will top $1.1 trillion in the United States alone.

Curative therapeutics targeting disease mechanisms as opposed to palliative curative therapeutics to treat symptoms, would have the most profound impact on quality of life for Alzheimer's patients and their families. And it would eliminate the financial burden associated with the disease.

The principal challenge in identifying curative therapeutics is our current dearth of knowledge of early molecular events leading to pathological disease processes, which can begin up to 20 years before the disease onset, and those are poorly understood.

The principal critical barriers are current technological limitations, such as lack of precise and accurate methods for noninvasive monitoring of pathological processes in organisms, and inadequate experimental animal models of the disease.

Because of this dearth of knowledge, there is also no definitive clinical diagnostic test for Alzheimer's disease. It is interesting that circumstantial evidence—such as family history, interaction with family members and friends, and a battery of cognitive tests—suggests whether the patient exhibits signs of dementia. And because the reason for dementia is likely Alzheimer's, that is the association given during diagnosis. By the time diagnosis is made, though, pathology has altered, significantly and irreversibly, the brain.

One of the hallmarks of Alzheimer's disease is the accumulation of barren protein deposits in a patient's brain. However, despite decades of research, we have not yet established the nature of the link between aggregation and toxicity, nor whether protein aggregates are indeed a driver of neuronal death or simply a consequence of some unknown processes.

Nevertheless, the protein aggregation has been the basis for many Alzheimer's disease drugs in the drug pipeline—which have been expensive failures. The for-profit private sector is driven by deliverables, and thus, despite remarkable spending on R&D, companies typically focus on only the established target drug therapies, which reflect our fundamental understanding of disease pathological processes, an understanding that is typically established in academia, because it takes a long time.

Hence, deeper integration of the private sector with academia may significantly reduce the inertia in the drug pipeline and increase the potential for new ideas to tackle neurodegeneration.

Translational science programs aimed at marrying these scientific fields with clinical research are critical to establishing a working model of the disease. The success of translational science relies on attracting scientists with backgrounds in diverse fields to build interdisciplinary programs. In addition, attracting industrial partners to these interdisciplinary consortiums will facilitate their progress.

Finally, I want to mention that there is an additional way we can help with Alzheimer's, because the dominant cost associated with caring for Alzheimer's patients stems from the expensive care requirements in later stages of the disease. Thus, reducing the cost of care is mostly an untapped direction in mitigating the financial burden of the illness.

Recent scientific and engineering innovations, especially in machine learning and artificial intelligence, wireless solutions, and miniature devices, may offer new and unparalleled means for caring for patients, especially in advanced stages of the disease.

Facilitating innovations through Federal and private-sector programs will have a major impact on improving the quality of care and reduce the financial burden on both government programs and individuals.

Thank you, Senators, for your attention.

[The prepared statement of Dr. Dokholyan appears in the appendix.]

[Pause.]

Senator TOOMEY. Dr. Bateman, can you hear me?

Dr. BATEMAN. Yes.

Senator TOOMEY. All right, you are recognized for 5 minutes.

STATEMENT OF RANDALL J. BATEMAN, M.D., CHARLES F. AND JOANNE KNIGHT DISTINGUISHED PROFESSOR OF NEUROLOGY; AND DIRECTOR, DOMINANTLY INHERITED ALZHEIMER'S NETWORK (DIAN), DIAN TRIALS UNIT (DIAN–TU), WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MO

Dr. BATEMAN. Chairman Toomey, Ranking Member Stabenow, and members of the committee, I would like to thank you for the opportunity to speak today on the important topic of Alzheimer's disease and advances in medical diagnosis and treatment.

In the research field, we have come a long way in our understanding of the disease; our ability to detect, track, and diagnose Alzheimer's; in research and in the clinic now; and in development of drugs which can stop and reverse some Alzheimer's disease pathologies.

We have specific tests that can identify the two key pathologies of Alzheimer's—amyloid plaques and tau tangles—in brain scans, cerebral spinal fluid, and now in the blood.

Treatments targeting amyloid plaques can remove these plaques to undetectable levels, something that was not possible just a few years ago. We are learning from clinical trials how to dose these medications more effectively and who is likely to benefit from them.

However, there are clear opportunities to accelerate the developments in the diagnostic, therapeutic, and research pipelines for Alzheimer's disease. New Federal strategies could enable breakthroughs in the disease's diagnosis and treatment similar to what has been accomplished for diagnostics and vaccines for the COVID–19 pandemic.

The two areas that represent challenges to therapeutic development are centered on issues of regulatory burden and risk-averse trial designs. And sometimes lack of urgency and not accounting for the cost of inaction leads to clinical trial delays and higher overall costs.

Extensive international regulatory reporting requirements and approval delays cause major trials to cost several hundred million dollars and take 3 to 5 years to complete, while prevention trials take even longer at about 7 years. These trials are too expensive and too long, causing potential treatments to be left on the shelf untested and some drug developers to abandon Alzheimer's drug development programs.

If we can learn from COVID–19 approaches in how to accelerate and implement better strategies to move more quickly, and appropriate incentives can be made, an accelerated development can occur to lead to faster treatment development.

How can this be helped? One way is that policy-makers and agencies can enable and support standards which account for the personal and the financial cost of Alzheimer's disease in terms of the opportunity costs of delays in decision-making. In other words, balance the risk/benefit analysis to account for time lost on deliberations.

Two, enable science and medicine to advance at optimal speeds, accounting for potential benefit while managing risk. This has largely been started with very significant support to the NIH

through the Senate and the government, and this is already paying out in dividends.

Number three, encourage investment in the development of treatments and preventions for Alzheimer's disease.

As a second discussion point on diagnostics, I believe that we are currently in a very good position in terms of having highly accurate diagnostic measures of Alzheimer's disease for amyloid plaques and tau tangles, the two pathologies which define the disease. These have been available for a number of years, and more recently simple blood tests have been developed that can also detect these pathologies. But they are not used in the clinic yet, for several reasons, including lack of payer support.

Symptomatic patients and their doctors have a need to know an accurate diagnosis. These tests can accurately identify who has Alzheimer's disease pathology and, importantly, who does not have Alzheimer's disease, so that other causes can be sought, including treatable or reversible causes.

For research purposes, measurable indicators of Alzheimer's disease pathology, what we call "biomarkers"—such as blood and cerebral spinal fluid, amyloid, and tau—offer immense promise. These biomarkers are being used to screen for the disease, track the effects of treatment on Alzheimer's disease processes, and are also being considered for surrogate biomarker development, which would greatly speed Alzheimer's disease trials.

Thank you.

[The prepared statement of Dr. Bateman appears in the appendix]

Senator TOOMEY. Thank you, Dr. Bateman.

Dr. Mohs, you are recognized.

STATEMENT OF RICHARD C. MOHS, Ph.D., CHIEF SCIENTIFIC OFFICER, GLOBAL ALZHEIMER'S PLATFORM FOUNDATION, CHICAGO, IL

Dr. MOHS. Thank you, Senators Toomey and Stabenow, and members of the subcommittee, for your support for Alzheimer's research and for the opportunity to testify.

For the past 40 years, both as an academic researcher funded by the National Institutes of Health, and subsequently leading drug development teams in the pharmaceutical industry, I have devoted much of my scientific career to trying to develop new medicines for Alzheimer's disease.

We have not been as successful as I would like, or as successful as patients need. Currently, I am the chief science officer for the Global Alzheimer's Platform, or the GAP Foundation. It is a patient-centered nonprofit organization devoted to accelerating the delivery of innovative therapies for AD by reducing the duration and cost of clinical trials.

More than 85 centers across the U.S. and Canada are part of the growing GAP network. These research sites are supported by GAP by assisting with study startups, with the recruitment activities, promoting diversity in research studies, and offering national programs that champion brain health and the citizen scientists who make research possible.

Based on my experience, I can offer some perspectives on barriers to progress and future initiatives that could speed progress that is urgently needed. I think you will find some of my recommendations mesh quite well with the remarks of the first two speakers.

The first and most significant barrier to progress is that we have not yet clearly identified the key biological processes that cause AD. As we have learned in recent months from the experience of COVID–19, once a causal agent is identified and characterized biologically, the search for preventative measures and treatments can proceed rationally through highly informative basic and clinical research.

For a chronic disease such as Alzheimer's with multiple risk factors and complex pathology, the path to effective treatments is very uncertain. In the private sector, there is a high degree of interest, and there has been considerable investment in Alzheimer's drug development, but it is considered more risky than other areas where the perceived likelihood of clinical and commercial success is higher.

We do know that AD is characterized by the presence of two abnormal proteins in the brain, amyloid and tau. Many drugs designed to slow the accumulation or speed the removal of amyloid or tau have been entered into large, time-consuming, and very expensive clinical trials.

While these approaches may show some efficacy in some patients, it is an imperative that the therapeutic value of targeting other factors associated with AD pathology be tested as quickly as possible.

Given the complexity of AD, we must expect that many clinical trials, even those testing the most scientifically promising drug candidates, will fail to show efficacy. By testing a variety of scientifically justified approaches, an efficient and well-executed clinical study, and learning from each set of studies, I am very confident that we will eventually develop effective medicines for the prevention and treatment of AD.

A second major barrier, following on Dr. Bateman's comments, is the disconnect that now exists between the way patients with AD are diagnosed in clinical practice and the way research studies identify participants. Most practicing physicians make a diagnosis of AD relatively late, when patients manifest clear symptoms and need counseling on how to manage those symptoms.

Recently, major advances have been made in the development of brain scans and blood-based biomarkers that will speed the early identification of patients with asymptomatic disease, both for trials and for early diagnosis in clinical practice.

Early diagnosis will allow for scaling up education efforts and counseling so that families can make plans for their loved one to have the highest degree of independence possible. Early diagnosis will also facilitate the rapid completion of clinical studies because we will identify and enroll appropriate participants in clinical trials much earlier and much faster.

The GAP Foundation is in the process of standing up a platform study that will test the efficacy of more than a dozen promising blood biomarkers and digital cognitive assessments for AD. Known

as the Bio-Hermes study, we will generate biological samples for over 1,000 participants. The Bio-Hermes study will include racially and ethnically diverse participants in order to assess whether biomarker risk factors vary by race and ethnicity.

Recruiting a diverse group of participants for Alzheimer's clinical trials is both extremely important and challenging. To help address this issue, GAP has committed to recruiting at least 20 percent African American or Latino volunteers for the upcoming Bio-Hermes study.

Our intention and hope is that the Bio-Hermes study will be a model for building back a clinical trial infrastructure that is more efficient and gets to better diagnostics and treatments faster.

The FDA, of course, is an essential partner when it comes to research for better diagnostics and treatments. We applaud the agency's approach to public engagement around their evaluations. Given the need for greater diversity in clinical trials, we hope Congress will use the Prescription Drug User Fee Act renewal process to encourage FDA to develop clear guidance on minimum standards for diversity.

Undoubtedly, Alzheimer's disease has proved to be one of the most difficult problems ever to confront biomedical researchers. I look forward to discussing how the subcommittee can take steps to speed the widespread use of blood and digital biomarkers; increase the speed and diversity of Alzheimer's clinical trials; enhance investment in the AD clinical research infrastructure and the clinical trial pipeline; and encourage further collaboration between commercial sponsors, academic researchers, NIH, FDA, patients, and CMS.

Thank you very much.

[The prepared statement of Dr. Mohs appears in the appendix.]

Senator TOOMEY. Thank you, Dr. Mohs.

Dr. Carrillo, you are now recognized.

STATEMENT OF MARIA CARRILLO, Ph.D., CHIEF SCIENCE OFFICER, ALZHEIMER'S ASSOCIATION, CHICAGO, IL

Dr. CARRILLO. Thank you, Chairman Toomey, Ranking Member Stabenow, and members of the subcommittee. I really appreciate you holding this important hearing today and the opportunity to testify on Alzheimer's and other dementia therapeutic and diagnostic pipelines, as well as of course Federal policies that can help address barriers to foster much-needed breakthroughs in diagnosis and treatment.

I have been personally touched by dementia, as I know many of you have. My mother-in-law Arcelia Pachicano, my father-in-law José Pachicano, passed away over 3 years ago, within 1 year of each other, Arcelia of Alzheimer's dementia and José of vascular dementia. Arcelia in fact was the third of four siblings to die of Alzheimer's, and her father died of it also.

Our family is committed to doing everything we can to eradicate this disease that affects so many, including the next generation.

In addition to the suffering caused by this disease to families like my own, like many of yours, Alzheimer's is an enormous drain on the health-care system and on our Federal and State budgets. And while there are, as we have already heard, over 5 million Ameri-

cans living with the disease today, without significant action, nearly 14 million Americans will have it by 2050.

And as you heard also earlier in this hearing, in 2020, Alzheimer's and other dementia alone will cost our Nation $305 billion, including $206 billion for Medicare and Medicaid. Unless we find a way to stop this, by 2050 Alzheimer's is projected to cost more than $1.1 trillion. But there is hope on the horizon.

We have great promise with historic funding increases coming from Congress that have made Alzheimer's and related dementia research more of a priority at the NIH. In fact, since Congress passed the bipartisan Alzheimer's Project Act 10 years ago, Alzheimer's NIH research funding has increased more than sixfold. This investment has been critical to progress towards our primary research goal to effectively treat and prevent Alzheimer's by 2025, including advances in new biomarkers to detect the disease.

You have also heard that biomarkers are the most promising paths because they can detect the earliest brain changes. The FDA has already approved PET scans to identify the hallmarks of Alzheimer's—amyloid plaques and tau tangles in the brain—and they are currently reviewing an application for cerebrospinal fluid as well. We are closer to a blood test, which you have also heard, and this breakthrough is critically important and actually was very well-represented for the first time at the Alzheimer's Association's International Conference this past July, showing that these blood tests might even be able to detect changes 20 years before Alzheimer's symptoms occur. Biomarkers will be the new diagnostic tools in the toolbox for primary care physicians and specialists in the early detection and most accurate diagnosis of Alzheimer's.

And in addition to these great advances, there is a drug under review right now at the FDA that for the first time may very well treat the underlying biology of the disease—a very important moment for the Alzheimer's field.

With more shots on goal than ever before, there is excitement in the research community and hope for the millions of Americans and families devastated by this disease. But even with these great strides, there is a lot left to be done. We all know that, and have heard this already from other witnesses here at the hearing.

We need to understand the changes, the underlying changes that really are underlying the disease progression. This is in large part, I think, important because we also do not know how to differentiate that impact, that underlying biology, in terms of the types of individuals to actually recruit for our clinical trials. So we have an extraordinary under-representation of black African Americans, Hispanic Latin Americans, Asian Americans, and Native Americans, which should be representative of the United States population.

This under-representation not only hinders the ability of researchers to understand health disparities but also restricts our knowledge on how approved therapies or diagnostics may be generalized to the whole population, and to those actually who may need the drug most.

It is crucial that we continue to increase our investment in order to maximize every opportunity for success. This will enable us to learn more ways in which Alzheimer's develops in the brain in ev-

eryone, develop better diagnostics, and discover more effective treatments.

The Alzheimer's Association and AIM urge Congress to finalize the additional $354 million for NIH Alzheimer's funding for fiscal year 2021, which was included in the recent Senate draft. We cannot afford to leave any stone unturned. With every study, we are illuminating more of the underlying biology of Alzheimer's and finding another piece in the puzzle.

Despite more than 2 decades of advances in this disease, Alzheimer's and other dementia are often unrecognized, or even misattributed in physicians' offices. This causes delays that you have already heard could be harmful to an individual, and even costly.

There clearly is no consensus for Alzheimer's diagnostic recommendations in primary care. That is why the Alzheimer's Association developed, along with a group of physicians, 20 recommendations for practitioners across the country. Thus, the Alzheimer's Association looks forward to working with all of you, and with physician groups, to ensure that primary care doctors and dementia experts, and even nurse practitioners, can adopt new guidelines.

With all of the recent progress in research in Alzheimer's, and biomarkers specifically, we need to make sure that there is actually coverage for these diagnostic tests. Coverage for diagnostics would spur our private sector in engagement on both diagnostics and therapeutics, actually—diagnostic testing with validated biomarkers crucial for Alzheimer's, which you have already heard as well. And the Alzheimer's Association has worked very well with the Centers for Medicare and Medicaid Innovation since 2013 to explore this coverage through the IDEAs Study.

As a co-chair of the IDEAs Study, we are seeking evidence to support that reimbursement that is very important, by Medicare of course, and third-party payers. But also we are building on the IDEAs Study in order to launch the New IDEAs Study which will actually specifically look for the impact of amyloid PET scans on diagnosis in more diverse, historically under-represented populations.

And one theory of course that you have already heard about is increasing the availability of therapeutics in the under-diagnosed populations because, as you have already heard, when the diagnoses are made, it may be very well too late.

So we must continue to work on early detection in order to provide dementia care for those who need it the most.

So thank you very much for the opportunity, Senators Stabenow and Menendez, and of course for introducing the bipartisan Improving HOPE for Alzheimer's Act, and we look forward to working with you on everything we can do in order to accelerate progress.

Thank you, very much.

[The prepared statement of Dr. Carrillo appears in the appendix.]

Senator TOOMEY. Thank you very much, Dr. Carrillo.

I am sorry to put Senator Carper on the spot here, but I have not had a chance to vote yet. We have run out of—time has expired, so I am wondering, Senator Carper, if I could impose on you

to lead off with questions, and perhaps to recognize the next Senator, until I am able to vote and get back to this hearing.

Senator CARPER. Pat, I have not voted.

Senator TOOMEY. Okay.

Senator CARPER. But I am happy to take the hand-off. And as soon as I am running out of time, I will—if nobody is here, I will just go to recess, and we will reconvene as soon as you get back, or——

Senator TOOMEY. Okay. All right; thank you very much. I will run right now and be back as soon as I can.

Senator CARPER [presiding]. Sure. Thank you

Let me just ask of our witnesses—first of all, I am Tom Carper from Delaware. I see Senator Cortez Masto. Catherine, have you already voted? Okay. A couple of questions, if I could—or, Catherine, do you want to go first?

Senator CORTEZ MASTO. If you like, Tom, I am happy to. I will be very quick. I will not use all of my 5 minutes.

Senator CARPER. Okay, go ahead. Go ahead.

Senator CORTEZ MASTO. I know we all have to vote. Thank you. I appreciate that.

So I would say, thank you for all of the good work. I am similar to many of you, in my family with Alzheimer's, and my grandmother died from Alzheimer's. So it has been something that has been so important for me. That is why—I was fortunate, when I first got to the Senate, to partner with Senator Susan Collins to pass the BOLD Infrastructure for Alzheimer's Act.

And so, let me start there. In 2018 we passed that act, and the bill aims to activate a full-fledged public health response to Alzheimer's disease by building up education opportunities through centers of excellence, expanding local and State public health infrastructure across the country, through cooperative agreements with the CDC, and by offering dated grants to improve analysis and timely reporting of data on the disease.

Now I am fortunate, also, in the State of Nevada to have the Lou Ruvo Center for Brain Health in Las Vegas. But let me ask this question, and maybe, Dr. Dokholyan, let me start with you. Can you speak to the work or research that you would like Federal partners to be engaged in that would support the public health approach to treating Alzheimer's? I am curious about your thoughts on that.

Dr. DOKHOLYAN. Thank you for—this is a very interesting question. So there are several—there is, unfortunately, not one single-scope solution. But there are things that the government and industry can work together on towards potential solutions.

The first one: I feel like there should be a better integration for the research that is done by medical companies with academic research. Most of the fundamental research is done in academia, and it is very expensive. And so by outsourcing all of the research—not all, but the majority of the fundamental research—to academia, the companies can save money on those processes and focus more on bringing the drugs to the market.

So, supporting those kinds of programs through centers that would combine expertise from both academia and industry would

naturally help, and governmental incentives may be a good way to go.

And companies like Merck and GSK, for example, already have programs in place like this. And I think it's one good way to go.

The second I would like to mention is that we focus on finding drug targets, true drug targets that would really eradicate the disease. It is still in process, and as a scientist, nobody can really—I cannot give a timeline when this will be discovered. But meanwhile, we have a huge burden associated with care management. And care management is a huge-ticket item, both to the government and also to family members. And developing new technologies that would help monitoring Alzheimer's patients—helping them not to wander outside of the range and get lost and get frozen to death, for example, as I heard from some doctors happens to patients.

This can be really stopped with simple solutions, innovative solutions that would use tracking devices and geotracing tools. So there are many ways we can combine approaches to help both reduce the suffering of the patients and the families, as well as the financial burden.

Senator CORTEZ MASTO. Thank you, Doctor. Thank you so much.

I am going to go vote. I will try to get back for the rest of the conversation, but, Tom, I will give it back to you.

Thank you so much.

Senator CARPER. Tell them I am on my way, okay?

Senator CORTEZ MASTO. I will

Senator CARPER. I will be right behind you.

Folks, we have a series of two votes. So this is the first of two votes. So we have to run and vote, and we will vote immediately on a second one, and then we will be back to rejoin you. So please be patient, and we will see you shortly. Thank you so much. This is of great importance to all of us, and personally as well. Thank you.

[Pause.]

Senator TOOMEY. I would like to resume the hearing, and my colleagues will be returning as they have a chance to cast their votes.

So let me recognize myself for some questions. And let me start with an observation. I alluded to this in my opening comment. The Federal Government years ago established the goal of having an effective treatment for Alzheimer's by 2025.

Each of your testimonies brought attention to issues that underscore what I think we already know, which is that it looks unlikely that we are going to reach that goal, at least on the path that we are on now, especially since, as best that I can tell, we still do not really understand the dynamics that cause this disease, which would presumably be an important precondition for having an effective cure.

But let me put it to you and get your take on this. In your professional opinions—and I would like to address this to each of our witnesses, and maybe you could just answer in the order in which you gave your testimony—do you think we are on track to reach the goal of having a cure, or at least an effective treatment, by 2025?

Dr. DOKHOLYAN. The ability to develop, to design therapies for complex diseases such as Alzheimer's depends on our understanding of the target. So there may—it is very hard to make pre-

dictions of what the science will bring in the next few months. It may be there will be a big breakthrough that will say "here is the problem."

But unfortunately, it is hard to predict. And unfortunately, there is also inertia regarding what kind of ideas we have about the disease. We still do not know whether the protein clumps that we believed before were toxic may not have anything to do with the toxicity, and are just some bystanders there. And so it creates a huge problem for us in order to even think about new ways to treat the disease.

Dr. BATEMAN. To answer the question, I do not think it is—excuse me. Should I speak?

Senator TOOMEY. Dr. Bateman, yes.

Dr. BATEMAN. Okay; thank you. To answer the question, I do not think it is likely that we will have a cure by 2025, or a highly effective treatment, at the current rate that we are moving. And effective—it needs to be qualified with what we mean by "effective." But clinically, what I mean by that is things that patients would recognize as stopping or preventing the disease, or slowing it to such a degree that it would be clinically recognizable by the patient and the family.

And as I tried to detail, I think one of the issues here is that Alzheimer's disease is a very challenging disease to do clinical trials on and to demonstrate therapeutic efficacy in. These trials are long. The disease progresses slowly. As has been highlighted, there are uncertainties as to what is causing the immediate damage.

That is not to say that we do not know of examples. For example, there are people for whom we know exactly what is causing Alzheimer's disease due to genetic mutations that alter these amyloid beta proteins. And on those individuals we have a strong understanding of what causes the disease. But it is not like an infectious disease where we can point to an infectious agent like a virus and say that is the sole cause of the disease.

That said, I do think there are ways to accelerate this over the next 4 years to move our chances of coming across and identifying and implementing these strategies. And I think one strategy is to try to accelerate the way that we do clinical trials—launch, implement, and run them.

Dr. Mohs had reviewed some of the strategies being developed to try to do that.

Two, is to try to treat the disease in a prevention mode. So intervening in the disease process before organ and brain damage is done, and that I think has, biologically and medically, perhaps one of the better shots of being able to have a large impact into this medical disease that afflicts so many.

Senator TOOMEY. Dr. Mohs?

Dr. MOHS. Yes, thank you, Senator.

Here is my perspective on this. I think failure to show efficacy is probably the norm in drug development. Anybody who has worked on developing drugs in any therapeutic area spends most of their time working on things that do not turn out to be efficacious.

The problem is even much greater in Alzheimer's disease where, if you looked across the industry and academia, the failure rate for

new compounds being tested is much higher for Alzheimer's disease than it is for, say oncology or diabetes or heart disease—not that they do not have failures as well. But what that tells me is that, to increase the likelihood of eventual success, we need to enter lots of different things into clinical testing.

There are ideas out there about other ways to approach this disease besides amyloid and tau, and we need to explore as many of them as possible.

So I guess my final answer to you about 2025 is, I think it is currently unlikely. My confidence that we would meet that goal would be a lot greater if I thought that there were a lot more things being tested in effective trials.

Senator TOOMEY. Thanks, Dr. Mohs. Dr. Carrillo?

Dr. CARRILLO. Thank you very much, Chairman Toomey. I am going to be a little bit more hopeful than my colleagues. I think that it is a very hopeful time for Alzheimer's and other dementia research. At this moment, for example, we have at least one drug that is very different from the others that we have approved today, sitting at the FDA for consideration.

I do think we have more shots on goal today than we did before in phase 2 and 3 of the FDA's rigorous process. And what happens with those drugs is really what is going to determine whether we will meet the 2025 goal.

I agree with others that investments now in biomarkers to help us identify the hallmarks of other brain changes are critical. And of course we can leave no stone unturned, and we ourselves with our Part the Cloud program are funding 65 trials, most of which are not in amyloid and tau, to look for these other approaches.

All of that is going to help us get to the end. Whether we make it by 2025 is really going to be determined by what is right now maturing in the phase 2 and phase 3 pipeline.

Thank you.

Senator TOOMEY. Thank you very much.

I want to go to Senator Stabenow now. Senator Stabenow, can you hear me?

Senator STABENOW. I can, Mr. Chairman. I apologize as I, after I voted, moved to a different office to resume the meeting. The wonderful technology is not allowing me to get in on video. But I am very appreciative of all of our witnesses and the important testimony, and the questions that you and colleagues have been asking.

So I would start with Dr. Bateman. You discussed the barriers to developing diagnostic tests in your testimony. And as I mentioned in my opening statement, I have introduced the CHANGE Act with several of our colleagues that would support, as you know, timely detection and diagnosis through using cognitive impairment tools during the Medicare annual wellness visit.

I wonder if you might discuss more how critical it is to diagnose the disease early, of course accurately, and additionally, could diagnostic tests be used to screen patients for Alzheimer's disease? And how can we support the research to really focus on that early detection, and potentially prevention at some point?

Dr. BATEMAN. I think this all goes together. And I like to point to several other areas in medicine where there is clear success in

terms of ability to muster resources and attack very difficult problems in substantial ways.

And so, for example in oncology and cancer trials, currently there are more than 12,000 active cancer trials. There are 348 actively enrolling Alzheimer's disease trials today. Why is that so different?

There are many reasons why that is different, but one of them is what you alluded to. And one issue is being able to identify the people for trials and having these people enrolled and involved in the disease process.

So for example, there are National Cancer Institute Centers where the majority of patients who are seen are diagnosed and referred to research clinical trials. And in Alzheimer's, we have the opposite problem. Most people who are diagnosed, of those who are diagnosed, are not referred to clinical trials or research trials.

And it is part and parcel of a bigger issue where the identification and the diagnosis are a challenge in the clinic, and it has been a very difficult challenge in research. Through technological advances, this is getting better because now, in addition to PET scans and spinal taps and cerebral spinal fluid tests, we have blood tests that have been developed and are being developed to implement.

So this will improve our ability to outreach to people in rural areas, a broader socioeconomic status class, across other populations, and engage more of the population in research and in trials.

In terms of what can be done, in the clinic when you see patients and families, oftentimes a specialty clinic like ours will interview and review with a patient and the family the symptoms they all see at the time. We will order a set of tests to look for further causes of the disease. We will do the cognitive testing you described, which is very important to assess the current stage of that person's cognitive performance.

But to date we have not really had available the ability to implement specific diagnostic tests of Alzheimer's disease. And if that can be accomplished, if we can bring into the clinic the ability to have specific tests of Alzheimer's pathology, this will change the way in which we manage patients; first, in the diagnosis of how we decide who has Alzheimer's and who does not, and then next, what we do in terms of treatment and management for these individuals.

And I think it is very reasonable that once people really get tested and understand with an objective test this either is or is not Alzheimer's, that will change the interest and the capacity to do many more trials.

As I tried to emphasize in my testimony, I do think the number of trials, the number of shots on goal, the number of attempts that we can make against this disease, is a direct function of how quickly we will achieve finding and implementing a highly effective treatment.

Senator STABENOW. Thank you. I know my time is running out here, but I have many questions we will follow up on. But, Dr. Carrillo, I wanted to ask, particularly as we are looking to an alternative payment model in what we want to work on next year, in your written testimony you discussed the importance of properly managing Alzheimer's and other dementias as a way to improve the quality of care and quality of life for people, and we know that

Alzheimer's is one of the costliest conditions facing seniors and families as well as, frankly, Medicare and our care system.

How will managing Alzheimer's and other dementias impact the cost of the disease?

Dr. CARRILLO. Thank you very much, Senator Stabenow, for that question. Health-care utilization is significantly higher among seniors with dementia than among seniors without. And that is an important fact that we all know.

The annual hospitalization rate is twice as high, and the use of skilled nursing facilities is nearly four times higher. And both hospital and skilled nursing facility stays are nearly four times longer.

Additionally, on average a senior living with dementia will visit the emergency room more than once a year. All that adds up. And I think one example, a clear example of the differentiation is, someone with diabetes and Alzheimer's costs Medicare 81 percent more each year than a senior who has diabetes alone without Alzheimer's.

So the total average per person for Medicare spending on seniors with Alzheimer's and other dementias is more than three times higher than seniors without Alzheimer's. Many of these costs are simply unnecessary and could be avoided if care was properly managed. Proper care for those diagnosed with dementia includes better coordination of the care, seamless navigation across the multitude of providers that older individuals have to see, and of course, finally, access to care and intervention.

This comprehensive coordination should be reimbursed accordingly. And ensuring that clinicians have the resources they need to deliver all of that is going to be critical to answering your question.

Senator STABENOW. Well, thank you. And, Mr. Chairman, I think that is such an important point, and not only about quality of care, but addressing costs in a better way as well.

So thank you very much, and thanks again to all of our witnesses today.

Senator TOOMEY. Thank you, Senator Stabenow.

I am going to ask another question, and I think we have several of my colleagues who are voting now and will be returning, so let me proceed while we await their return.

And maybe Dr. Dokholyan could take the first shot at this one. And my question is, within the community of researchers, I imagine there is a wide range of opinions and ideas, but are you aware of whether much research has been done on the possibility that the initial cause of Alzheimer's is some kind of pathogen?

Dr. DOKHOLYAN. Certainly that is a really great question. Certainly there is a lot of discussion of a sort of infectious origin. However, there is really no definitive answer yet to that.

The problem, I feel, is more—the problem is more diverse in the sense that it is multi-scale. The problem is multi-scale, because the physiology and manifestation that we see in patients happens when some proteins misbehave at a tiny little scale, on a nanometer scale.

And so, connecting the scales is creating a huge problem of generating ideas of what happens at each scale and connecting the scales between them. For example, the principal challenge in understanding pathophysiology to me is creating a cell-consistent

model of disease across the scales from molecules to cells to organs. And in many cases, our models at the molecular level do not translate to what happens at the cellular level.

A good example of it is data that the peptide does not actually like aggregating at the molecular level and physiological concentration. But for some reason, in the cellular milieu, it forms clumps. So there is a lot of disconnect between scales. And while we can guess that there may be some triggers—so there are triggers potentially—that are of foreign origin, it does not really rule out the triggers within us.

And so at this point, I feel like it is too early to tell. That is my take on it. Thank you.

Senator TOOMEY. And is there research that is underway to try to shed more light on this question?

Dr. DOKHOLYAN. There were several papers that were published last year in *Nature,* a very prestigious scientific journal, stating that there is an infectious origin that triggers production, overproduction of amyloid beta in the brain, as sort of a defense mechanism. And that trigger produces the pathological effect.

However, it is not—I do not think it is well-established knowledge yet, and I am sure people are working on it at this moment.

Senator TOOMEY. Thank you very much.

Dr. Mohs, maybe you want to take this question. My perspective as a layman is that a number of leading pharmaceutical companies, after years and many billions of dollars of research, seem to have pulled back from some of the research, especially with respect to early-stage disease drugs. And I wonder, first of all, if that is an accurate perception, if you think that is in fact what is happening? And if so, what can and should be done to increase drug manufacturer engagement in the early stages of this disease?

Dr. MOHS. Yes, thanks. I think your perception is partly true, but it is not completely true. It is a fact that several companies spent very, very large amounts of money moving molecules which looked scientifically very interesting into these large late-phase phase 3 trials that cost hundreds of millions of dollars. And, for the most part, those compounds did not show efficacy.

So I think there has been, not a leaving of the field, but I would say a retrenchment a bit, where pharmaceutical companies large and small are looking more broadly at different approaches to amyloid and tau, but also other potential approaches to the disease. And they are searching for ways to resolve some of the scientific uncertainty about these approaches with smaller studies, rather than always going to these very large, late-phase trials.

So there has been a shift, in my view, in a lot of the activity from late-phase trials, high-profile and very expensive, to lots of looking at earlier-stage molecules, smaller trials, trying to understand whether or not any of these new approaches might be valuable. And in many cases, these smaller trials are being undertaken either exclusively or in partnership with smaller biotechnology companies.

One of the problems some of those companies face, though, is that they may have more difficulty in securing funding.

So that is the way the field has changed, I think. I would like to see efforts taken to make sure that that pipeline of early-stage

compounds remains very large and very robust, because eventually some very, very effective compounds will emerge there.

And to go back to Dr. Bateman's point, one of the steps that could be taken in the clinical practice world is to implement and make widely available these diagnostic techniques so that patients who are potential participants in clinical trials could be identified much more easily than is currently the case without the use of biomarkers.

I hope that helps answer your questions.

Senator TOOMEY. Thank you. Thank you, Doctor. I see several of my colleagues have returned.

So, Senator Carper, my understanding is you were not able to ask your questions the last time I handed it off to you. So if that is okay with you, I will hand it off to you again. I will go run and vote, and I see Senator Menendez has joined us, and maybe you could recognize him when you finish, if that is okay.

Senator CARPER. Yes. This is the second of the two votes, right, that you are going to?

Senator TOOMEY. Correct.

Senator CARPER. I think this may be the last vote of the day.

Senator TOOMEY. That is my understanding.

Senator CARPER. That is good. Okay. Good enough.

Well, I tried to ask questions of the witnesses. They would not answer. They said they wanted to wait until you came back. [Laughter.] So we will go to this side. Thanks.

Senator TOOMEY. All right; thank you.

Senator CARPER [presiding]. Let me say "hi" to everybody. I am Tom Carper from Delaware. And several of the folks who spoke, and the members and the witnesses, talked about how this is a family affair—Debbie Stabenow was saying it is a family affair.

And in our own family, my mother, her sister, had dementia. My grandmother, their mother, had dementia. My great grandmother had dementia. And generally it was recognized in their late 70s, and my mom passed when she was about 83, and her sister almost the same age, maybe a year or two earlier. So this is something that we care about intensely and personally.

I appreciate very much your work and its venues, and your willingness to be with us today. I want to—I am a person who likes to work out. I was a naval flight officer, a 21-year-old naval ensign in the Navy down in Pensacola, trying to become a naval flight officer. They put us through a really rigorous physical conditioning regimen. I was 22 when I left Pensacola, heading to Southeast Asia, and I was in great shape. I said, "I am going to stay in shape as long as I can," and I have never stopped. I am 73 now, and I work out almost every day of my life.

I tell people I cannot remember what I had for breakfast, but actually I can remember what I had for breakfast. And I try to eat really healthy foods as well. And where I am going with this is, in addition to—setting aside medicines and pharmaceuticals and so forth, therapeutics—in terms of lifestyle, the amount of sleep we get, the exposure to the sun, the food that we eat, have we learned that any of this helps, or not? If somebody could tackle that, I would be most grateful. I would like to start with that.

Dr. CARRILLO. Well, I am happy to start. This is Maria Carrillo. Thank you for that question, and for all of your support.

We have actually found that much more research is pointing to the fact that there is a lot of dementia that is modifiable. And that is through changes in risk reduction, lifestyle changes like the ones that you have mentioned. I do the same thing. I try to work out as often as I possibly can in order to actually help my brain. And——

Senator CARPER. I also do it because exercise, as you know, rigorous exercise creates something called beta endorphin, that morphine-like substance that makes us feel good.

Dr. CARRILLO. And I think I feel sharper on those days because of all that is happening to benefit the brain through exercise. So it is crucial and it is important. We have seen results from the SPRINT MIND study, for example, studies funded by the National Institutes of Health that have shown us that even reducing your blood pressure to about 120, 125, has such an important benefit to the brain. And that study was so impactful in over 9,000 individuals. And that was without exercise. So imagine with exercise, nutrition, that impact could actually even be greater.

That is why the Alzheimer's Association launched the U.S. POINTER study. It is going to look at four different modifiable risk factors to see if we can translate that into a public recipe that we can recommend. And we hope to work with the bipartisan BOLD Infrastructure for Alzheimer's Act, which became law in 2018, so that we can work together to advertise, to make public that risk reduction is one of the strategies that we should all be using. And through the Public Health Centers of Excellence, and funding through State, local, and tribal health departments, we hope to work together.

As has been noted, one of the Centers of Excellence awards went to ourselves, and we are grateful for that opportunity to work with all of you. We continue to urge—AIM and the Alzheimer's Association both continue to urge all of you to fund next year's BOLD implementation act that provides the CDC the full $20 million authorized by the law in order to continue this important work. Because we have some answers now, we have to get them out to the public.

Senator CARPER. I agree. In terms of food, the diet, the kind of food that we eat and consume, is there anything there that is helpful in terms of risk reduction?

Dr. CARRILLO. Sure. I can share with you that——

Senator CARPER. Tell us chocolate is really great for risk reduction. [Laughter.]

Dr. CARRILLO. Chocolate, especially dark chocolate, has flavonoids and a lot of very good things for you, and I think it is always best—and I think my colleagues would agree—that we should eat all of those nutrients instead of taking a pill, for example, right, a nutritional supplement.

However, if we think we cannot have access to one natural supplement or another, having a pill is certainly a good thing. But there is no evidence on any specific pill or nutritional supplement or nutraceutical that is actually beneficial for Alzheimer's. However——

Senator CARPER. What about blood pressure, which can be controlled by a pill?

Dr. CARRILLO. Correct. But I am talking about nutraceuticals, vitamins——

Senator CARPER. I understand.

Dr. CARRILLO [continuing]. Blueberries, eating those kind of things. We just know that antioxidants are good for you. All that is actually encompassed in several diets——

Senator CARPER. If we are what we eat, Maria——

Dr. CARRILLO. Correct. Yes. And the diet that we are using in our study, for example, is actually the Mediterranean Diet. So there are quite a few diets that have demonstrated some benefit, and we hope that the Mediterranean Diet—which is more leafy greens, more colored fruits and vegetables like blueberries, like kale, things like that, and less of the saturated fats, and less of the bleached carbohydrates like white flours, et cetera—is going to be more beneficial. But it is also not only for your brain; we have found that there are foods that are anti-inflammatory, which we know as a Nation is such a critical part of what happens in our brain not only as we age, but with disease.

So all of this is telling us that food is so important to staying healthy with our heart, and of course with our brain.

Senator CARPER. Well, that is great. Lynn Sha, who is my legislative aide on health-care issues, is on the line with us, and she and I were talking on the phone the other day with Francis Collins, Dr. Collins, who heads up NIH, as you know, and we were getting a little bit of an update on the vaccines. You know, we have had two vaccines that have launched—one that has launched and one about to launch. And we have a couple of others in the wings—AstraZeneca in joint venture with Oxford in England, a couple with J&J as well. And what we have seen in response to COVID, I think is a collaboration that has been facilitated by NIH in large part.

But you have pharmaceutical companies which oftentimes have competed against each other, not shared information, not collaborated, and in this instance they have been encouraged to collaborate and share information. And it has been possible to take a process from the beginning to actually having the vaccine that is safe to take, and instead of taking 5 or 10 years, it has taken about a year.

What lessons, if any, can we take from this process, this collaboration in developing the vaccine, that can help us shorten the time to actually get the help we need to get pharmaceuticals for dementia?

Are there any lessons learned? I like to say, "Find out what works and do more of that." Is there anything that we can take away from our success in going from idea to launch on a vaccine?

Dr. MOHS. Yes, I think—this is Dr. Mohs—I think there are some things that we can learn. I mean, different players in this space—the pharmaceutical companies, the large companies, the small companies, the NIH, the FDA, et cetera—they all have different roles to play. And if there is somebody to facilitate communication and sharing of information among those to make sure that they are all playing their role, that just makes the process go faster

because the information goes faster to the person or the group that can act on it more quickly.

It is my understanding that also, though, there were some financial incentives that were put in place to make sure that some of the actors, or some of the participants in this—say the smaller companies that had very promising technology but maybe did not have the funds themselves internally to advance it rapidly through manufacturing and testing—that some financing was provided by the government. And I think that that helped that process go very fast, to allow even small companies that had promising technologies to move it very rapidly.

Senator CARPER. That is a good point. Anybody else on this point?

Dr. BATEMAN. Yes. I just want to second what Dr. Mohs is saying and, Senator Carper, your point about finding out what works, what has worked before, to learn from it. Because I think something like a task force that would take the strategies that were used for COVID–19, these things can—some of them can be applied, I think, to the Alzheimer's problem.

And just as Dr. Mohs said, I think there are ways for us to accelerate therapeutic drug development and bring more targets, more tests, more interventions into therapeutic trial development. The issue really is one of numbers, and trying to get enough treatments going in parallel that we increase the odds of finding highly effective treatments more quickly.

And I think the urgency that was applied to COVID–19, the coordination that was applied, and the massive amount of support and fiscal resources that were applied have, directly led to that acceleration. We have seen this in our field already with increasing the budget of the NIH, the incredible growth in scientific understanding that has happened in the past 5 years, fantastic changes that have occurred in research. But I think we can continue to push this forward in a COVID–19 urgency and make differences in Alzheimer's therapeutic trials.

Senator CARPER. That is great. Thank you.

Dr. DOKHOLYAN. Senator Carper, this is Nilolay Dokholyan. So I think one big area, again an untapped area, is industry/academia centers that would unite forces to tackle the problem. It is a cross-disciplinary problem where you have a lot of fundamental processes that require understanding, that need to be understood and translated to knowledge that can be used for drug discovery.

And as such, I think facilitating cross-disciplinary research that connects, links scales across disciplines, would really promote development of the drugs and treatments.

And NIH has already facilitated some of those kinds of translational research programs, and I know some companies have already created centers within universities. And I think incentives to create these kinds of centers that would combine efforts with representatives from both companies and academia working together, would really, I feel, facilitate the program.

Senator CARPER. All right; thanks. Thank you all.

May I ask, Nikolay, where are you from? You have a great accent. Where are you from?

Dr. DOKHOLYAN. I am originally from Georgia—the Republic of Georgia, not Atlanta. [Laughter.]

Senator CARPER. The other day I was listening—I love music, and I have a service called "Alexa," which allows you to tell your speakers, or whatever, to play music. And you would say, "Alexa, play so-and-so." And I just happened to, I do not know why—I like Ray Charles, but I have not listened to Ray Charles for a long time, and I said, "Alexa, play Ray Charles." And immediately I heard Ray Charles singing "Georgia on My Mind." And we have two runoff elections there on January the 5th. So whoever wins is in the majority in the Senate. So——

Dr. CARRILLO. Senator, you just initiated my Alexa, so she started playing. Thank you. I had to tell her to stop. [Laughter.]

Senator TOOMEY. That is the problem.

Senator Carper, were you—did you have any more questions?

Senator CARPER. I do, but I have probably more than used up my time.

Senator TOOMEY. All right, then, let me go to Senator Menendez.

Senator MENENDEZ. Well, thank you, Mr. Chairman. And let me thank all of our witnesses for being with us today and sharing your insights.

This subcommittee held an Alzheimer's disease hearing last year, and the world is obviously quite different today than it was then. We are in the midst of a global pandemic that has upended everything. But in the midst of all this, I must say that I have been amazed by the innovation that has emerged in the past 9 months from new diagnostic tools and therapies to a vaccine that was approved last week.

So if we as a Nation can innovate at such a rapid speed to defeat COVID–19, I think we can also put that energy into defeating Alzheimer's. And we have to be sure, however, that every American benefits from medical innovations. Even the most revolutionary new medicines are ultimately worthless if they do not reach the people who need them.

So I believe we have to commit to ensuring that every American benefits from advancements in Alzheimer's diagnosis and treatment. And part of that includes improving clinical trial diversity.

So let me ask Dr. Carrillo and Dr. Mohs—I have been working to engage pharmaceutical companies and other researchers to improve diversity in clinical trials.

In your written testimony, you highlighted the need for increased participation by minority communities in Alzheimer's disease trials. How are your organizations working to address this urgent need? And what role can the Federal Government play to address this need?

Dr. CARRILLO. Well, I can start, and thank you, Senator, for that question. And it is nice to hear my name pronounced correctly, actually. Thank you very much for that.

It is an important thing to study under-represented populations, so I will just speak for Latinos in particular. It is important that all my colleagues here, I think, recognize that not all Hispanic and Latin Americans can actually be painted with the same brush. We are all very different. And even recently, Dr. Hector Gonzalez at the University of California published some work from the SOL–

INCA study, of course funded by NIH, highlighting that even the most well-studied to date risk factor gene, APOE–E4, does not confer the same risks on all the populations, depending of course upon their background.

This is important. And so we need to really think about how we are going to invest in research that really highlights the importance of understanding diverse populations, especially if we are going to apply that to any kind of therapeutic or early detection diagnostics. So that is an important point.

And we at the Alzheimer's Association are actually working very closely with the NIH on something that they have published recently, and are now currently revising, called "Alzheimer's Disease and Related Dementias: Clinical Studies Recruitment Planning Guide and National Strategy for Recruitment of Participation."

Now, my organization in particular is working of course with the Federal Government, but we also have decided to put our money where our mouth is, and all clinical trials that we fund now require you, if you want our money, to ensure that you have diverse populations represented in those study populations you are recruiting.

And that is an important point. On top of that, the U.S. POINTER study is shooting for 30-percent recruitment, and the new IDEAs platform, which is going to study 7,000 people with an amyloid PET scan, is requiring 2,000 black Americans and 2,000 African Americans of those 7,000. So that is a majority.

So that is what we are trying to do in order to ensure that when we do find those diagnostics and those treatments, they are actually for everyone. Thank you for the question, and for your efforts.

Dr. MOHS. This is Dr. Mohs. Thank you for the question, and it is a pleasure to follow Dr. Carrillo and to address this.

We have not been nearly as good as we should be in getting members of minority groups to participate in clinical trials. And as a result, the conclusions that can be drawn from those trials are still uncertain as to whether or not they apply to all segments of the population.

So we need to fix this problem. The organization that I currently work with has taken two approaches. One is to try to bring members of the minority community, African Americans and Latinos, to clinical trial sites. And we have done a lot of things to try to do that, bringing in speakers who would resonate with members of minority groups, et cetera, and to some extent that has worked. It helps with engagement, but it has not always translated into enrollment in clinical trials, because interest does not necessarily lead people to want to volunteer. And there may be many reasons for that.

A second approach is, we try to take the research centers, and the research activities, to the communities where African Americans and Hispanic patients reside. And I think ultimately that is likely to be more successful. Unfortunately, right now most of the clinical research centers are not located in the communities where those patients reside. So we have tried to take some steps to encourage health systems that serve primarily African American and Hispanic patients to become involved in research, and that may produce more salutary results.

I do think that there is some value, as I mentioned in the written testimony, to ask FDA to provide clear guidance to sponsors on what they expect to see in terms of ethnic diversity in clinical trials. Because most commercial sponsors will respond to guidance from regulatory authorities. Thanks.

Senator MENENDEZ. Mr. Chairman, may I have one final question?

Senator TOOMEY. Sure.

Senator MENENDEZ. Okay; thank you.

With Latinos 1½ times more likely to develop Alzheimer's than their white counterparts, in your testimony, Dr. Mohs, you mention that we are not diagnosing enough people in the early stages of Alzheimer's, when they might still be candidates for a trial.

In lower-income communities, there remain many barriers to assessing an appropriate diagnosis of Alzheimer's, let alone an early one. What can be done to improve access for patients in underserved communities to ensure they are able to access resources and information, and be eligible for these clinical trials?

Dr. MOHS. Yes; thank you. As I also mentioned in the written testimony—and as was discussed by some of the other participants—we are making substantial progress in what I hope will be low-cost, potentially widely available blood-based and digital biomarkers that will assist in the early diagnosis, and may make it possible to make very clear diagnoses without the time-consuming and expensive and highly specialized resources that are now required to make the diagnoses earlier.

Those technologies, the blood-based simple ones, which could be very inexpensive, are advancing. I think we need additional support to do further clinical research to understand exactly how good they are, and how they should be applied in conjunction with other things in clinical practice. And there need to be some incentives, financial incentives, through insurance and health-care reimbursement systems, to make sure that clinicians are reimbursed for using those tests.

Senator MENENDEZ. Thank you, Mr. Chairman. Thank you.

Senator TOOMEY. Thank you.

Senator Young?

Senator YOUNG. Well, thank you, Mr. Chairman, for holding this important hearing.

This question is directed to all members of the panel who would like to address it. What lessons can we learn from the successful public-private partnership between the industry on the one hand, and BARDA on the other, during COVID–19? Is a similar approach needed here, given the pandemic-like scale of Alzheimer's disease?

Dr. BATEMAN. Senator Young, I might start with that. We have a public-private partnership trial platform running in Alzheimer's disease of a very special kind. It is an early-onset—it is called autism undominant, and it is caused by mutations in families that inherit these mutations, and it causes Alzheimer's disease.

And when we began that, 12 pharmaceutical companies came together in a consortium and, with support from the Alzheimer's Association, the National Institutes of Health, and our pharmaceutical partners, we launched one of the first prevention trials for Alzheimer's disease, testing more than one therapy at a time.

And in this parallel approach, we were able to accomplish things that I do not think would have been possible without that public-private partnership. And so I think, as we have said throughout this meeting, that COVID–19 offers many opportunities to look towards efficiencies and ways to get things done quickly, and this is one more way to do this.

I do believe that a public-private partnership for therapeutic development, one that focuses on preventable trials, focuses on multiple shots on goal, focuses on bringing forward a variety of therapeutic approaches, is consistent with what NAPA had outlined to be a goal of an effective treatment or a cure by 2025.

I think the other panelists here can speak to a lot on public-private partnerships, and I would be happy for them to say more about this, because it really is a promising approach that can enable things to happen that otherwise would not be possible.

Senator YOUNG. Dr. Mohs?

Dr. MOHS. Yes, I can follow on to Dr. Bateman's comments here. In the development of therapeutics, there are many players that are required. There are large pharmaceutical companies, small companies, the NIH, the FDA, et cetera, and they each have their own skill sets and things that they can do well. But the amount of drugs that come through, the treatments that eventually come through, require all of those participants to do the activities that they are good at, and do them quickly and in coordination.

One role that I understand the Federal Government has played in the development of COVID–19 vaccines and therapeutics is to provide coordination of the activities of the different actors in this ecosystem, maximizing the utilization of the skill sets that they have. So that is one role.

The second is that, where there is one of the potential participants—say a small company that has technology that could play a critical role—that may not have the financial resources to make that resource as productive as it can be, they have then stepped in, as I understand it, to provide some financial resources to allow that entity, usually a commercial entity, to maximize the use of their technologies.

So I think those are two roles that the Federal Government can play to speed up this whole process of moving potential therapies through the pipeline and to patients.

Senator YOUNG. Thank you. I am going to move on, and there may be an opportunity on the back end to add to that, if others would like to.

Dr. Dokholyan, you described how a deeper integration of the private sector with academia could provide new solutions in the drug pipelines for neurodegenerative diseases. Could you elaborate on this idea of deeper integration between academia and the private sector, and describe how private partnerships with academic institutions could be fostered?

Dr. DOKHOLYAN. Thank you for this question. Naturally, companies are driven by investors' interests and will evolve to optimize expenditures and drive discovery. But the dominant part, in this case especially, is the basic research, which is often invisible to investors. Therefore, one way to mitigate this is to move the exorbitant R&D costs of pharmaceutical companies, or of technological

companies, and to outsource them to academia more, or rather, create centers that would actually focus academic research on a particular problem of interest, in this case Alzheimer's research.

And in this case, it is not only that the companies can work together with academia, but also associations. And the Alzheimer's Association is doing a great job. But I want to bring attention—I have been working on protein misfolding diseases for a while, and I have worked on cystic fibrosis. And the Cystic Fibrosis Foundation, I think—it was really a huge breakthrough that they have developed a drug for one case of cystic fibrosis. But that was a success story to me, this deep integration of all of these moving pieces together. And what government can do is to incentivize companies to invest in academia and go forward with that.

If I may add, I think there is another thing that is missing here, which is training. The problem is that, as I mentioned, the disease is cross-scale. It is multi-scale, has multi-scale origins. And so as such, we are dealing basically with molecules, with cells, with organisms, with populations, and we have niches for science to deal with that. But we need a new breed of scientists that will be able to, while specializing in their own field, have the vision outside and see beyond.

And that is the translational research. NIH has been really behind that initiative, but I think we do need a bigger push in that direction to facilitate scientists of that thought.

So, thank you.

Senator YOUNG. Thank you, Doctor.

Dr. Mohs, in your testimony you encourage greater collaboration between FDA and CMS. How would increased FDA and CMS collaboration help patients access diagnostics or therapies sooner?

Senator TOOMEY. And if we could maybe try to sum this up quickly, because we are well over time here.

Senator YOUNG. My apologies.

Dr. MOHS. The basics are that for a commercial sponsor, somebody who is developing a product which is intended to be either a therapeutic or a diagnostic, they need to know the path for regulatory approval, which goes through the FDA. And generally the FDA is pretty good about giving guidance as to what they expect to make a thorough evaluation. But particularly in the area of diagnostics, the path to reimbursement is uncertain. And even if you may have an effective diagnostic, if it's not reimbursed, it is not going to be widely available to patients, and it is not going to be able to enable clinicians to improve patient care or to enroll patients in clinical trials.

So I think that parallel review of both the standards for regulatory approval through the FDA, and for reimbursement through CMS, would speed this process.

Senator TOOMEY. Thank you, Dr. Mohs.

Senator Warner?

Senator WARNER. Thank you, Mr. Chairman. I want to just make a quick comment first, referring back to Senator Menendez's points about health-care disparities. I know the Latino population is 1½ times more likely to develop Alzheimer's, and the African American population, two to three times more likely.

One practice we started in Virginia was a technology-based solution to get people into these trials called a "senior navigator," where we would train some—we created a Statewide site with all assistance to senior programs, Alzheimer's and otherwise related, and would go either through a church or through a senior center and usually train at least one healing front-end navigator that could then access these sites, access diagnosis, access getting into trials.

I appreciate the panel's comments about trying to make sure that we get the appropriate patient mix, with the disparate effects on minority communities.

My question—and again, let me thank the whole panel. I am sure others have their own personal stories. My mom had Alzheimer's for 11 years, 9 years of which she did not speak. My father and sister took care of her at home until the last few weeks. I could not imagine having taken on that challenge. So something I have been working on since I was Governor and throughout my time in the Senate is on advanced care planning in bipartisan legislation. I think Senator Stabenow raised this issue earlier.

I would just like to have the panel speak to this: how we can do a better job of this team-based approach for families to treat Alzheimer's-related patients who sometimes cannot make these decisions if they do not do that planning early enough with their loved ones, with their religious counselor, with an appropriate medical professional—whether it is around advanced directives and allowing those advanced directives to move easier from State to State; whether we can make sure that we have, frankly, better reimbursement for some of these types of discussions and conversations. Most families do not like to have these end-of-life discussions.

And I would just like to have the panel speak to each point individually. In this area, it has been harder to move than I would have thought, because it is clearly bipartisan. But where do you feel the state of advanced care planning stands, both legislatively and in terms of new directives?

And that will be my only question, Mr. Chairman.

[Pause.]

Senator WARNER. Panel, who wants to go first?

Dr. MOHS. Well, this is Richard Mohs. I can try to go first, and I am maybe not the most qualified person on the panel to address this, but years ago I used to see quite a number of patients, back when I worked in a hospital, and a new diagnosis of dementia is an overwhelming experience for patients and families.

They have a hard time coming to grips with it, understanding its full implications, and oftentimes the medical system, the way it is currently constituted, is not very good at helping them step through all the decisions that they are going to have to make once they get the diagnosis.

I do think on the technology side, the discussions we have been having around advances in early diagnosis, and the certainty that that can provide about what is going on with a patient, may allow patients and their families much more time to begin this process of planning and allow them to begin the process at a time before

the patient is severely impaired, so that the patient can participate in the planning process and make their wishes very well-known.

I think it would also be helpful if there could be some mechanism to institute model care plans that include things like instructions on how to do advance directives of various types that would be geared toward people of different backgrounds, different financial means, et cetera. And there probably is a role for States and the Federal Government in developing those model plans once we have earlier diagnosis being much more common in the community.

Senator WARNER. Any other panelists? I know the chairman wants to move on, but are there any other panelists who would like—I know you are more on the research side, but——

Dr. CARRILLO. Well, I will be able to—Senator, thank you very much for the question. I think that is why the Improving HOPE for Alzheimer's Act is so important, because it would more than ensure that providers have the awareness of, not only codes that they have to use, but how to use them and how then they actually help the families to maneuver and get through that complicated process.

The online navigator sounds fantastic, but the bottom line is that helping people to navigate through that advanced care planning that has to happen, through how to ensure they understand all of the different aspects of their health care that actually comes to bear on the diagnosis of dementia that they experience with their loved one, is so important. And so, in absence of a treatment, we have to actually make sure we do all we can to ensure that quality care and quality of life are actually most prominent and important for all of us. So, thank you very much.

Senator WARNER. I will cede back my time. I will just say we have made some progress on making sure the health-care provider gets some reimbursements. I do think it is critical that we do that. We will spend plenty of money on reimbursing, diagnosing, or prescribing meds. We do not have that kind of most difficult of all conversation that needs that health-care provider's input, time, and effort.

Thank you, Mr. Chairman. Thank you for holding this hearing.

Senator TOOMEY. Thank you, Senator Warner.

Senator Cassidy?

Senator CASSIDY. Hey, everybody. I apologize. I was on another conference call, so if I am asking questions that others have, I apologize.

Dr. Bateman, I will start with you. I have read that since Down syndrome children and adults have an incidence of Alzheimer's that has earlier onset, this kind of gives a model, if you will, to follow folks. And maybe it would show insights into the genetic basis of this, and interventions. And I understand there is a study doing this. Can you comment on that study? And has it given us any information which is helpful?

Dr. BATEMAN. Yes. There are actually several studies underway which are looking at Down syndrome, or trisomy 21, to better understand the risk of Alzheimer's disease in those individuals.

It is actually one of the foundations of current Alzheimer's theory and research. The discovery that people who carry this extra chromosome—and later we found out that it was a certain part of the chromosome that encodes a protein called amyloid precursor pro-

tein—is one of the pieces of evidence that amyloid can be an essential and necessary, although not sufficient, factor that leads to Alzheimer's.

The other is families that we study in our research studies of dominantly inherited Alzheimer's, these mutations that alter amyloid's processing. The animal models that have developed therapeutics that are now in clinical trials testing for amyloid have largely been built on these findings, and our current generation of treatments was built on those factors.

The Down syndrome studies are revealing other factors that we think are important in Alzheimer's disease. There were several funded through the NIH. There are funded studies in Europe and in other places that are continuing to add to the information.

I would just comment that all of this has to do with the foundation of basic science that then leads to translational research that——

Senator CASSIDY. Dr. Bateman, I need to interrupt, because I have only about 2 minutes left.

Dr. Carrillo, now clearly though, we have this genetic basis just described by Dr. Bateman, but there are also these risk factors that have a dominant role.

Now we read about PET scans showing somebody has amyloid—I am told there are studies out there that, if somebody has a PET scan showing that they have amyloid deposition, there is a high frequency of adjustments to their medical regimen within 90 days of that discovery.

So it is a duality, right? It is the amyloid, and it is the lifestyle. Is anything being done, for example, in MA plans that would reward them to attempt to make an early diagnosis of Alzheimer's? Or are there any projects that you know of that would, on a clinical scale, implement this screening for amyloid to allow this adjustment of lifestyle factors? You can probably phrase the question better than I, but I think you know what I am going after.

Dr. CARRILLO. That is a great question. We do have the IDEAs Study that has demonstrated that there is a definite change to patient care within 90 days of having a positive PET scan. And that can go both ways. You can test negative, so you have some other type of dementia, or you can test positive and you will definitely have Alzheimer's, so let us see what we can do about it and treat it properly.

But you are talking about risk factors, and we are currently launching the U.S. POINTER study that includes imaging. So the U.S. POINTER study is paid for and led by the Alzheimer's Association and academic sites across the country. It combines four modifiable risk factors, and we will try to slow cognitive decline in the aging at-risk population.

Thanks to the NIH and additional dollars at the National Institute on Aging, we are adding imaging, amyloid and tau, to see if we can correlate changes in our behavior, changes for reducing our risks, with those changes that are the hallmarks of——

Senator CASSIDY. Let me ask you. At some point, end organ damage has been done, and so modifiable risk factors then become less capable of modifying the end organ. So do we know if there is an age at which we really—you know, there is going to be some trade-

off, right? Somebody with clear clinical Alzheimer's will have a positive PET scan that does not help us.

We want to move back, probably before Medicare age. So please comment on that.

Dr. CARRILLO. Correct. And that is why these individuals are 60 and over, and at risk. They do not have dementia currently. So we are trying to see if we can modify things and measure those early markers, to measure amyloid and tau earlier, before you have dementia. So if you can actually modify those things, can you stop that cell death, that nerve degeneration that actually is the start of the cognitive decline?

Senator CASSIDY. And so that is the whole—let me ask you one more thing, because I am out of time. To what degree could you move that earlier than 60? Because intuitively, if you find somebody at risk at age 50, you have more time to do the lifestyle modification, et cetera.

Dr. CARRILLO. You absolutely can, and there are some studies that are actually going on that are going much earlier, at 45. Certainly Randy Bateman's with the Down inherited are going even earlier. We start at 60 because we want, at least in 5 years, a glimmer of hope of seeing a change. So that is why we are starting at 60. But absolutely, yes.

Senator CASSIDY. Okay; I am over time. I yield back. Thank you, Mr. Chairman.

Senator TOOMEY. Thank you, Senator Cassidy.

Senator Cantwell, you are recognized for 5 minutes.

Senator CANTWELL. Thank you, Mr. Chairman. Can you hear me?

Senator TOOMEY. Yes.

Senator CANTWELL. Thank you so much for holding this important hearing. And thank you so much for yours and Senator Stabenow's work in this area.

I wanted to ask Maria Carrillo about the Allen Institute work on brain science as it relates to Alzheimer's, and what you think we have learned from that information thus far, and what additionally do you think we should be doing to follow up with that research?

Dr. CARRILLO. Thank you for the question, Senator Cantwell. The Allen Institute—and we have visited and actually collaborated with them as well—is a fantastic institute that creates tools for basic scientists on the importance of really understanding, really the miraculous brain at the animal level, and I think they are venturing also now into human brains.

And that is such an important thing because, as you have already heard through earlier testimony, so many of the underlying causes of brain dysfunction are unknown. But you know, even more so sometimes we do not even understand how the brain does the miraculous things it actually does when it works. So that is why it is so important to have this type of work continue.

Now the only suggestion I would have is that it is important for what they are doing at the Allen Institute to then penetrate into additional human work in clinical trials. And that means working with industry and making sure that those scientists understand what is happening there; continuing to work with us and other government groups to get that word out.

But that is a very important institute for the science.

Senator CANTWELL. Well, I think the thing that I am interested in—and obviously, I appreciate the chairman mentioning it in his opening statement—about the goal of finding a cure, I think was the word he used, is the timeline that was set out.

I think we have to ask ourselves an important question: how many Americans are truly affected by this? And how many more in the bow waves of baby boomers reaching retirement are going to be affected by this? And what is that exponential cost?

And I think the Allen Institute, when they distinguish markers, brain markers that might be indicators, the question becomes, what kind of testing, what kind of analysis could we do that would apply that to the broader public?

I think we are seeing a bow wave of costs coming at the Federal Government on this issue. I have hope that the chair is right, and we will meet that goal and timeline, but I am telling you that we really need to analyze these numbers. And I think we are going to see how important it is for us to really get even more specific about our goals, our accomplishments, and how to continue to zero in on this, because I just think that it is impacting way more people than people realize.

Thank you, Mr. Chairman.

Senator TOOMEY. Thank you, Senator Cantwell. And I think that covers all of the Senators who have attended this hearing.

Senator Stabenow, did you have a comment you wanted to make here at the close?

Senator STABENOW. Well, thank you, Mr. Chairman. I did. Once again, I am sorry for the technology of losing the video here where I am, but I have listened to all of the testimony and the questions, the very thoughtful questions.

And to follow on Senator Cantwell, there is no question that we know right now 1 out of every 5 Medicare dollars is connected to Alzheimer's. And that is only going to go up. So I appreciate all the thoughts from the discussion on therapeutics and diagnostics.

I would just emphasize again the importance of supporting families and caregiver planning, and having SAMHSA really implement a strong education outreach campaign to ensure providers are aware of the new reimbursement for caregiver planning sessions—and that families are as well—and that ultimately we develop some alternative payment models that really focus on managing Alzheimer's and quality of care and so on as we reach for the cure, which is what we all want.

So thank you, Mr. Chairman.

Senator TOOMEY. Thank you, Senator Stabenow. And I really want to sincerely thank each and every one of our witnesses today. Your testimony was really very, very interesting, and informative, and helpful. As we strive for a cure, or an effective therapy by 2025, I think it is clear—and was made clear during our conversation today—that the Federal Government, the scientific community, and the private sector all need to work together to gain a better understanding of this disease, and further reduce the barriers that remain to the research and the development that we have discussed here today.

Please be advised that members will have 2 weeks to submit written questions that can be answered later in writing. Those questions and your answers will be made part of the formal hearing record.

And with that, this subcommittee stands adjourned. Thank you.

[Whereupon, at 4:26 p.m., the hearing was concluded.]

APPENDIX

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

PREPARED STATEMENT OF RANDALL J. BATEMAN, M.D., CHARLES F. AND JOANNE KNIGHT DISTINGUISHED PROFESSOR OF NEUROLOGY; AND DIRECTOR, DOMINANTLY INHERITED ALZHEIMER'S NETWORK (DIAN), DIAN TRIALS UNIT (DIAN–TU), WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Chairman Toomey and Ranking Member Stabenow, members of the committee, I want to thank you for the opportunity speak today on the important topic of Alzheimer's disease and advances in medical diagnosis and treatment. Alzheimer's disease is one of the greatest medical challenges facing patients, families, the medical community, and society due to its immense personal and financial impact. We must stop this disease as outlined in the National Alzheimer's Project Act. Recent advancements in our understanding of the disease, our ability to detect, track, and diagnose the disease in research and the clinic, and drug development which can stop and reverse some of Alzheimer's disease pathologies hold promise to meet our shared goal of ending Alzheimer's disease. This is due in large part to the Senate's support of the NIH and long-term investments in research and training talented investigators.

We have come a long way in our understanding of the disease, our ability to detect, track, and diagnose Alzheimer's in research and the clinic, and development of drugs which can stop and reverse some of Alzheimer's disease pathologies. We have specific tests that can identify the two key pathologies of Alzheimer's, amyloid plaques and tau tangles, in brain scans, cerebrospinal fluid, and now in the blood. Treatments targeting amyloid plaques can remove these plaques to undetectable levels, something that wasn't possible just a few years ago. We are learning from clinical trials how to dose these medications more effectively and who are likely to benefit from them. Based on recent trials, we think patients early in the disease process when they have Alzheimer's disease pathology but don't yet show clinical symptoms, may benefit the most from a preventive approach to targeting the disease. The first generation of Alzheimer's prevention trials have been launched, and initial results show that we are getting closer to maximizing drug effects and approaching the goal of delaying and ultimately stopping the onset of Alzheimer's disease. A potential strategy to achieve this in the general population is using highly sensitive and accurate measures of the disease, for example blood tests, to first identify those who have Alzheimer's disease pathology and are at high risk of progressing to dementia. We would then treat these individuals with drugs to halt and reverse the Alzheimer's process in the brain before significant and irreversible brain damage occurs. The tools are now at hand to implement this strategy in large-scale prevention trials.

However, there are clear barriers to developments in the diagnostic, therapeutic, and research pipelines for Alzheimer's disease, and new Federal strategies could enable breakthroughs in the disease's diagnosis and treatment, similar to what has been accomplished for diagnostics and vaccines for the COVID–19 pandemic. Summarized below are some of the ongoing challenges, and the associated opportunities that could greatly accelerate the discovery and validation of Alzheimer's disease treatments and preventions:

(1) Barriers to therapeutic development
   a. Regulatory burden, risk-averse trial designs, and sometimes lack of urgency and not accounting for the costs of inaction lead to clinical trial delays and higher overall costs. Because Alzheimer's progresses over

years until dependence on others for care and eventually death, Alzheimer's disease trials are long. Extensive international regulatory reporting requirements and approval delays cause major trials to cost several hundred million dollars and take 3 to 5 years to complete, while prevention trials are even longer (about 7 years). These trials are too expensive and too long, causing potential treatments to be "left on the shelf" untested, and some drug developers to abandon Alzheimer's drug development programs. In order to implement large scale global trials, the field needs to move quickly and test more drugs in parallel, creating more "shots on goal."

b. If regulations could be made more facile and appropriate incentives made (for example, incentivizing and enabling faster trials similar to COVID–19 treatment development), then accelerated development would occur and lead to faster treatment development. This is an urgent issue—there is a tsunami of at-risk people (estimated at 5 million in the U.S.) who could be spared Alzheimer's disease—if we can develop treatments and preventions in time.

c. How can this be helped? Policy-makers and agencies can enable and support standards which: (1) account for the personal and financial cost of Alzheimer's disease in terms of the opportunity costs of delays into decision making (*i.e.,* a balanced risk-benefit analysis accounting for time lost on deliberations); (2) enable science and medicine to advance at optimal speed, accounting for potential benefit while managing risk; and (3) encourage investment in the development of treatments and preventions for Alzheimer's disease.

(2) Diagnostics

a. Highly accurate diagnostic measures of Alzheimer's disease amyloid plaques and tau tangles have been available for a number of years, and more recently, simple blood tests have been developed, but they are not used in clinics yet for several reasons, including lack of payer support. Symptomatic patients and their doctors have a need to know an accurate diagnosis. These tests can accurately identify who has Alzheimer's disease, and importantly, who does *not* have Alzheimer's disease. Because about 50 percent of Alzheimer's disease is not accurately diagnosed through a clinical assessment alone, testing for pathology would provide specific and accurate treatment to those with Alzheimer's, while informing the physician to investigate other causes if problems with memory and thinking are not due to Alzheimer's disease. Because some of the causes (*e.g.,* depression, medication side effects, thyroid disorders, etc.) are treatable or reversible, it is important to have an accurate diagnosis. We must identify the disease in order to treat and manage it.

b. For research purposes, measurable indicators of Alzheimer's disease pathology (biomarkers), such as blood and cerebrospinal fluid amyloid and tau, offer immense promise. These biomarkers are being used to screen for the disease, track the effects of treatments on Alzheimer's disease biological processes, and are also being considered for surrogate biomarker development, which would greatly speed Alzheimer's disease trials.

c. When preventions are developed, screening biomarkers will be essential to identify those on the Alzheimer's path to appropriately treat those with high risk.

PREPARED STATEMENT OF MARIA CARRILLO, PH.D.,
CHIEF SCIENCE OFFICER, ALZHEIMER'S ASSOCIATION

Chairman Toomey, Ranking Member Stabenow, and members of the committee, my name is Maria Carrillo, and I serve as the chief science officer of the Alzheimer's Association. Thank you for holding this important hearing today and for the opportunity to testify on the Alzheimer's and other dementia therapeutic and diagnostic pipelines, and on the Federal policies that will help address barriers to foster much-needed breakthroughs in diagnosis and treatment.

Founded in 1980, the Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support, and research. The Alzheimer's Association is the nonprofit with the highest impact in Alzheimer's research worldwide

and is committed to accelerating research toward methods of treatment, prevention, and, ultimately, a cure. The Alzheimer's Impact Movement (AIM) is the advocacy arm of the Alzheimer's Association, working in strategic partnership to make Alzheimer's a national priority. Together, the Alzheimer's Association and AIM advocate for policies to fight Alzheimer's, including increased investment in research, improved care and support, and development of approaches to reduce the risk of all dementia.

Alzheimer's is a progressive brain disorder that damages and eventually destroys brain cells, leading to a loss of memory, thinking, and other brain functions. Ultimately, Alzheimer's is fatal. We have yet to celebrate the first survivor of this devastating disease.

In addition to the suffering caused by the disease, Alzheimer's is also an enormous strain on the health-care system, on families including my own, and Federal and State budgets. Alzheimer's was projected to be the most expensive disease in America in 2020, with costs set to skyrocket at unprecedented rates. While there are over 5 million Americans currently living with the disease, without significant action, nearly 14 million Americans will have Alzheimer's by 2050. In 2020, Alzheimer's and other dementia will cost the Nation $305 billion, including $206 billion in Medicare and Medicaid payments. Unless a treatment to slow, stop, or prevent the disease is developed, in 2050, Alzheimer's is projected to cost more than $1.1 trillion (in 2020 dollars).

BARRIERS TO PIPELINES

Medical Research

We have seen great scientific progress with the historic funding increases Congress has made in Alzheimer's and related dementia research at the National Institutes of Health (NIH). In fact, since Congress passed the National Alzheimer's Project Act (NAPA) 10 years ago, Alzheimer's NIH research funding has increased more than sixfold. This investment has been critical to progress toward the primary research goal to effectively treat and prevent Alzheimer's by 2025, including advances into new biomarkers to detect the disease.

Biomarkers offer the most promising paths because they can detect the earliest brain changes. The Food and Drug Administration (FDA) has approved positron emission tomography (PET) scans to identify the hallmark amyloid plaques and tau tangles in the brain and is currently reviewing an application for cerebrospinal fluid (CSF). We are also closer to a blood test for Alzheimer's than ever before: breakthrough research presented at the Alzheimer's Association International Conference (AAIC) 2020—the largest convening of dementia scientists in the world—this past July found that specific markers in the blood may be able to detect changes in the brain 20 years before Alzheimer's symptoms occur. These biomarkers will be new diagnostic tools in the toolbox for primary care doctors and specialists to assist in the early and more accurate diagnosis of Alzheimer's. In addition to these great advances, there is a drug under review at FDA, for the first time, that may treat the underlying biology of the disease.

However, even with these great strides, there is still much left to be done. Investment in Alzheimer's research is still only a fraction of what's been applied over time to address other major diseases. Between 2000 and 2017, the number of people dying from Alzheimer's increased by 145 percent while deaths from other major diseases have decreased significantly or remained approximately the same.

Alzheimer's is one of the most complex challenges science and medicine has ever faced. The reality is that we don't yet know as much as we would like to about the underlying causes of Alzheimer's, compared to some other major diseases. It is a heterogeneous disease, marked by the accumulation of beta-amyloid plaques and tau tangles in the brain, and neurodegeneration. We are still learning about other brain changes such as inflammation, changes in the way our brain cells process energy and nutrients, the role of the immune system and how our brain cells communicate. This heterogeneity underscores the need for diversification of research targets. Funding diverse avenues of investigation and understanding the causes of the disease will ultimately enable us to discover effective Alzheimer's diagnostics and treatments.

It is critical to note that while the field of Alzheimer's biomedical research has made great gains over the years in understanding the brain changes associated with the disease and how the disease progresses, much of the research to date has not included sufficient numbers of blacks/African Americans, Hispanics/Latinos, Asian

Americans/Pacific Islanders, and Native Americans to be representative of the U.S. population. Studies indicate that older blacks/African Americans are about twice as likely to have Alzheimer's or other dementia as older whites. Some studies indicate older Hispanics/Latinos are about one and one-half times as likely to have Alzheimer's or other dementia as older whites. However, Hispanics/Latinos comprise a very diverse group in terms of cultural history, genetic ancestry and health profiles, and there is evidence that prevalence may differ from one specific Hispanic/Latino ethnic group to another, for example Mexican Americans like myself, compared with Caribbean Americans. Moreover, because blacks/African Americans and Hispanics/Latinos are at increased risk for Alzheimer's, the underrepresentation of these populations not only hinders the ability of researchers to understand these health disparities, it also restricts their knowledge of how an approved therapy or diagnostic may affect the population most likely to need the drug.

Current and future Alzheimer's research must include greater numbers of underrepresented populations in clinical trials, observational studies, and other investigations to ensure everyone benefits from advances in Alzheimer's science. In order to increase the recruitment and retention of these populations, researchers must understand how to foster and maintain partnerships with trusted community-based organizations, ensure that members of their research team reflect underrepresented groups, and budget adequately for recruitment and retention efforts. These strategies are outlined in the National Institute on Aging's *Alzheimer's Disease and Related Dementias Clinical Studies Recruitment Planning Guide and National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research.* Congress should prioritize policies that will help apply these strategies, and others, to increase the participation of underrepresented populations in Alzheimer's clinical trials. The Alzheimer's Association and AIM look forward to working with the committee and other congressional members to accomplish this.

It is crucial that we continue to increase investment in research in order to maximize every opportunity for success. This will enable us to learn all of the ways Alzheimer's affects the brain, develop better diagnostics, and discover effective treatments for the disease. The Alzheimer's Association and AIM urge Congress to finalize an additional $354 million for NIH Alzheimer's funding in fiscal year (FY) 2021, which was included in the recent Senate draft. We cannot afford to leave any stone unturned. With every study, we are illuminating the biology of Alzheimer's and finding another piece of the Alzheimer's research puzzle.

Coverage of Diagnostics

With all of the scientific progress researchers are making in the field of Alzheimer's biomarkers, we need to ensure there is access to these diagnostic tests. Coverage for diagnostics would help spur private-sector engagement on both diagnostics and therapeutics.

Diagnostic testing with a validated biomarker for Alzheimer's is critical. Even in the absence of a treatment, early and accurate diagnoses allow individuals to plan, participate in clinical trials, and express preferences to friends and family. The Alzheimer's Association has worked with the Centers for Medicare and Medicaid Services (CMS) since 2013 to explore coverage of amyloid PET scans, resulting in the IDEAS Study, of which I am a co-chair. The IDEAS Study seeks to gather evidence to support reimbursement by Medicare and third party payers to determine if amyloid PET scans can help clinicians accurately diagnose the cause of cognitive impairment, provide the most appropriate treatments and recommendations, and improve health outcomes. Building on what we have learned from IDEAS, we are now partnering with CMS to launch New IDEAS, which will study the impact of amyloid PET scans on more diverse and historically underrepresented populations.

The IDEAS Study demonstrated amyloid PET scans changed medical management in nearly two-thirds of cases, demonstrating that PET imaging can be a powerful tool to improve the accuracy of the causes of cognitive impairment, including Alzheimer's diagnosis, and lead to better medical management, especially in difficult-to-diagnose cases. If a treatment that addresses the underlying biology of the disease were to become available, accurate diagnostic testing would be a crucial first step in determining appropriate access to the drug. Additionally, the increasing availability of therapeutics in the coming years will also raise the awareness of Alzheimer's and other dementia and drive the public's desire for assessment. Our health care system, including the FDA and CMS, must be prepared to evaluate and provide coverage of these assessment and diagnostic services.

Clinical Practice Guidelines

Despite more than 2 decades of advances in diagnostic criteria and technology, symptoms of Alzheimer's disease and other dementia too often go unrecognized or are misattributed. This causes delays in accurate diagnoses and appropriate care that are harmful and costly. There currently are no consensus Alzheimer's diagnostic recommendations for primary care physicians. Guidelines were created some years ago but were only developed for neurologists.

As reported at AAIC 2018, a work group convened by the Alzheimer's Association under leadership by Dr. Bradford Dickerson, Dr. Alizzera Atri, and I developed 20 recommendations for physicians and nurse practitioners to provide practical and specific U.S. guidelines that are relevant to both primary and specialty settings. The recommendations range from enhancing efforts to recognize symptoms to compassionately communicating to individuals and their caregivers. They can then guide U.S. health-care practitioners in the evaluation of individuals for memory, thinking, communication and personality changes, and symptoms of cognitive impairment, Alzheimer's or another dementia. There are several benefits of early and accurate diagnosis including participation in clinical trials which allows individuals to enroll in clinical trials that advance research and may provide medical benefits.

The Alzheimer's Association looks forward to working with physician groups and medical societies to encourage primary care doctors, dementia experts, and nurse practitioners to adopt the new guidelines.

Risk Reduction

As the scientific field continues to search for a way to cure, treat, or slow the progression of Alzheimer's, it is crucial that we also focus on reducing the risk of developing the disease in the first place. Researchers are increasingly studying the impact that lifestyle behaviors may have on the risk of developing Alzheimer's and other dementia. The future of reducing Alzheimer's could be in treating the whole person with a combination of drugs and modifiable risk factor interventions, as we do now with heart disease.

The Alzheimer's Association is leading a 2-year clinical trial to evaluate whether lifestyle interventions that simultaneously target multiple risk factors can protect cognitive function in older adults at increased risk for cognitive decline. The U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) is the first such study to be conducted in a large group of Americans and will enroll approximately 2,000 older adults, with a particular focus on enrolling under-represented populations. The study will evaluate the effects of lifestyle interventions, like physical exercise, a healthier diet, cognitive and social stimulation, and self-management of heart and vascular health, on changes in cognitive function. Vascular and metabolic health, physical function, mood, and quality of life will also be assessed, and we look forward to sharing the study results in 2023. Leveraging the Alzheimer's Association investment in U.S. POINTER, NIH funding has enabled several important ancillary studies to look deeper into the science of the main study. There is a neuroimaging ancillary study, which is the first large-scale investigation of how lifestyle interventions affect biological changes in the brain associated with Alzheimer's and dementia. There is a sleep ancillary study to examine whether changes in sleep predict changes in overall cognitive function or in specific areas, such as memory. And researchers from the Alzheimer's Gut Microbiome Project will examine the effects of dietary interventions on microbiome composition and function in samples collected from three clinical trials, including U.S. POINTER, to understand how variations in the gut microbiome relate to cognitive decline and other Alzheimer's-relevant outcomes.

We are already seeing promising advances in risk reduction research. Last year, the *Journal of the American Medical Association (JAMA)* published the groundbreaking results of the SPRINT MIND study, the first randomized clinical trial to demonstrate that intensive medical treatment to reduce blood pressure can significantly reduce risk of mild cognitive impairment (MCI). The study found a statistically significant 19-percent reduction in risk of MCI, which is important because everyone that develops dementia passes through MCI. Preventing new cases of MCI therefore prevents new cases of dementia. NIH just announced additional funding to build upon this initial finding and further explore the effects of lowering systolic blood pressure.

It is crucial that significant research findings like SPRINT MIND are translated into effective public health interventions across the country. In 2018, Congress passed the BOLD Infrastructure for Alzheimer's Act (Pub. L. 115–406), which would

do just that, by investing in a robust Alzheimer's public health infrastructure across the country. This infrastructure includes Alzheimer's and Related Dementias Public Health Centers of Excellence and funding to State, local, and tribal public health departments. Congress appropriated $10 million for the first year of BOLD's implementation in FY 2020, which allowed the Centers for Disease Control and Prevention (CDC) to award funding to three Public Health Centers of Excellence and 16 public health departments across the country this fall. Importantly, one of those Centers of Excellence is focused entirely on risk reduction, and the Alzheimer's Association is grateful for the opportunity to lead this center. While this is a meaningful step forward, CDC must receive the full $20 million authorized for BOLD's second year of implementation in FY 2021 to ensure the full and necessary impact that Congress intended.

FEDERAL POLICIES FOR BREAKTHROUGHS

Care Planning

One barrier to the increasing availability of therapeutics in the future is the under-diagnosing of Alzheimer's and other dementia. When diagnoses are made, they are too often undisclosed by clinicians. Without detection and diagnosis, people living with dementia cannot get the help they need and may not be able to access therapeutics in a timely manner when available. Education of clinicians and individuals features prominently in the *National Plan to Address Alzheimer's Disease.*

Since January 1, 2017, Medicare has reimbursed physicians and other health-care professionals for providing comprehensive care planning to individuals with cognitive impairment—a critical step in improving the quality of care and quality of life for those with Alzheimer's and their caregivers. A care planning visit includes an evaluation of cognition and function, measuring neuropsychiatric symptoms, a safety evaluation, identifying and assessing a primary caregiver, development of advance care directives, and referrals to community services.

The bottom line is that care planning helps ensure those with Alzheimer's get on the right care path. Analyses show dementia-specific care planning can lead to fewer hospitalizations, fewer emergency room visits, and better medication management. It allows diagnosed individuals and their caregivers to access medical and nonmedical treatments, clinical trials, and support services available in the community. Alzheimer's and related dementia also complicate the management of other chronic conditions, so care planning is key to better care coordination and management of comorbid conditions. The availability of the care planning code, CPT® code 99483, is an important step in that direction.

The Alzheimer's Association and AIM contracted with the Health Care Cost Institute to analyze the use of the care planning benefit among Medicare fee-for-service (FFS) beneficiaries and among those in some Medicare Advantage (MA) plans. Unfortunately, the results illustrate that very few Medicare beneficiaries received care planning in 2017, the first year it was available. Specifically:

- 18,669 FFS Medicare beneficiaries received care planning, a rate of 55.6 per 100,000 beneficiaries.
- 2,857 individuals in the Medicare Advantage plans that were analyzed received the services, a rate of 39.4 per 100,000 beneficiaries.
- In seven States and Washington, DC, not a single FFS Medicare beneficiary received care planning services.

In short, fewer than 1 percent of those living with Alzheimer's and other dementia received care planning in 2017.

For the benefits of care planning to reach more Americans affected by Alzheimer's, more clinicians must use the care planning benefit. Introduced by Senator Stabenow, the bipartisan Improving HOPE for Alzheimer's Act (S. 880/H.R. 1873), would help achieve that goal by requiring the Department of Health and Human Services to (1) educate clinicians on the existence and importance of Medicare's care planning benefit; and (2) report to Congress on the barriers to individuals receiving care planning services and how to increase their use. This bill has already garnered significant bipartisan support in both chambers.

Robust care planning is the first step to learning about long-term care options and selecting the preferred, most appropriate services for persons with dementia, families, and caregivers. Because persons living with Alzheimer's and other dementia often use a variety of supports over the course of the disease and because many—if not most—people need help coordinating those services, a care plan can help these individuals sort through options and choose the long-term services and supports

that can contribute the most to the quality of their life. The Alzheimer's Association and AIM urge Congress to pass this critical, bipartisan legislation which garnered support from over half of Congress in its 20 months since introduction, to support individuals living with Alzheimer's and other dementia, and their families, while they await treatment options.

IMPROVEMENTS TO HEALTH-CARE PROGRAMS FOR CARE COORDINATION, DIAGNOSIS, AND TREATMENT

Alternative Payment Model

In a recent letter from Chairman Toomey and Ranking Member Stabenow to Department of Health and Human Services Secretary Alex Azar, recommendations were offered on how to strengthen care and services for persons living with dementia as well as foster innovation in Alzheimer's and dementia research. We support the recommendation to the Center for Medicare and Medicaid Innovation (CMMI) to create and test alternative payment and coordinated care models targeted toward Medicare and/or Medicaid beneficiaries with Alzheimer's and other dementia.

A person with dementia is 4.4 times more likely to have six or more other chronic conditions as someone without dementia. Managing these chronic conditions is impeded by an individual's cognitive impairment. As a consequence, health-care utilization is significantly higher among seniors with dementia than among seniors without dementia. The annual hospitalization rate is twice as high; the use of skilled nursing facilities is nearly four times higher; and hospital/skilled nursing facility stays are nearly four times longer. In addition, on average, a senior with dementia will visit the emergency room more than once each year.

Many of these costs are simply unnecessary and could be avoided if care was properly managed including better coordination of care, seamless navigation across the multitude of providers, and timely access to care and interventions. There are proven ways to improve the quality of care and quality of life—and reduce Medicare spending—if the payment barriers standing in the way are broken down. Much of the discussion surrounding Alzheimer's disease has focused, importantly, on the need for biomedical research to find means to prevent it and treatments. It is important to not forget that millions of people living with Alzheimer's and other dementia need better care.

CONCLUSION

It is imperative that Congress and the private sector continue to invest in research as we work—together—toward the primary research goal to effectively treat and prevent Alzheimer's by 2025. In the absence of a treatment that would change the underlying course of the disease, we must do all we can to ensure the best quality of care and quality of life for those living with Alzheimer's and the people who care for them. We look forward to working with the committee to advance bipartisan solutions that will have a meaningful impact on people living with Alzheimer's and other dementia, including passage of the Improving HOPE for Alzheimer's Act. Thank you for your continued leadership on investment in NIH funding for Alzheimer's disease and other dementia, and improving care, supports, and services for those living with Alzheimer's and their caregivers, and we appreciate the opportunity to be a resource to the committee.

QUESTIONS SUBMITTED FOR THE RECORD TO MARIA CARRILLO, PH.D.

QUESTIONS SUBMITTED BY HON. DEBBIE STABENOW

Question. We know that patients with dementia have been particularly suffering during the pandemic due to social isolation and the tragically rampant spread of the virus through many long-term care facilities.

Could you discuss how you see the pandemic affecting dementia and Alzheimer's patients and caregivers long-term, and how caregivers are likely to be impacted?

Answer. Over 136,000 residents and employees of nursing homes and long-term care facilities have died from COVID–19 representing 36 percent of the total death toll in the United States. These communities are on the front lines of the COVID–19 crisis, where 48 percent of nursing home residents are living with dementia, and 42 percent of residents in residential care facilities have Alzheimer's or another dementia. Residents with dementia are particularly susceptible to COVID–19 due to their typical age, their significantly increased likelihood of coexisting chronic condi-

tions, and the community nature of long-term care settings. Across the country these facilities, their staff, and their residents are experiencing a crisis due to a lack of transparency, an inability to access the necessary testing, inaccurate reporting, and more. The Alzheimer's Association and ATM released policy recommendations aimed at improving the State and Federal response to COVID–19 in long-term care settings. We continue to advocate for dedicated funding for daily, rapid-response testing in these settings; immediate and accurate reporting; adequate personal protective equipment; surge activation like strike teams when needed; and televisitation to combat the devastating effects of social isolation. The Association has also released COVID–19 Tips for Dementia Caregivers to help the 16 million people across the country caring for a loved one with Alzheimer's navigate the stress, risks, and additional safety precautions needed during the pandemic.

Question. Are there specific questions related to the pandemic that should be researched to better understand how the virus may have affected dementia and Alzheimer's patients now and in the future?

Answer. There is a clear connection between COVID–19 and brain dysfunction. Many people have reported loss of smell and taste and "brain fog." The damage done by the pandemic will not be limited to the acute effects, but will have long-term health consequences that may impact many individuals' quality of life and independence. We need to better understand the potential damaging effects of SARS–CoV–2 on the brain, memory, and behavior. The Alzheimer's Association and representatives from more than 30 countries have formed an international consortium to study the short and long-term consequences of COVID–19 on the brain and nervous system in people at different ages, and from different genetic backgrounds. This includes the underlying biology that may contribute to higher risk of Alzheimer's and other dementia, as well as how COVID–19 may increase the severity, pace, and progression of diseases such as Alzheimer's, and psychiatric diseases including depression.

Question. You discussed the need for care planning and the importance of Medicare coverage of the service. As I mentioned earlier, my Improving HOPE for Alzheimer's Act would require CMS to create and implement an education outreach campaign to ensure providers are not only aware of the code, but also know how to use it.

How will the increased use of the care planning code reduce costs to Medicare?

Answer. Senator Stabenow, thank you for your work on the Improving HOPE for Alzheimer's Act and ensuring its inclusion in the Consolidated Appropriations Act of 2021. The Alzheimer's Association and AIM greatly appreciate your continued leadership on issues important to people living Alzheimer's and other dementia, and their families.

For individuals living with Alzheimer's and their caregivers, care planning is essential to learning about medical and non-medical treatments, clinical trials, and support services available in their communities. Alzheimer's and related dementias complicate the management of chronic conditions. Access to these services help to manage these other conditions and result in a higher quality of life. Analyses show getting on the right care path reduces costs to Medicare as a result of fewer emergency department visits, fewer hospitalizations, and better medication management.

PREPARED STATEMENT OF NIKOLAY DOKHOLYAN, PH.D., M.S., G. THOMAS PASSANANTI PROFESSOR AND VICE CHAIR FOR RESEARCH, PENNSYLVANIA STATE COLLEGE OF MEDICINE

Thank you, Senators Toomey and Stabenow, for your invitation to talk to the Senate Committee on Finance Subcommittee on Health Care about the emerging crisis in health care due to Alzheimer's disease. I am a scientist whose research is focused on fundamental and translational research in neurodegenerative diseases at the Penn State University College of Medicine. I have studied neurodegenerative disorders for over 20 years, focusing on the fundamental processes that lead to the pathological behavior of proteins in human diseases. Besides a scientific desire to understand the processes leading to neuronal degeneration, like many Americans, I have family members who have suffered from Alzheimer's disease, so I know well the emotional as well as financial toll it takes on families.

The burden that the lack of effective therapies and accessible diagnostics exerts on public health-care programs like Medicare and Medicaid. This includes the fiscal

burden stemming from the high costs of care for Alzheimer's patients, as well as the unstoppable erosion of beneficiaries' health as a result of the disease.

Alzheimer's disease is a progressive, irreversible, and degenerative brain disease. Patients with Alzheimer's disease suffer a range of symptoms including memory loss, dementia, confusion, aggression, and, especially at the later stages, require significant attention from caregivers. Currently, close to 8 million Americans are living with diagnosed Alzheimer's disease;[1] this number is likely a significant underestimate due to the lack of early diagnostic tools or access to healthcare,[2] causing many individuals in the early stages of disease to remain undiagnosed. Currently, one in 10 people older than 65 suffer from Alzheimer's disease,[1] and one in three adults will be diagnosed with the disease by age 85. Women are almost twice as likely as men to develop Alzheimer's disease, even after accounting for their longer lifespan.[3, 4]

Among many genetic and epigenetic risk factors, age is perhaps the most critical one. As the U.S. population ages, the number of Americans with Alzheimer's disease is projected to double1 by 2050. Today, we diagnose a new case roughly every minute; by 2050, we will be diagnosing a new case every 30 seconds. Alzheimer's disease is the sixth leading cause of death, and the fifth leading cause among adults of 65 years or older,[3] meaning that roughly one in three American seniors dies from the disease. The Alzheimer's disease death toll increased a staggering 146 percent from 2000 to 2018, while the number of deaths attributed to stroke and heart disease, the current leading cause of death, decreased roughly 10 percent during this time, indicating that Alzheimer's disease in increasing importance as a public health issue. Among the top 10 leading causes of death, Alzheimer's disease is the only one that cannot be prevented, cured, or have its disease progression slowed.[3, 5] These numbers, however, represent only our best knowledge, and do not accurately depict the real penetration of the disease in society. Due to the complexity of Alzheimer's disease and its manifestations, as well as gaps in scientific knowledge, the illness is often not diagnosed and attributed correctly, and so the burden in the population is likely higher than it is currently reported.

Due to the duration of the illness, disease complications, and required caregiver attention, the national cost of care for Alzheimer's patients and related dementias is a staggering $300 billion, not including the over $240 billion cost of unpaid labor from caregivers, family, and friends.[3] These numbers make Alzheimer's disease the most expensive disease in the USA. Worldwide, the annual cost of Alzheimer's disease exceeded $800 billion in 2015.[6] The projected costs of Alzheimer's disease by 2040 may exceed $500 billion,[7] and by 2050 will top $1.1 trillion in the United States alone. A significant fraction of the financial burden of the disease falls on the State and Federal Governments through the Medicare and Medicaid programs. In 2020, these programs will cover over $200 billion of expenses associated with Alzheimer's disease. The total cost of health care and long-term care payments for Alzheimer's patients were at least three times that for beneficiaries without Alzheimer's disease. Medicaid expenses covering nursing homes and long-term care services are 23 times higher for Alzheimer's disease patients compared to other beneficiaries. Medicare and Medicaid cover close to 70 percent of Alzheimer's disease patients' expenses, with the remaining 30 percent being uncompensated, private insurance, and out-of-pocket expenses. Medicare expenses are projected to grow 400 percent to $589 billion by 2050, while out-of-pocket expenses will increase 350 percent to $198 billion. The cumulative costs between 2015 and 2050 are estimated to be $20.5 trillion. This projected financial burden is prohibitive and demands radical reassessment and prioritization of strategies to mitigate Alzheimer's disease.

THE CURRENT STATE OF THE ALZHEIMER'S DISEASE THERAPEUTICS AND DIAGNOSTIC PIPELINES

The four principal modalities of health care are diagnostics, prognostics, therapeutics, and care (preventative, curative, and palliative). All of these modalities contribute to the well-being of patients and are aimed at maximizing human health and quality of life. Among these modalities, curative therapeutics would have the most profound impact on eliminating the financial burden associated with the disease, as well as the quality of life of Alzheimer's disease patients and their families. The principal challenge in identifying curative therapeutics is the current gap in scientific knowledge of the early molecular events leading to pathological disease processes, which can begin up to 20 years before disease onset. Curative therapeutics targeting disease mechanisms, as opposed to palliative therapeutics that treat symptoms, strongly depend on an understanding of the mechanisms of disease etiology, which is currently sparse. One of the hallmarks of Alzheimer's disease is the accu-

mulation of aberrant protein deposits in patients' brains. These deposits contain protein fragments called amyloid-beta peptide or tau protein. The observation of these aggregated proteins has become the central premise for the *amyloid cascade hypothesis*:[8] that the aggregation process results in a toxic gain of function of these proteins, ultimately resulting in neuronal death. However, despite decades of research, we have not yet established the nature of this link between aggregation and toxicity, nor whether protein aggregation is indeed a driver of neuronal death or simply a consequence of some unknown underlying processes. Nevertheless, the amyloid cascade hypothesis has been the basis for the Alzheimer's disease drug pipeline: the majority of drugs that have been developed or are currently in clinical trials target either amyloid-beta production, promote peptide clearance, inhibit aggregation, or promote neuronal resistance to aggregation. Some drugs target tau aggregates. However, no significant successes have been reported based on the strategies associated with the amyloid cascade hypothesis. Many expensive and long clinical trials have been halted at the last stages:[5, 9, 10] verubecestat,[11] semagacestat,[12] bapineuzumab,[13] and solanezumab.[14] The failed drugs succeed in performing their intended functions (*e.g.,* inhibiting BACE enzyme in case of verubecestat),[15] but these functions did not translate to the desired clinical outcomes as expected. For example, "verubecestat did not reduce cognitive or functional decline in patients with mild-to-moderate Alzheimer's disease and was associated with treatment-related adverse events."[16] In fact, "no significant new drug for Alzheimer's has been approved in the past 14 years, despite massively expensive trials aimed at tackling the disease. The pipeline has been littered with big failures, which have come in a steady drumbeat of defeat and discouragement."[11] No preventative therapeutics exist. Although a number of palliative therapeutics are either in current clinical use or in trials, they ameliorate symptoms but do not significantly alter the course of disease. Device-driven interventions such as transcranial electromagnetic treatment (TEMT),[17] transcranial direct current stimulation (tDCS),[18] and photobiomodulation (PBM)[19] are currently being tested for palliative care.

Presently, there is no definitive clinical diagnostic test for Alzheimer's disease. Circumstantial evidence, such as family history, interaction with family members and friends, and a battery of cognitive tests suggest whether a patient exhibits signs of dementia. Alzheimer's disease is the prevalent cause of dementia in older adults, accounting for 60–80 percent of cases. In some cases, positron emission tomography (PET), magnetic resonance imaging (MRI), and lumbar puncture aid in confirming or ruling out Alzheimer's disease in patients with dementia. Definitive diagnosis requires histopathologic examination, which is necessarily performed only upon autopsy. Diagnosis is particularly challenging because the disease may take 20 years to manifest. By the time the diagnosis is made, pathology has already significantly and irreversibly altered the brain.

No prognostic models exist for Alzheimer's disease. Genetic markers, most notably the presence of one or two ε4 variants of apolipoprotein E,[20, 21] can suggest a higher likelihood that a person will develop Alzheimer's disease. However, the presence of these genetic risk markers cannot predict with any certainty the time frame for disease manifestation, nor whether the carrier will even develop the disease at all. Genetic information therefore offers potential but not definitive knowledge.

GAPS IN DATA OR UNDERSTANDING OF THE DISEASE THAT ARE PREVENTING THERAPEUTIC AND DIAGNOSTIC DEVELOPMENT

Alzheimer's disease has a complex etiology. Processes that lead to neurodegeneration arise at the molecular level and consequently result in cellular death, but physiological disease onset and consequent cognitive manifestation occurs only after massive and irreversible neuronal loss (Figure 1). As a result, neurodegenerative diseases are age-related and take from years to decades to manifest, by which time the only treatment available to mitigate the disease is alleviation of noxious symptoms, including palliative care. The paramount challenge of developing treatments for neurodegenerative diseases lies in identifying the early pathological events that would eventually result in cell death, and targeting those events to rescue the afflicted neurons.

Molecular etiologies of neurodegenerative diseases are among the greatest mysteries and challenges in medicine. One common denominator in all neurodegenerative disease is the presence of pathological protein deposits that occur in distinct and specific regions of the brain and/or spinal cord. This common denominator has become the central premise for the *amyloid cascade hypothesis.*[8] The presence of amyloid-beta plaques and tau neurofibrillary tangles are the patho-

physiological hallmarks of Alzheimer's disease, and for decades this association has fueled research focusing on the amyloid cascade hypothesis.

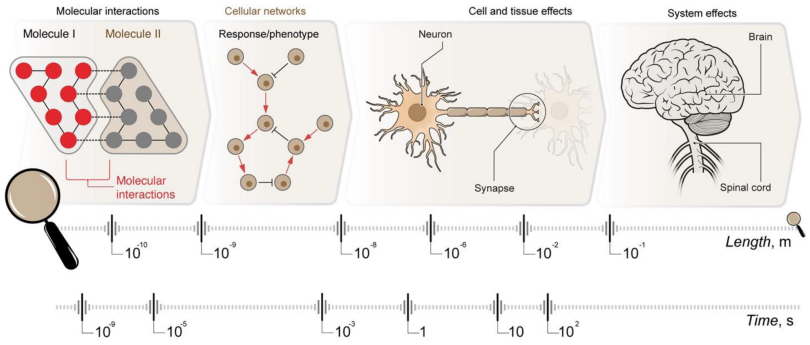

Figure 1. Multiscale processes in neurodegenerative diseases requiring translational approaches. Molecular interactions resulting in the formation of toxic species that manifest themselves at the level of cellular networks, which ultimately result in cellular and physiological phenotypes. The latter processes may take years to present as disease symptoms.

The uncertainty of whether the disease will manifest in a particular individual poses a challenge in identifying the abnormal events leading to neuron death. Identifying early pathological events is also challenging due to current technological limitations, such as a lack of precise and accurate methods for non-invasive monitoring of pathological molecular processes. A second significant limitation is our lack of disease model systems that faithfully replicate the pathology seen in human disease. The current state-of-the-art animal models, which are engineered to represent human disease in experiments, exhibit significant differences in the aging process between experimental animals and humans, as well as artifacts and biases brought about by introducing human genes into animals. These studies, therefore, require extensive validation from orthogonal studies using different methods to test the same question. Hence, we need to not only challenge the methods of interrogating the complexities of neurodegenerative diseases, but even how we design methods to approach these complexities.

Alzheimer's disease and other neurodegenerative diseases like Parkinson's disease and amyotrophic lateral sclerosis share many commonalities, such as protein aggregation, neuronal death, and the age of onset is typically in the sixties. Such similarities point towards fundamental processes common to these diseases, which are still unknown. Yet, such similarities suggest that understanding one neurodegenerative disease etiology will likely have a profound impact on understanding of other ones. As of now, neurodegenerative diseases do not have therapies that would even slow down the progression, unlike other diseases such as cancer and heart disease. No biomarkers that detect early events in the disease are established. Hence, the field of neurodegeneration needs new and disruptive thoughts and approaches to have a hope of altering their courses.

CHALLENGES TO PRIVATE-SECTOR ENGAGEMENT IN THE DEVELOPMENT OF THERAPEUTICS AND DIAGNOSTICS, AND POTENTIAL SOLUTIONS TO THESE CHALLENGES

The for-profit private sector is driven by deliverables, and, thus, balances knowledge of drug targets against the risks associated with them. Although Alzheimer's disease is a potentially lucrative area for the pharmaceutical and biotechnological industries, the cost associated with clinical trials and their length is a significant deterrent. The pharmaceutical industry is under significant pressure to create novel and innovative solutions and, thus, has one of the highest research and development expenditures among all industries. Despite remarkable spending on research in the pursuit of such innovation, pharmaceutical companies typically focus on already established drug targets. These drug targets are a reflection of our fundamental understanding of disease pathological processes, an understanding that is typically established in academia. Currently, we do not have a validated model of these processes in Alzheimer's disease. Fundamental studies of basic science are prohibitively expensive to industry, which relies on academia to develop such models. Several drugs currently in the clinical trials pipeline, as well as those already approved and those that failed clinical trials, have been developed based on the amyloid cascade

hypothesis and are aimed at reducing the amyloid-beta load in patients' brains. Some scientists attribute the failure of these drugs to the late timing of intervention in trials, when disease is already advanced to irreversible neuron death and consequent cognitive decline. However, evidence stemming from other fields suggest that this hypothesis needs to be revisited. For example, the research in my laboratory on amyotrophic lateral sclerosis suggests that very early events in molecular life are responsible for neuronal toxicity,[22] while the large protein deposits actually serve as protective buffers against those events.[23] Deeper integration of the private sector with academia may significantly reduce the inertia in the drug pipeline and potentially offer new ideas to tackle neurodegeneration. Additionally, further outsourcing basic scientific research to academia will significantly reduce the financial burden associated with therapeutic development.

Charitable foundations are typically driven by donors' immediate need to help their loved ones. Their mission is mostly centered around research that promotes drug discovery and other short-term goals, but the resources are significantly more limited than those available to for-profit organizations. Nevertheless, these organizations have been instrumental in offering support to academia, thus providing a critical springboard for risky and innovative research. In addition, organizations such as the Alzheimer's Association foster scientific advances not only through research but also through education and shared resources.

The failure to discover curative therapeutics for Alzheimer's disease may be a consequence of the exclusive focus on specific targets without a validated model of the molecular underpinnings of disease. Given the high rate of failure thus far, such a model is likely to come from innovative research that disrupts common thought about the disease. Hence, stimulating such research by the private sector will likely have an immense impact on our progress toward a cure for Alzheimer's disease.

OTHER BARRIERS THROUGHOUT THE RESEARCH AND DEVELOPMENT PROCESS AND APPROVAL PROCESS FOR ALZHEIMER'S DISEASE AND POTENTIAL SOLUTIONS TO THESE BARRIERS

Federal grant programs, specifically those sponsored by the National Institutes of Health, offer support for both fundamental and translational biomedical research. At the NIH, scientific merit reviews are performed by scientists, and, therefore, offer a broad and fair coverage of research directions. These grant programs are highly competitive, and thus proposals that offer something radically different and risky ("high risk, high reward") tend to fair worse than risk-averse proposals that continue established lines of research. While the NIH has provided venues for high-risk high-return projects, they remain extremely competitive, especially for younger scientists and those with new ideas who come from outside of a traditional neuroscience background.

Protein aggregation is a hallmark of neurodegenerative diseases, including Alzheimer's disease. The mechanisms of protein aggregation are understood from a biophysical perspective, but how this molecular knowledge relates to physiology remains unknown. Thus, translational science programs aimed at marrying disparate scientific fields with clinical research are critical to establish a working model of disease. The success of translational science relies on attracting scientists with backgrounds in diverse fields to build inter-disciplinary programs. In addition, attracting industrial partners to these inter-disciplinary consortiums will facilitate their progress.

The dominant cost associated with caring for Alzheimer's disease patients stems from the extensive care required in later stages of the disease. Reducing the cost of care is mostly an untapped direction in mitigating the growing cost of the disease in the United States. Recent scientific and engineering innovations, especially in machine learning and artificial intelligence, wireless solutions, and miniature devices, may offer new and unparalleled means of caring for patients, especially in the advanced stages of the disease. For example, wearable devices with geofencing abilities may allow automated remote monitoring of a patient's health state, while location services may significantly reduce the risk of a patient with dementia wandering from home, thus allowing those with Alzheimer's disease to remain at home and out of care homes for longer. Facilitating such innovations through Federal and private sector programs will have a major impact on improving the quality of care and reduce financial burden on both government programs and on individuals.

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QUESTIONS SUBMITTED FOR THE RECORD TO NIKOLAY DOKHOLYAN, PH.D., M.S.

QUESTIONS SUBMITTED BY HON. CHUCK GRASSLEY

ALZHEIMER'S SCREENING AND DIAGNOSIS

Question. You testified that Alzheimer's disease is under-diagnosed and under-reported. With other diseases, particularly cancer, we've seen the impact that an early diagnosis can make on a patient's life. Other than stigma or lack of diagnostic testing resources, what are some of the typical reasons for a delayed Alzheimer's diagnosis? Is there more that we could be doing to encourage earlier screening for Alzheimer's disease?

Answer. Currently, Alzheimer's disease diagnosis relies on reports of memory loss and early stages of dementia. More sophisticated and expensive approaches rely on positron emission tomography (PET) imaging that measures the levels of amyloid beta peptide in the brain (one of the key markers of Alzheimer's disease) to confirm Alzheimer's disease in patients with dementia. More recently, a significantly less expensive blood-based biomarker, also based on amyloid beta peptide load, has been developed by Dr. Randall Bateman at the Washington University School of Medicine. This new development will revolutionize our ability to screen patients with early signs of dementia.

Even these new advanced methods for diagnosis of Alzheimer's disease rely on the outcomes of processes that have been active in patients' brains for years. We still do not know how early these processes start, but by the time diagnosis is possible, even with new advanced techniques, sufficient irreversible brain damage is present to result in cognitive decline or even full-blown dementia. The catch-22 here is that in order for a patient to be tested, s/he needs to exhibit cognitive decline, which is the result of the irreversible brain damage. Resources to perform early screening of patients with mild cognitive decline will certainly help inform patients of lifestyle choices to mitigate the condition. However, we desperately need to examine early molecular events that result in neuronal death.

Question. It's been reported that researchers have found specific markers in the blood that could detect changes in the brain 20 years before Alzheimer's symptoms occur. Are you aware of this research, and if so, what more can you tell us about how close we are to having a widely available blood test for Alzheimer's? What other challenges remain?

Answer. Several labs, notably Dr. Randall Bateman's laboratory, have been pushing the boundaries of Alzheimer's disease diagnostics via blood-based biomarkers, which measure either amyloid beta or tau loads—both peptides associated with Alzheimer's disease. These tests are highly accurate for Alzheimer's disease pathology (>90 percent), but are not stand-alone diagnostic tools yet and they require orthogonal confirmation of the disease by a physician confirming cognitive impairment. Furthermore, even though they are significantly less expensive than PET scans, the expenses associated with such tests may still be prohibitive for massive utilization in the clinic, because the CLIA approved tests are not yet covered by CMS or insurance. Implementation in the clinic and coverage by CMS continue to be major challenges.

QUESTION SUBMITTED BY HON. JOHN THUNE

Question. I understand that there have been multiple studies to explore how artificial intelligence (AI) can help predict Alzheimer's in patients. Some of these studies have involved training computers to analyze clinical data and scans, and others have utilized handwriting and linguistic analysis to predict future diagnoses. What role do you see AI playing in the fight to address Alzheimer's and the financial effects it has on Medicare and Medicaid?

Answer. The progress in machine learning, a sub-field of mathematics and computer science, has led to significant breakthroughs across multiple disciplines, in-

cluding the biomedical and clinical sciences. In Alzheimer's disease, I see three principal domains for application of machine learning and artificial intelligence. First, machine learning and artificial intelligence may find application in identification of early biomarkers of the disease, which would precede detectable abundance of amyloid beta peptides, but such a technology would strongly depend on our understanding of the biological processes associated with the disease. Second, these computational approaches may be able to detect early signs of cognitive decline and behavioral changes that would predate mild cognitive decline states of Alzheimer's patients. Third, machine learning coupled with innovation in electronics and wearable devices may help mitigate behavioral changes in Alzheimer's disease patients, thereby significantly reducing the burden on care providers. These three domains require translational science approaches to successfully implement them by connecting scientific and engineering knowledge with clinical practice.

QUESTION SUBMITTED BY HON. TODD YOUNG

Question. While CMS has made some minor changes to the provider guidance regarding the detecting cognitive impairment requirement of the Annual Wellness Visit (AWV), it seems that the AWV continues to be a missed opportunity for early detection of cognitive impairment.

Would the detection of cognitive impairment requirement be enhanced by the use of NIA-identified assessment tools or is "direct observation" an acceptable standard for evaluating cognitive impairment in aging populations?

Answer. While implementation of more comprehensive assessments may help with earlier detection of dementia, there may be much more innovative and less expensive means to this end for Alzheimer's disease, for example, using machine learning and artificial intelligence approaches.

PREPARED STATEMENT OF HON. CHUCK GRASSLEY, A U.S. SENATOR FROM IOWA

Alzheimer's is a devastating, irreversible disease that strips individuals of their memories and their life. At least 5 million people in the United States are living with it today, according to the Alzheimer's Association. That number will only increase as our population continues to age.

Alzheimer's also profoundly affects family caregivers. We need to do more to respond in more ways to the issues facing the 16 million Americans who currently provide unpaid care for people with dementia. The brunt of this work is done by family members.

Through investments in scientific research, we've made some advances in detecting and tracking this devastating disease. Congress has played a supportive role in this respect, and I expect we'll continue to do so, by providing resources for research to find the cause and the cure for Alzheimer's. We still have much more work to do on this front, however, as we've yet to find a cure or ways to prevent Alzheimer's.

I also am concerned about the exploitation of individuals living with Alzheimer's or other forms of dementia. During my tenure as Judiciary Committee chairman, I championed bipartisan legislation to update and extend the Missing Alzheimer's Patient Alert Program.

More recently, I joined Senators Collins and Menendez in championing a bill requiring the Justice Department to take into account people with Alzheimer's disease when creating or compiling elder abuse training materials. This measure builds on legislation I sponsored in 2017, which required the Justice Department to appoint an Elder Justice Coordinator and create training materials to help Federal investigators respond to elder abuse cases.

I thank my colleagues, Senators Toomey and Stabenow, for convening this very important hearing of our Health Subcommittee. I also extend a warm welcome to each of our witnesses. I look forward to hearing more from them about their latest research on Alzheimer's disease and the potential for a cure.

PREPARED STATEMENT OF RICHARD C. MOHS, PH.D., CHIEF SCIENCE OFFICER, GLOBAL ALZHEIMER'S PLATFORM FOUNDATION

Thank you, Senators Toomey and Stabenow and members of the subcommittee, for your support for Alzheimer's research and for the opportunity to testify before the Senate Committee on Finance Subcommittee on Health Care.

Today I will address the state of Alzheimer's research, the importance of pursuing multiple approaches to treatment, the importance of fast and low-cost blood biomarkers and digital cognitive assessments, the need for greater diversity in clinical trials, the innovative Bio-Hermes study, and recommendations for Congress.

For the past 40-plus years, both as an academic researcher funded by the National Institutes of Health (NIH) and subsequently leading drug development teams in the pharmaceutical industry, I have devoted much of my scientific career to trying to develop new medicines for Alzheimer's disease (AD). We have not been as successful as I would like or as successful as patients need. So far only two groups of medicines have been approved for use in patients with Alzheimer's disease. They are the cholinesterase inhibitors and one NMDA (N-Methyl-d-aspartate) antagonist; these medicines provide relatively small symptomatic improvements in patients with mild or moderate disease but do not prevent the disease or slow its relentless progression.

Currently, I am the chief science officer for the Global Alzheimer's Platform (GAP) Foundation. GAP is a patient-centered non-profit organization devoted to accelerating the delivery of innovative therapies for neurological disorders by reducing the duration and cost of clinical trials. More than 85 clinical research centers across the U.S. and Canada are part of the growing GAP Network, known as GAP-Net. GAP supports GAP-Net research sites by assisting with study start up and recruitment activities, promoting diversity in research studies and offering national programs that champion brain health and the citizen scientists who make research possible.

I joined GAP in 2015 after retiring from Eli Lilly and Company; prior to joining Lilly in 2002, I was on the faculty of the Mount Sinai School of Medicine in New York. Based on my experience both in academic research and in the pharmaceutical industry I can offer some perspectives on the work that has been done in AD therapeutics, barriers to progress and on future initiatives that could speed progress that is so urgently needed.

The first and most significant barrier to progress in developing new medicines is that we have not yet clearly identified the key biological processes causing AD. As we have learned in recent months from experience with COVID–19, once a clear causal agent is identified and characterized biologically, the search for preventative measures and treatments can proceed rationally through the conduct of highly informative basic and clinical research. For a chronic disease such as Alzheimer's with multiple risk factors and with complex pathology the path to effective treatments is quite uncertain. In the private sector, there is a high degree of interest and considerable investment in Alzheimer's disease drug development, but it is considered more risky than other therapeutic areas where the perceived likelihood of clinical and commercial success is seen as higher. This is one reason why we haven't seen the number of successful new medicines we have seen in oncology, autoimmune diseases, diabetes and other conditions.

We do know that AD is characterized by the presence of two abnormal proteins in brain, amyloid plaques and tau tangles. Many drugs designed to slow the accumulation or speed the removal of amyloid plaques have been entered into large, time-consuming and very expensive clinical trials. Some of these drugs have been shown to have potent biological effects on amyloid and it is likely that some clinical benefit may follow but much uncertainty remains. Drugs to reduce the spread of the abnormal tau protein in brain are currently being tested and their clinical efficacy remains uncertain. While these approaches may show some efficacy in some patients it is unlikely that either approach will be sufficient to prevent most cases of AD or to completely stop disease progression. It is imperative that the therapeutic value of targeting other factors associated with AD etiology and pathology be tested as quickly as possible. As examples, drugs targeting apolipoprotein E (APOE), a major risk factor for AD, brain inflammation, mechanisms of brain cell death, and neuronal activity should be developed and tested as quickly as possible. The GAP Foundation has worked over the past several years to develop a network of clinical trial sites using common processes for clinical study contracting, Ethical Review,

participant recruiting and citizen engagement to help clinical sites conduct studies quickly and produce reliable, informative data.

Speeding the delivery of highly informative clinical data on promising drug candidates will require renewed effort and collaboration of government agencies, pharmaceutical companies, clinical trial sites, and, importantly, citizens willing to engage as informed and willing participants in clinical trials. Broadly speaking, academic and government investigators provide many of the insights into etiology and brain pathology that could be targeted with new medicines; commercial entities discover and provide the early evaluation of most of the viable drug candidates; pharmaceutical companies, clinical trial sites and the government funders such as the NIH then work to support the collection of clinical data, all of which can then be submitted to Food and Drug Administration (FDA) for review.

Given the complexity of AD we must expect that many clinical trials, even those testing the most scientifically promising drug candidates, will fail to show efficacy. We should not regard these as complete failures, however, since well-designed and executed clinical trials of good candidate molecules provide information that is essential for planning future drug discovery and development activities. By testing a variety of scientifically justified approaches in efficient and well executed clinical studies and learning from each set of studies, I am very confident that we will develop effective medicines for the prevention and treatment of AD. We need to take lessons from earlier unsuccessful programs using large, expensive and time-consuming studies to identify faster and more efficient methods to test promising new molecules.

A second major barrier is the disconnect between the way patients with AD are diagnosed in current clinical practice and the way research studies identify study participants. Most practicing physicians wait and make a diagnosis of AD relatively late, when patients manifest clear symptoms and need counseling on how to manage those symptoms. We now know that the pathology of AD begins in the brain many years before patients develop symptoms such as memory loss and impairment in activities of daily living. Biomarkers, particularly PET (positron emission tomography) brain scans now enable the detection of amyloid and tau pathology well before symptoms of AD are noticeable. Many drugs in development are expected to be most effective by intervening when pathology is just starting rather than when it has advanced enough to cause major impairment. As a result, clinical trial sponsors must evaluate many potential study participants with cognitive tests and expensive, time-consuming PET scans in order to enroll appropriate trial participants; that is, participants with AD pathology but with only mild or no symptoms.

Very recently major advances have been made in the development of simple blood-based biomarkers that will speed the identification of people with asymptomatic disease both for trials and for early diagnosis in clinical practice. The development of blood biomarker tests and incentivizing their widespread use in clinical practice is very important. They will allow us to make diagnoses earlier and at a lower cost. Early diagnoses will allow for scaling up education efforts and counseling, so that families can make plans for their loved one to have the highest degree of independence possible, ideally in their own homes. Early diagnoses also will facilitate the rapid completion of clinical studies because we will identify and enroll appropriate participants in clinical trials much earlier.

The GAP foundation is in the process of standing up a platform study that will test the efficacy of more than a dozen promising blood biomarkers and digital cognitive assessments as prognostic or diagnostic indicators for Alzheimer's disease. Known as the Bio-Hermes study, it will generate biological samples and digital biomarker data from 1000 participants; the study will also enable development of a data algorithm to produce next-generation clinical trial enrollment solutions. The Bio-Hermes study will include racially and ethnically diverse participants in order to assess whether biomarker risk factors vary by race and ethnicity.

Recruiting a diverse group of informed and willing participants for an Alzheimer's clinical trial is both extremely important and challenging. Despite making up about 30 percent of the US population, African American and Latino people usually make up only about 3–8 percent of clinical trial participants. To help address this issue, GAP has committed to recruiting at least 20 percent African American or Latino volunteers for the upcoming Bio-Hermes study, and will not close recruitment for this trial until we have a group of study participants that accurately reflects the community of people living with Alzheimer's disease. Our intention is for the Bio-Hermes study to be a model for building back a clinical trial infrastructure that is more efficient and gets us to a better diagnostics and medicines faster.

Of course, the Food and Drug Administration (FDA) is an essential partner to the pharmaceutical industry and academic researchers when it comes to the search for better diagnostics and treatments for Alzheimer's disease. We applaud the agency's approach to public engagement around their evaluations. We appreciate that the FDA has been transparent and energetic in its collaboration with a broad range of stakeholders, including patient advocates, researchers and pharmaceutical companies. Given the need for greater diversity in clinical trials, we hope Congress will use the Prescription Drug User Fee Act renewal process to encourage FDA to develop clear guidance on minimum standards for diversity in clinical trials.

We hope that Congress will encourage greater collaboration between FDA and the Centers for Medicare and Medicaid Services (CMS) so that future reviews regarding efficacy of new diagnostics and medicines and consideration of their merits for reimbursement can occur concurrently. This would help speed the delivery of innovative diagnostics and medicines to patients and clinicians.

Undoubtedly Alzheimer's Disease has proven to be one of the most difficult problems ever to confront biomedical researchers. I look forward to discussing how the subcommittee can take steps to speed the widespread use of blood biomarkers and digital cognitive assessments, increase the speed and diversity of Alzheimer's clinical trials, enhance investment in the AD clinical research infrastructure and encourage further collaboration between commercial sponsors, academic researchers, NIH, FDA, patient stakeholders and CMS.

QUESTIONS SUBMITTED FOR THE RECORD TO RICHARD C. MOHS, PH.D.

QUESTIONS SUBMITTED BY HON. JOHN THUNE

Question. South Dakota has long embraced telehealth, including in long-term care settings where residents may experience Alzheimer's. Of course, the pandemic has brought telehealth even further to the forefront, connecting patients to their doctors from the safety and convenience of their own home. What further can policymakers and CMS be doing to expand telehealth to assist Alzheimer's patients?

Answer. Remote clinical visits with physicians or other health-care providers can be done effectively using several modalities including video conference, telephone, email, and text message. In some regions of the U.S., Internet speeds may be slow and prohibit telemedicine services but still allow other types of remote assessments and treatments. All forms of remote assessment and treatment that have been shown to be effective should be reimbursed. Currently some clinical services may not be reimbursed if given remotely even though data indicate that remote administration is effective.

I also note that a full diagnostic evaluation of persons with cognitive impairment involves expensive, time consuming, and, for some patients, intimidating procedures. This barrier makes it difficult to diagnose Alzheimer's disease early, particularly in poor communities and communities without sophisticated health systems. Blood and digital biomarker tests such as those to be evaluated in the Bio-Hermes study are simple, cheap and accessible for neighborhood and sophisticated health systems alike. Widespread adoption of these tests could help people get diagnosed earlier, greatly and equitably increasing the patient population available for clinical trials.

Question. I understand that there have been multiple studies to explore how artificial intelligence (AI) can help predict Alzheimer's in patients. Some of these studies have involved training computers to analyze clinical data and scans, and others have utilized handwriting and linguistic analysis to predict future diagnoses. What role do you see AI playing in the fight to address Alzheimer's and the financial effects it has on Medicare and Medicaid?

Answer. Annual screenings of the very large number of people at risk for Alzheimer's disease will be very costly and cumbersome if done entirely by clinicians. Evidence indicates that AI applied to data in electronic health records and collected from electronic devices such as activity monitors, smart watches, phones and computers could increase the number of Alzheimer's disease patients identified and make the process less costly. Privacy and consent issues regarding the use of individually identified data need to be resolved. Research to determine the most effective AI approaches should be encouraged and supported.

QUESTIONS SUBMITTED BY HON. TODD YOUNG

Question. While CMS has made some minor changes to the provider guidance regarding the detecting cognitive impairment requirement of the Annual Wellness Visit (AWV), it seems that the AWV continues to be a missed opportunity for early detection of cognitive impairment.

Would the detection of cognitive impairment requirement be enhanced by the use of NIA-identified assessment tools or is "direct observation" an acceptable standard for evaluating cognitive impairment in aging populations?

Answer. Many different tools, processes, and technologies may be useful for detecting cognitive impairment; cognitive tests done in person, direct observation by a trained clinician, remote tests, data from electronic health records and wearable devices may all assist clinicians in identifying persons with cognitive impairment. The NIA-identified tests will be useful for clinicians who have the training and experience needed to use them properly. I think that the Food and Drug Administration (FDA) has the most well-developed process for evaluating the usefulness of any new technology or algorithm. The FDA can evaluate data on new technologies and approve language that accurately informs clinicians about how the technology should be used. Their evaluation provides an appropriate context of use for each technology.

Question. CMS allows a variety of providers to conduct an AWV, ranging from physicians, PAs, and nurse practitioners to dietitians and nutrition professionals.

Given this provider range, what type of training do these providers receive when it comes to detecting cognitive impairment?

Answer. Clinicians with a variety of different backgrounds can be trained to detect cognitive impairment; this can include physicians, nurses, psychologists, social workers and others. Specific, supervised training on test administration should be required along with supervised experience evaluating patients with dementia.

Question. Given progress made in assessment tools sensitivity to detecting cognitive impairment, should the use of an assessment tool included in the NIA's toolbox of resources for professionals be standard practice at Medicare annual appointments, or is direct observation an equal substitute?

Answer. Both cognitive tests such as those included in the NIA toolbox and direct observation can be used to identify patients with cognitive impairment. The clinicians using the test or making the observation should have supervised training and experience needed to interpret the observations. As noted previously, new technologies such as those involving AI, wearable devices, and remote assessments can also assist in identifying persons with cognitive impairment. An approval process for these new technologies can be based on the biomarker evaluation process available through the FDA.

Question. Do you think there is a reasonable argument against CMS directing providers to use assessment tools that the NIA already refers providers to in other areas?

Answer. The tools recommended by NIA are reasonable and should be used by clinicians with appropriate training and experience. Other procedures and tools for identifying patients with cognitive impairment can also be useful. As noted above, standards for evaluating new tools and technologies are available through FDA. Such evaluations can provide clinicians with guidance on how to administer and interpret any approved test.

Question. Do you think CMS has a valid reason to be against directing providers to use assessment tools that the NIA already refers providers to for use in other Medicare benefits?

Answer. The NIA-recommended tools are useful and should be used by clinicians with appropriate training and experience.

QUESTION SUBMITTED BY HON. DEBBIE STABENOW

Question. You discussed the need to encourage diversity among trial participants as well as ensure early diagnosis to enroll patients in clinical trials.

How would the CHANGE Act and standardizing cognitive assessment tools help patients enroll in clinical trials?

Answer. The CHANGE Act provides for cognitive assessments at the Annual Wellness Visit and, for patients with evidence of cognitive impairment, encourages referral to clinical trials. If these provisions of the CHANGE Act were widely adopted the number of persons with suspected cognitive impairment would likely increase substantially and the number of patients referred for clinical trials would also increase. This would lead to improved care, counseling and patient management for patients with cognitive impairment. It would also increase the number of patients enrolling in clinical trials and reduce the time needed to evaluate potential new medicines and other therapies.

PREPARED STATEMENT OF HON. DEBBIE STABENOW,
A U.S. SENATOR FROM MICHIGAN

Thank you, Mr. Chairman. It is my pleasure to join you in hosting this subcommittee hearing, and I know how passionate we both are on this issue, and I really appreciate the work that we have been doing together on this subcommittee. And I appreciate all of our colleagues joining us today.

Also, thank you to our witnesses for all you are doing and for being here—virtually—today as we discuss this incredibly important topic.

There are 5.8 million Americans living with Alzheimer's today, and that includes 190,000 people in my home State of Michigan. In just the next 30 years, that number is expected to more than double to 14 million Americans.

And we know that the pandemic has hit dementia patients especially hard, with well over 13,000 excess deaths attributed to Alzheimer's since March. Behind these numbers, though, are what's most important, and that's grandparents and parents, aunts and uncles, and friends, moms and dads, loved ones who have faced this horrific diagnosis and the limited treatment options right now.

Today, we will learn the latest developments on Alzheimer's treatments and testing. There's still no drug, as the chairman said, to cure Alzheimer's disease or slow its progression—but there is hope.

I am pleased that the Federal funding for Alzheimer's research is five times higher now than it was just 9 years ago. And I agree that we need to do much more.

With this funding, many researchers have been able to make strides toward new treatments. I know in my home State, there's tremendous work being done. We need to continue to support their groundbreaking work and to expand on it.

We also need better testing, so we can identify the disease early, help families plan, and get people enrolled in clinical trials. And when we have a treatment, early and affordable testing and diagnosis will make sure that people who need it, get it.

I have introduced legislation with Senators Capito, Menendez, and 19 others called the CHANGE Act, which will encourage timely and accurate detection and diagnosis using evidence-based tools.

Finally, while working toward a cure, we must not forget the people who care for their loved ones with the disease, and we all know that Alzheimer's really is a family disease.

I am so glad that my HOPE for Alzheimer's Act was implemented on a bipartisan basis, and now newly diagnosed Alzheimer's patients can access a doctor's visit to create an individual care plan. However, not everybody knows of this benefit, and not everyone is using it. My Improving HOPE for Alzheimer's Act, cosponsored by 47 members, many on this subcommittee, requires HHS to conduct a nationwide campaign to increase awareness of this care planning visit and the importance of supporting families.

We also must ensure that once patients and their caregivers have a plan, that they can actually implement the plan. That's why I will be introducing legislation next year—and I welcome my colleagues to be a part of this—directing the Department of Health and Human Services to test a payment model to support coordinated care for dementia patients, as well as support for caregivers. By coordinating care, we can reduce complications and ensure that families have resources to help care for their loved ones.

So I'm very proud of the progress we have made, and the work we are doing together on a bipartisan basis, but there is so much more to do. And I look forward

not only to today's discussion, but also for ways we can continue to work together on diagnosis, treatment, and ultimately, what we all want, which is a cure for Alzheimer's.

Thank you, Mr. Chairman.

COMMUNICATIONS

ARIZONA ALZHEIMER'S CONSORTIUM

Statement of Eric M. Reiman, M.D., Director

ADVANCIING THE SCIENTIFIC AND CLINICAL FIGHT AGAINST ALZHEIMER'S DISEASE

Thank you for the invitation to provide my thoughts about the fight against Alzheimer's disease, and thank you and your colleagues for your wonderful support of our efforts to address this problem here in Arizona. My name is Eric Reiman. I am Executive Director of Banner Alzheimer's Institute and CEO of Banner Research, Professor of Psychiatry at the University of Arizona, University Professor of Neuroscience at Arizona State University, Clinical Director of the Neurogenomics Division at TGen, and Director of the Arizona Alzheimer's Consortium.

Allow me to begin with the bad news:

Alzheimer's disease (AD) is the most common form of disabling memory and thinking problems (*i.e.,* "dementia") in older people. It affects nearly 10% of those over the age of 65 and between a third and half of those over age 85. It takes a devastating to toll on the affected person and an intolerable toll on family caregivers. Due to the growing number of people living to older ages, the number of people with Alzheimer's dementia is expected to triple in the next 30 years, such that it is expected to account for disabling memory and thinking problems in more than 100 million patients and have an overwhelming impact on countries around the world. According to an Alzheimer's Association report, the number of affected persons is growing at a faster rate in Arizona than in any other state in the country.

We have a woefully inadequate standard of dementia care for patients and their families. 60% of patients with dementia never have an evaluation, diagnosis or exclusion of potentially reversible contributions to their memory and thinking problems. Too many people, including many clinicians, think there is nothing you can do about the problem, not recognizing the range of coping strategies, non-medical management options that are available to support the patient and their families. Meantime, we still need more effective medication strategies to improve a person's cognitive symptoms, manage their distressing behavioral symptoms like agitation and paranoid delusions, and we need a compensated user friendly way to help patients and family caregivers navigate the range of issues and daily living, safety, financial, legal, medical, assisted living, and social resources that they may face after a diagnosis.

While there has been great research progress, we have not seen a new medication therapy for Alzheimer's disease approved since 2003, and about 99% of studied treatments since that time have failed to work. We have needed the public policies, state and federal funding, and public-private partnerships needed to create a much more successful drug development paradigm and encourage makers of promising treatments to spend the funds and take the years needed to put promising disease-stopping and prevention therapies to the test; we have needed biological indicators of a drug's efficacy to inform the development of those drugs with the greatest chance of success; we have needed new strategies to accelerate the evaluation and approval of prevention therapies, which are started before the disease has ravaged the brain. While this is far more to do, we have seen major progress in each of these areas.

Looking ahead, we need to anticipate what it will take to optimize the accessibility and affordability of effective treatments when they become available. While

there has been exciting progress in the development of brain imaging and spinal fluid biomarkers of AD, their accessibility has been limited by the cost of PET scans, relatively uncommon performance of sometimes uncomfortable lumbar punctures (*i.e.,* spinal taps), and an interest on the part of CMS to demonstrate the value of these diagnostic techniques in the clinical setting before approved disease modifying treatments are available.

Now, some good news:

In the last decade, researchers have made substantial progress in the scientific fight against AD. We have identified processes involved in the development of the microscopic abnormalities that are used to support the diagnosis of AD at the end of life, including amyloid plaques, tau tangles, and a characteristic and progressive loss of neurons and their connections. We have identified nearly 30 genetic risk factors, as well as potentially modifiable non-genetic risk factors that can be targeted by new treatments, including both drug and emerging gene therapies. We have recently demonstrated the potential of blood tests to diagnosis, detect and track AD, inform a person's prognosis and management, and further inform the evaluation of promising disease-modifying and prevention therapies. We have seen more interaction between basic science researchers, clinical researchers and big data scientists to generate molecular models that are informed by changes observed in the human brain, including potential drivers of those networks that have been suggested to account for the pathological features of AD and which could be targeted by new investigational drugs or already available drugs that could be repurposed for the treatment and prevention of AD. I expect to see the use of extremely large-scale electronic health record data and big-data techniques-in people who do or do not have AD blood tests-to provide a complementary way to find new treatments.

In my opinion, three research developments may turn out to be particularly impactful when it comes to advances in the research, drug development and clinical settings:

(1) Development of promising blood tests of AD and its different neuropathological (amyloid, tau, inflammatory, degenerative and related) features. These blood tests could begin to impact research studies and clinical trials in the coming year, have a major impact on affordable and widely accessible diagnosis and management of AD and related dementias within the next 2–3 years, and provide a way to ensure the widespread accessibility and affordability of AD prevention therapies, if they are proven to be effective, by 2025. Imagine the chance to increase the likelihood that primary care physicians would ask about memory and thinking problems, order a blood test to support a symptomatic person's diagnosis, prognosis and management, hand off the patient and family to affordable and accessible navigators to gather additional information about a person's memory and thinking abilities, communicate what the test results mean, and help the family with important decisions and resources such that they are not left in the lurch to address their challenges on their own. Imagine the chance to conduct a blood test every two years after age 50 to help identify those people who would benefit from an effective AD prevention therapy. We still need to see those diagnostic tests reimbursed, before or after a disease-slowing treatment becomes available, and we still need to see navigator services developed, including those that can be provided virtually, and reimbursed to have the greatest impact on patients and family caregivers. I expect to see major progress in each of these areas in the next 2–5 years.

(2) Suggestive but not yet definitive evidence that some amyloid-reducing therapies may slow the progression of AD in persons with symptoms. If confirmed (whether or not the first amyloid-reducing antibody drug aducanumab is approved for restricted use in March 2021), effective treatments would provide a shot in the arm for patients and families, provide support for the still debated contributions of amyloid to the development of the disease, and clarify which of the treatments biological (PET, spinal fluid and blood test) effects are associated with a clinical benefit, such that those biological measurements could inform and accelerate the evaluation of new disease-stopping and prevention therapies.

(3) We are just beginning to see more diverse treatments under consideration in drug discovery and drug development. These include several strategies to slow down or reverse the accumulation of potentially harmful amyloid proteins, the spread of potentially harmful tau proteins, and some of the neuroinflammatory and degenerative changes also found in the disease. We are also excited about emerging gene therapies, including those that modify or turn off the expression of APOE4, the major genetic risk factor for developing AD at older ages-and we look forward to possibility to put some of those gene therapies to the test within the next 2–3 years.

Given the magnitude of the problem, some of the challenges involved in AD research. and the failure to find effective AD-modifying treatments so far, researchers from academia and industry, NIH and other funding agencies, FDA and other regulators, the Alzheimer's Association and other stakeholder groups—and policy makers themselves—have recognized the idea that when it comes to the fight against AD, we are all in this together. They have developed new ways to work together and support shared goals and, following approval of the National Alzheimer's Care Act (NACA) in 2012, there has been nearly a ten-fold increase in research funding, helping to attract the best and brightest minds to this endeavor. I'm pleased to report that those funds are being used in strategically compelling and sometimes bold ways, and with clear measures of accountability. I expect that we will see dividends of this and other investments sooner than some might think.

Arizona's Leadership Roles

Thanks in large part to you, Arizona has been a leader in the fight against AD. With your support, Arizona's researchers were the first to demonstrate the ability to detect and track AD years before the onset of symptoms. They have provided critical resources to support the validation and FDA approval of amyloid PET and tau PET scans in the diagnosis of cardinal AD features, and it has recently used some of its resources to demonstrate the accuracy of a promising blood tests and their potential to revolutionize the field. They have launched a new era in AD prevention research, forged ground-breaking research strategies, methods and enrollment strategies to accelerate the evaluation and approval of a prevention therapy, and provided the best possible chance to find and support the approval of an effective AD prevention therapy within the next five years. Arizona researchers are world leaders in the study of the aging brain, they have generated invaluable resources of data and biological samples for the study of AD, related brain disorders and normal aging to researchers around the world-including those volunteers in our Brain Donation Research Program and those at different levels of genetic risk. They have been leaders in the evaluation of investigational drug therapies, they established the Alzheimer's Prevention Initiative, which includes the first NIH and industry supported AD prevention trials. They have a chance to find an effective AD prevention therapy by 2025, fulfilling a primary goal of the National Plan to Address AD.

We have capitalized on the collaborative efforts of nearly 200 researchers from 11 organizations and many different scientific disciplines in the state and institutionally supported Arizona Alzheimer's Consortium to address our goals. The Consortium provides the glue that binds us together and the fuel needed to propel new collaborative research institutions. Its researchers include world leaders in brain imaging and blood-based biomarkers, computational and statistical data analysis, the basic, cognitive and behavioral neurosciences, experimental therapeutics and clinical trials, and clinical and neuropathology research, and dementia care. They have made pioneering contributions to the field, they are internationally known for its collaborative model and leadership roles, and with your support, they have made Arizona a destination center for the fight against AD.

Arizona's elected officials and its partners at the Arizona Department of Health Services recognized the importance of this problem and the chance to make a difference right here in Arizona, and they have supported this effort since 1998—long before any other state or the federal government itself. There is a lot more that needs to be done to advance AD research, find and support the development of new treatments, support the development of medication and non-medication prevention therapies, address both the medical and non-medical needs of patients and their families, and do so in highly accessible and affordable ways. Thanks to you and your colleagues, we have a chance to have a transform AD research, the development of effective treatments, and clinical care, and we have a chance to find an effective prevention therapy in the next few years.

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Today, Alzheimer's disease is usually diagnosed after an already symptomatic patient with a cognitive impairment undergoes an extensive clinical diagnostic workup. This workup typically includes family and medical history, physical and neurological examinations, psychiatric screen, laboratory tests and imaging proce-

dures such as computed tomography ("CT") or magnetic resonance imaging ("MRI") scans. However, despite advances, we are still far from being able to assess patients more accurately and earlier in the course of their disease and determine if the underlying cause of the presenting cognitive impairment is due to Alzheimer's disease. In fact, a definitive diagnosis of Alzheimer's disease was only made post-mortem by looking for and identifying the presence of beta-amyloid plaques and neurofibrillary tangles in the patient's brain. We now know that despite these advances, post-mortem studies looking for Alzheimer's disease pathology have shown that 10–30% of diagnoses based on clinical examinations alone are incorrect. Through inaccurate diagnosis, we miss the opportunity to better manage and provide care for these patients.

Amyloid positron emission tomography ("PET") imaging can help to ensure the early detection and diagnosis of Alzheimer's disease. Life Molecular Imaging ("LMI") is one of three companies with a U.S. Food and Drug Administration ("FDA")-approved diagnostic radiopharmaceutical indicated for PET imaging of the brain to estimate beta-amyloid neuritic plaque density in patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. Amyloid PET imaging is aimed at bringing Medicare beneficiaries a diagnostic test for early detection of one of the key neuropathologies of Alzheimer's disease, leading to a better quality of life.

The Centers for Medicare and Medicaid Services ("CMS") is taking steps to provide patients and their physicians with new potential coverage of amyloid PET imaging to detect beta-amyloid, a hallmark of Alzheimer's disease. CMS issued a Medicare National Coverage Determination ("NCD") on September 27, 2013, which allows *conditional* coverage of amyloid PET under Coverage with Evidence Development ("CED") studies. In 2016, the Imaging Dementia—Evidence for Amyloid Scanning ("IDEAS") Study was initiated as a CED trial for amyloid PET imaging. A second CED study, known as New IDEAS will enroll 7,000 new Medicare-eligible patients.

The original IDEAS Study enrolled more than 18,000 Medicare beneficiaries and provided evidence that amyloid PET imaging can change medical management in 60.2% of mild cognitive impairment patients and 63.5% of dementia patients of uncertain etiology. It also found that diagnosis changed in 35.6% of patients. This resulted an increase in diagnostic confidence and a decrease in utilization of alternative diagnostics.

The results of the IDEAS Study provide compelling evidence that there is a health benefit to getting an accurate and early diagnosis. When patients and caregivers learn of their diagnosis, earlier planning for the patient can occur, patients are able to enter clinical trials, receive appropriate therapeutic treatment, and possibly delay entering nursing homes. Many therapeutic candidates have not been successful because clinical trials have not included the correct patients. To appropriately test anti-Alzheimer's disease drugs, clinical trial participants must have Alzheimer's disease. Prior to amyloid PET imaging, 30–40% of patients were incorrectly enrolled. Driving the correct patients into clinical trials can help lead to a cure for Alzheimer's disease.

While there may be no cure for Alzheimer's disease today, symptoms are treatable. Ensuring early detection and accurate diagnosis of Alzheimer's disease will increase access to long-term services and supports that assist people with dementia and their caregivers in their home.