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HIF210140

THE PATH FORWARD:

ADVANCING TREATMENTS AND CURES FOR NEUROGENERATIVE DISEASES

THURSDAY, JULY 29, 2021

House of Representatives,

Subcommittee on Health,

Committee on Energy and Commerce,

Washington, D.C.

The subcommittee met, pursuant to call, at 11:00 a.m. in Room 2123, Rayburn House Office Building, Hon. Anna Eshoo [chairwoman of the subcommittee], presiding.

Present: Representatives Eshoo, Butterfield, Matsui, Castor, Sarbanes, Welch, Schrader, Cardenas, Ruiz, Dingell, Kuster, Kelly, Barragan, Blunt Rochester, Craig, Schrier, Trahan, Pallone (ex officio); Guthrie, Upton, Burgess, Griffith, Bilirakis, Bucshon, Mullin, Hudson, Carter, Dunn, Curtis, Crenshaw, Joyce, and Rodgers (ex officio).

Also present: Representatives Schakowksy and Lesko.

Staff Present: Jeff Carroll, Staff Director; Waverly Gordon, General Counsel; Jessica Grandberry, Staff Assistant;

Tiffany Guarascio, Deputy Staff Director; Stephen Holland, Health Counsel; Zach Kahan, Deputy Director Outreach and Member Service; Mackenzie Kuhl, Press Assistant; Aisling McDonough, Policy Coordinator; Meghan Mullon, Policy Analyst; Juan Negrete, Junior Professional Staff Member; Kaitlyn Peel, Digital Director; Tim Robinson, Chief Counsel; Chloe Rodriguez, Clerk; Andrew Souvall, Director of Communications, Outreach, and Member Services; Kimberlee Trzeciak, Chief Health Advisor; Alec Aramanda, Minority Professional Staff Member, Health; Sarah Burke, Minority Deputy Staff Director; Theresa Gambo, Minority Financial and Office Administrator; Seth Gold, Minority Professional Staff Member, Health; Nate Hodson, Minority Staff Director; Peter Kielty, Minority General Counsel; Emily King, Minority Member Services Director; Bijan Koohmaraie, Minority Chief Counsel, O&I Chief Counsel; Clare Paoletta, Minority Policy Analyst, Health; Kristin Seum, Minority Counsel, Health; Kristen Shatynski, Minority Professional Staff Member, Health; and Michael Taggart, Minority Policy Director.

*Ms. Eshoo. The Subcommittee on Health will now come to order.

Due to COVID-19, today's hearing is being held remotely, as well as in person.

For members and witnesses taking part in person, we are following the guidance of the CDC and the Office of the Attending Physician, so please wear your mask when you are not speaking, and I thank you for doing so.

For members and witnesses taking part remotely, microphones will be set on mute to eliminate background noise, and you will need to unmute your microphone when you wish to speak.

Since members are participating from different locations at today's hearing, recognition of members will be in the order of subcommittee seniority.

Documents for the record should be sent to Meghan Mullon at the email address that we have provided to your staff, and all documents will be entered into the record at the conclusion of the hearing.

The chair now recognizes herself for five minutes for an opening statement.

My colleagues, I called for today's hearing to discuss the challenge of advancing treatments and cures for neurodegenerative diseases. My constituent, Jamie Berry, was diagnosed with ALS one year ago. As she wrote a letter to me

saying that, "With ALS, a piece of you dies every single day. We are simply asking for a fighting chance to live the lives we were meant to live.''

Today we are going to hear from four patients and caregivers who, like Jamie, are simply asking for a fighting chance against the neurodegenerative diseases that have afflicted their families. Brian and Sandra, Kala and Yvonne, thank you, especially for traveling across the country to offer your testimony to us. It was a difficult journey that you have made, and we thank you for being profiles in courage, and being here to offer that testimony.

Our work today is to help create the fighting chance against these deadly diseases. According to the National Institute of Neurological Disorders, each year 50 million Americans are affected by neurological disorders such as ALS, Alzheimer's, Huntington's disease, and Parkinson's. These diseases exact an enormous personal toll, and a cost to the U.S. economy as much as $800 billion annually.

Despite the prevalence, the deaths, and the heart-rending impact on families across our country, there are few effective treatments for neurological disorders. Lack of investment, difficult drug approval processes, and limited understanding of these extremely heterogeneous diseases all keep effective drugs off the market. Private companies invest one-fourth as much into neurological drugs as they do

for oncology treatments. Only 7.9 percent of drugs for neurological disorders successfully make it from phase one to approval. And when they are successful, neurologic drugs take, on average, 50 percent longer to reach approval than drugs for other disease areas.

There have been recent breakthroughs in understanding the genetic basis of the diseases and potential biomarkers, but this has yet to translate into effective treatments. For patients, a diagnosis is still a death sentence.

I think every member of our committee has heard from ALS patients fed up with their lack of options. Two drugs, AMX0035 and NurOwn, have captured attention and sparked a debate over whether the potential benefits of the drugs outweigh the risks. Everyone here shares the same goal: full approval for effective drugs. But the question before us still stands: How do we best get there?

An obvious first choice is full funding to the FDA to ensure they are completely staffed and working at capacity. We made progress with the House fiscal year 2022 appropriations bill that increases the FDA's budget by nearly $250 million. But I am still interested in hearing from FDA about what more should be done to support their important mission.

Second, we need better multi-discipline coordination between FDA, NIH, academic researchers, private drug

companies, and patients. Breakthroughs in cancer and HIV came from a better understanding of the basic science of the diseases, but also through better collaboration, data sharing, and a coordinated strategy. These efforts will bring the breakthroughs from the bench to the bedside.

That is why I am pleased to be working with the Biden-Harris Administration to create the Advanced Research Projects Agency for Health, ARPA-H. This new, independent agency will take on projects like Alzheimer's and ALS, where the market has failed to invest, due to risk, and bring new strategies and collaborations to our current siloed system.

Finally, there needs to be clarity and transparency about the standards for approval for deadly diseases with unmet medical needs. A promise of flexibility rings hollow when it is undefined. I believe these challenges are not insurmountable, that these diseases are not incurable, and that we can provide, as my constituents said, a fighting chance for patients to live the lives they were meant to live.

That is our work today, and for the days and the years ahead.

[The prepared statement of Ms. Eshoo follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. The chair now is pleased to recognize Mr. Guthrie, our distinguished ranking member of the Subcommittee on Health, for five minutes for his opening statement.

*Mr. Guthrie. Thank you, Chair Eshoo, for holding this important hearing about advancing treatments and cures for neurodegenerative diseases.

I want to recognize and thank Kala Booth, who is here today to testify on her experience with Huntington's disease. Kala is a constituent of mine from Cecilia, Kentucky. When not advocating for patients with Huntington's disease and their families, she is -- often can be found face painting at community events. Kelly is the fourth known suspected generation of her -- of HD in her family, and is a strong advocate and voice for the Huntington's disease community.

We are here today to examine how we can further advance treatments, and hopefully find cures for patients suffering from neurodegenerative diseases. We have made progress to create an environment in the United States that encourages innovation for treatments. Thanks to Representative Upton and Representative DeGette in this committee, the 21st Century Cures modernized our health care innovation infrastructure, and included more flexibility to capitalize on this exciting time in science, and enable private-sector innovation.

This committee has also worked on reauthorizing the

National Institutes of Health, and ensuring its budget is adequate to foster research for treatments and cures. Congress has provided FDA the resources and tools to expeditiously review drugs for serious unmet needs and rare diseases. We have continued to examine the expanded access pathway to drugs outside of clinical trials, and added a flexible, right-to-try pathway for patients seeking access to experimental drugs. While we have come far, we have a long road ahead to help patients and their families.

One neurodegenerative disease that I have focused on ever since coming to Congress is Alzheimer's. Alzheimer's is the sixth leading cause of death in the United States. In 2021, an estimated 6.2 million Americans aged 65 and older are living with Alzheimer's. By 2060, that number is expected to reach 13.8 million, barring the development of a medical breakthrough to prevent, slow, or decrease the disease.

My bill, the Bold Infrastructure for Alzheimer's Act, was signed into law in 2018, which created a public health infrastructure across the country to support prevention, treatment, and care for Alzheimer's patients and related neurodegenerative diseases. I have continued my commitment to this issue by introducing the Comprehensive Care for Alzheimer's Act this Congress. This bill works to reduce medical complications for these patients by creating a new

way to fund dementia through Medicare.

It is not just Alzheimer's disease, but the other neurodegenerative diseases that are devastating for the person who suffers with the disease and their family, friends, and loved ones. Huntington's disease is a progressive brain disorder caused by an inherited gene, and can appear as early as age 2, or as late as 80 years old. More than 200,000 Americans are at risk of inheriting the gene from a parent with HD.

Parkinson's Disease is another of the progressive brain disorders that affects approximately 60,000 Americans each year. An estimated 50 to 80 percent of individuals with Parkinson's disease may experience dementia in their lifetime.

ALS, referred to as Lou Gehrig's disease, is a progressive nervous system that affects vital nerve cells in the brain and spinal cord. For people with ALS, the average survival time is 3 years, and reports suggest 15,000 Americans have ALS.

Well, I think we can all agree, while we want to advance treatment for cures for all neurodegenerative diseases, let me point out that H.R. 3, the drug pricing bill, is not the path forward. If this bill becomes law, I believe innovation for therapies to treat neurodegenerative diseases will be in jeopardy, or quite possibly decimated all together. We have

seen estimates that 15 drugs over 10 years, or as many as 100 lifesaving drugs would not come to market due to H.R. 3, because it disincentivizes research and development. H.R. 3 would directly hurt patients like the ones before us today.

I support the bipartisan alternative, Lower Cost and More Cures Act, to reduce drug prices and protect innovative cures.

I am glad to have Kala with us today. Also, we have Brian Wallach and Yvonne Latty here with us today to share how Congress can keep hope alive, and promote innovation for lifesaving cures.

I look forward to working on a solution for American patients. I look forward to working with the chair, and I look forward to seeing a better future, where people can live the life that they were meant to live.

[The prepared statement of Mr. Guthrie follows:]

**********COMMITTEE INSERT**********

*Mr. Guthrie. I yield back.

*Ms. Eshoo. The gentleman yields back, and the chair thanks him for his opening statement.

And the chair is pleased to now recognize the chairman of the full committee, Mr. Pallone, for his five minutes for an opening statement.

*The Chairman. Thank you, Chairwoman Eshoo.

Our understanding of the human brain has rapidly increased in recent years, thanks to advancements in science and research. Yet neurodegenerative diseases and their causes continue to be a mystery in many ways. Few treatments for the symptoms of neurodegenerative diseases exist, and there are also no known cures that significantly slow or eliminate disease progression. As a result, millions of Americans and their families face the heartbreaking daily challenges that come with a neurodegenerative disease.

Congress and this committee in recent years have supported substantial investments in neurodegenerative disease research, and flexibilities for clinical research. In 2016 we passed the 21st Century Cures Act, which authorized over $1.5 billion to support the National Institutes of Health brain research through Advancing Innovative Neurotechnologies, or BRAIN Initiative. This initiative's mission is to revolutionize our understanding of the human brain, and discover new ways to treat, cure, and

prevent brain disorders, including neurodegenerative diseases.

By accelerating the development of novel technologies to map a new picture and understanding of the brain, the BRAIN Initiative is providing a revolutionary foundation for future research and clinical development. And this work will be augmented by the Advanced Research Projects Agency for Health, or ARPA-H, proposed by President Biden.

The FDA also plays a key role. The agency is responsible for the safety and efficacy of all drugs and treatments and development, including those to treat brain disorders. FDA also provides guidance to industry on clinical trial design, meaningful endpoint considerations to determine whether a treatment is beneficial, and market approval. It also works with physicians and patients when treatment options may be unavailable.

Through both the 21st Century Cures and the FDA Reauthorization Act, this committee has encouraged greater guidance on the use of novel clinical trials, and the inclusion of patients in the drug development process. These are all promising steps, but it is clear that a lot more must be done to support the discovery and development of safe and effective treatments and cures, and to provide quality, affordable, and equitable care to patients and their families.

In order to protect patients, caretakers, and the American public, it is important that we understand the current state of science for neurodegenerative diseases, and how we can further improve access to clinical trials and the development of potential treatments or cures. And it is our responsibility to provide Federal agencies with the necessary resources.

So we have two panels. On our first panel we will hear from government representatives at the FDA, the National Institutes on Aging, and the National Institutes of Neurological Disorders and Stroke. And I am particularly interested in hearing about the progress that has been made since the passage of both the 21st Century Cures Act and the FDA Reauthorization Act in 2017, and how these programs are affecting clinical research and drug development, and what more needs to be done.

On our second panel we will hear from researchers, industry, patients, and caretakers, and their experiences are critical to our work here today. Patients and their caretakers live the physical and emotional symptoms of these diseases every day, including the arduous process of enrolling and participating in a clinical trial, and searching for available treatments. These are our neighbors and friends, and for many of us, our family.

So I also look forward to hearing from those on the

cutting edge of research into ALS and neurodegenerative diseases who have conducted clinical trials, and treated patients with the disease.

We will also hear from industry about therapies in the pipeline, and the challenges manufacturers face in developing treatments for neurodegenerative diseases.

I thank all the witnesses for appearing here today. Thank you, Madam Chair, for your role in making sure that we have this hearing today, and I yield back the balance of my time.

[The prepared statement of The Chairman follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. The gentleman yields back. The chair now recognizes Representative Cathy McMorris Rodgers, the ranking member of the full committee.

Good morning to you. You are recognized for your five minutes for an opening statement.

*Mrs. Rodgers. Thank you, Madam Chair. Good morning, everyone.

I was thinking this morning of our work before the pandemic, the many meetings we have all had to listen to advocates fighting for cures and treatments. Hundreds of disease and rare disease groups came to the people's house for the opportunity to share their stories, advocates like my friend from Spokane, Gail Gleason, Steve Gleason's mom. They, like millions of other people, have an extraordinary amount of hope in the promise of American innovation.

Whether it is ALS, Alzheimer's, Huntington's, or another disease, the hope for lifesaving treatments and cures is here, in the United States of America. We cannot forget that. We have led the world. The United States of America is where hope becomes a reality.

That brings me to H.R. 3, Speaker Pelosi's harmful government price controls for prescription drugs. As one mom told this subcommittee, research will stall under H.R. 3. She said other countries have price controls and, "innovation deserts, and innovation deserts are relentless when you need

access to a rare disease treatment to save your children.''

Her son's name is Hunter. He has spinal muscular atrophy, and he is alive today -- in fact, it is his birthday, his 10th birthday -- because of a breakthrough treatment. For children like Hunter, it would be devastating if price controls were jammed in the majority's reckless tax and spending. It would lead to less innovation, fewer cures, and no hope for many people who deserve a fighting chance for life. For that fighting chance, we should be working on bipartisan solutions like H.R. 19, the Lower Cost and More Cures Act.

In addition, we should be leading the way in a bipartisan way to fund more basic research, support research around the causes of diseases, and unleash the private sector, just like we did with COVID-19 vaccines.

This is very personal for me. My son, Cole, has Down Syndrome. It is the most common chromosomal abnormality. Yet there is still a lot that we don't know about that twenty-first chromosome. For example, the scientific community has acknowledged that 100 percent of people with Down Syndrome will develop the brain pathology for Alzheimer's in their lifetime, but only about half will experience the symptoms of dementia. The reason for this is still not understood.

Imagine what it would mean if we unlocked the mysteries of the twenty-first chromosome. It would lead to major

medical discoveries, maybe even a cure for a disease like Alzheimer's. It is why I was surprised to see the Biden budget proposed to move NIH's INCLUDE program from the Office of the Director to the National Institute of Child Health and Human Development without any explanation.

What problem does this reorganization solve? We will have the same cross-institute center collaboration and coordination. This program has been one of my top priorities, and I am disappointed that, if there were concerns, NIH didn't consult with Congress.

I want to be very clear. I have historically been a champion for NIH. I have supported doubling their funding. I co-chair the Neuroscience Caucus. And I have promoted the BRAIN Initiative from the beginning. That NIH is on the verge of a trust crisis with this committee and the American people, this is a warning. Proposing moving a program like INCLUDE with no consultation with the authorizing committee in Congress is one thing. Another is a lack of respect for congressional oversight on how NIH money, research money, is received and spent.

To inform a scientific and objective investigation into the origins of COVID-19, I have made many requests to NIH to be transparent and provide documents. We have received no documents, including for grant documents releasable to the general public under Federal law. It is unacceptable. I

have told Dr. Collins this directly, when we spoke about ARPA-H.

President Biden has requested more than $6 billion for ARPA-H, with less accountability and transparency than we have now. If I were to support this, I would need more confidence and trust in the oversight and management of the 44 billion in taxpayer funding going to NIH now, including a clear picture of how much of that research is going to China.

I will close by thanking the patients, the families, the caregivers, and the researchers that are with us today. We are grateful, and we share your mission to unleash American innovation, support clinical trials, improve early diagnosis, and improve the lives of millions of Americans. That is why I am passionate about making sure NIH research dollars are spent wisely and accountable. That is what we can do, and help unleash -- we need to unleash the private sector also to tackle these diseases, with the same sense of urgency as we had with COVID-19.

[The prepared statement of Mrs. Rodgers follows:]

**********COMMITTEE INSERT**********

*Mrs. Rodgers. I yield back.

*Ms. Eshoo. The gentlewoman yields back.

The chair would like to remind members that, pursuant to committee rules, all opening statements shall be made part of the record.

I would now like to introduce our witnesses for our first panel. And colleagues, we have terrific witnesses today. And I thank, of course, the minority for your role in bringing people forward, as well.

First, Dr. Richard Hodes is the director of the National Institute on Aging at the National Institute of Health.

Welcome to you, Dr. Hodes.

Dr. Walter Koroshetz is the director of the National Institute of Neurological Disorders and Stroke at NIH.

Welcome to you, and I hope I haven't butchered your name.

Dr. Patrizia Cavazzoni is the director of the Center for Drug Evaluation Research at the U.S. Food and Drug Administration.

And welcome to you, Dr. Cavazzoni. I think this is -- welcome to the committee. I think it is the first time that you are testifying here.

So the chair now recognizes Dr. Hodes for your five minutes for testimony.

STATEMENT OF RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTE OF HEALTH; WALTER J. KOROSHETZ, M.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, NATIONAL INSTITUTE OF HEALTH; AND PATRIZIA CAVAZZONI, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

STATEMENT OF RICHARD J. HODES

*Dr. Hodes. Good morning, Chair Eshoo and Ranking Member Guthrie, and members of the committee. Thank you for the opportunity to be here. I am Richard Hodes, the director of the National Institute on Aging, which aids Federal efforts to identify ways to prevent, treat, and care for those who are currently afflicted with Alzheimer's disease.

As noted, Alzheimer's disease is one of the most common and tragic of the neurodegenerative diseases affecting some 6 million people now, and as noted, again, expected to double, if nothing changes, by 2050 or 2060.

Thanks to the investment that has come from congressional appropriations over the past years, we have made enormous progress in understanding this disease. This understanding has ranged from basic fundamental science through the translational trajectory. It has demonstrated the complexity of disease, and given us new insights into

potential targets.

From the most basic level of cellular and molecular biology, enterprises such as the AMP AD, or Accelerating Medicines Partnership for Alzheimer's. I brought together pharmaceutical, corporate, fundamental basic science supported by NIH, as well as philanthropic and foundational funds, all to generate, in the spirit of open science and acceleration, a process that has leaded to the identification of some hundreds of new novel targets for Alzheimer's, the changes that occur in the brain that represent potential targets for intervention.

The second phase of this, just announced this year, will move towards the important note of personalized, or individual medicine, which recognizes what we have discovered to be the complexity and difference in Alzheimer's disease's underlying process from person to person.

Translating this basic science into clinical interventions has been identified as a particular challenge. And here, too, NIH has instituted infrastructure to try to accelerate and de-risk for public and private sectors the transition from basic science to clinical studies.

We now support, by NIA alone, more than 50 drug trials that are targeting a variety of processes, including inflammation, a protein folding stability, as well as amyloid and tau. These are moving to recognize the complexity of

disease, and understanding that it is unlikely that any one treatment is going to be sufficient to address all.

We are also looking at the science of clinical research itself, and, as noted, the importance of recruiting a diverse population represented within the U.S., and including some of those most vulnerable, such as, as noted, again, Down Syndrome.

We have come to realize that the neurodegenerative diseases like Alzheimer's actually reflect a process that goes on for years and decades prior to the appearance of symptoms. And therefore, the importance of being able to identify and intervene in these processes before massive loss of brain cells and their connections.

Until recently, Alzheimer's was diagnosed only at postmortem, or autopsy. Now biomarkers such as PET scans have allowed us to see the processes that go on in the brain earlier than symptoms appear, and could track the response to interventions. Most recently, blood markers, which have the promise of being less intrusive, less invasive, and less expensive, will bring a new ability to recruit people into studies, track their disease, and track the outcomes of intervention.

For people currently living with Alzheimer's disease, it is also important that research be conducted as NIA makes it a priority to understand the best ways to support those

living with and those caring for people with Alzheimer's disease. A collaboratory (sic) recently established has now identified an infrastructure through collaborations and partnerships with health care components that allow us now to conduct pragmatic trials, in short notice and short turnaround, to identify success early, for the best ways to care for people with Alzheimer's, improving quality of life for both them and those who care for them.

We understand that prevention is also an important way, in addition to treatments and the arrest of disease, once identified. And most recently, in terms of preventive interventions, we have promising news from the study SPRINT MIND, which showed that a very intensive approach to controlling blood pressure has the ability to decrease the appearance of mild cognitive impairment, a kind of precursor of dementia.

Similarly, we currently are pursuing interventions that affect diet, exercise, cognitive training, combinations of them, all in attempt to find ways in which we can intervene to prevent disease, and the science of behavior change itself, to make sure that we know how to best inform people so they can modify their lifestyles in concert with those discoveries.

So, again, I thank you for the ability to appear here, and thank you profoundly for the support that Congress has

given that has allowed this progress across the --

[Audio malfunction.]

*Dr. Hodes. -- as we come to understand Alzheimer's disease and, therefore -- to better intervene. Thank you so much.

[The prepared statement of Dr. Hodes follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Dr. Hodes.

Next we call on Dr. Walter Koroshetz for your five minutes of testimony. And thank you for your work, and for being here with us today.

STATEMENT OF WALTER J. KOROSHETZ

*Dr. Koroshetz. Well, thank you, Chair Eshoo, Ranking Member Guthrie, and distinguished members of the committee. So, yes, I am Walter Koroshetz, I am a neurologist currently leading the National Institute of Neurological Disorders and Stroke, or NINDS, where we strive to understand the nervous system, its hundreds of disorders, and to use that knowledge to reduce the burden of illness.

In neurodegenerative disorders, the nerve cells in the brain and the spinal cord die over time. And unfortunately, once a neuron dies, it is not replaced. So there are many forms of neurodegenerative diseases, each affecting different parts of the brain or spinal cord. They all rob individuals of the ability to move, or think, or communicate and, eventually, even to take care of themselves. And most tragically, they rob people of years of life.

This motivates the tremendous urgency among the NINDS research community to uncover highly-effective treatments. I am hopeful that a host of new discoveries and tools will lead to real breakthroughs, but I am going to focus my remarks on just three.

The first is genomic therapy. As Congressman McMorris Rodgers just mentioned, recently we saw an almost miraculous effect of genomic therapies in spinal muscular atrophy. It

is a genetic disease that causes degeneration of the same motor neurons that are affected by ALS. But gene treatment in infants has restored function and saved lives. But this is not a one-off. This success should drive a whole new genomic approach to the inherited neurological diseases. Genomic therapies are already underway for Huntington's disease and some forms of ALS, and I believe that we are on the doorstep of a revolutionary era of neurogenomic therapies, especially as they become linked to the cell-specific delivery tools being developed by the BRAIN Initiative.

Secondly, these genomic tools are now in the clinic for inherited neurodegenerative disorders, but their promise is much broader. In most neurodegenerative disorders there is a subgroup of patients who have an inherited form, due to a known mutation. But most persons have what is called a sporadic form, which is not inherited. Luckily, fruitful studies of the inherited disease-causing mutations have uncovered pathways of neurodegeneration that are common to the non-inherited forms, as well. So therapies are now being developed to manipulate these common pathways to prevent neuron dysfunction and death.

Thirdly, there has emerged a somewhat common theme in the treatment -- potential treatment of multiple neurodegenerative disorders. When we look under the

microscope at the brains of people who died from neurodegenerative disorders, we almost always see clumps of a protein inside the sick or the dying cells. The specific protein in the brain areas involved vary, disease to disease. These abnormally aggregated proteins seem to have the ability to spread from a sick nerve cell to a healthy one, and thereby damage one brain region after another.

As an example, in Parkinson's disease, there is some evidence that protein aggregation may actually start in the nerves that supply the gut, due to interactions with bacteria in our guts. Over the course of years, these aggregated proteins spread from the nerves of the gut, first to the lower part of the brain, and then higher up to cause Parkinsonism. Treatments to block the spread of aggregative proteins are being developed for Parkinson's, but for many other neurodegenerative disorders.

And furthermore, new biomarkers will allow the identification of at-risk individuals, and enable early treatment that blocks the spread before the disease leads to any disability whatsoever.

So very exciting things in these three specific examples, but let me turn to NINDS's overall strategy for fighting neurodegenerative diseases.

On the basic science side, we apply what is learned in one disorder or area of science to others. We place great

emphasis on the nervous system, as a whole, coordinating a network of cells, and how it integrates with other body systems. For instance, elderly persons with a diagnosis of dementia commonly have signs of Alzheimer's disease, along with diseased brain blood vessels caused by years of high blood pressure and evidence of injury to the brain's connecting fibers, or so-called white matter disease.

As Dr. Hodes mentioned, the NIH SPRINT MIND study showed that aggressive blood pressure control reduces cognitive impairment over time, and suggests that, from what we know now in how to control blood pressure, we can decrease not only heart attack and stroke, but also cognitive decline and, potentially, dementia.

And our public health campaign called Mind Your Risks, we are targeting Black Americans in their late to -- twenties to mid-forties, as this group suffers from the greatest disparities in brain health due to hypertension.

In summary, I would emphasize the tremendous scientific challenges that remain as we strive to save persons from neurodegenerative disorders, but offer my optimism, which stems from seeing the emergence of really powerful new tools, just in the last 5 to 10 years to be able to combat these diseases.

Thank you very much.

667 [The prepared statement of Dr. Koroshetz follows:]

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669 **********COMMITTEE INSERT**********

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*Ms. Eshoo. Thank you, Doctor. That is compelling testimony, and we so appreciate your work, and your being with us today.

Next we have Dr. Patrizia Cavazzoni.

Welcome to the committee, and the chair recognizes you for your five minutes of -- to present your testimony to us today.

[Pause.]

*Ms. Eshoo. Do we know why Dr. Cavazzoni is not on the screen?

What?

*Voice. Ask her to unmute.

*Ms. Eshoo. You need to unmute, Doctor.

*Dr. Cavazzoni. My apologies, we were double-muted. Chair Eshoo --

*Ms. Eshoo. Welcome to you. There you are, there you are.

*Dr. Cavazzoni. Thank you, here I am. Thank you. Apologies for the technical difficulties. So let me start.

STATEMENT OF PATRIZIA CAVAZZONI

*Dr. Cavazzoni. Chair Eshoo, Ranking Member Guthrie, and members of the committee, thank you for the opportunity to testify before you today.

Also, I would like to thank my colleagues from NIH for their ongoing support and willingness to collaborate with FDA as we translate research into therapies.

In recent years, drug development advancements have been life-changing. New therapies are brought to patients faster, thanks to more efficient clinical trials and the use of expedited regulatory pathways. One need only look at the pace of development of the COVID vaccines and therapeutics to see how quickly scientific research can result in widespread benefit.

Many diseases which would have resulted in a patient's death just a few years ago, can now be treated and, in some cases, cured by FDA-approved therapies. While FDA has approved countless transformative therapies for life-threatening diseases, these stand in stark contrast to the conditions for which there are few or no available treatment options.

I applaud the subcommittee's attention to this topic by holding this hearing today.

Neurodegenerative disease has caused tremendous

suffering for patients and their loved ones. We need to adopt additional innovative approaches for these diseases to bring new drugs to people who desperately need them. There are three primary elements to our approach that I want to highlight today: the need for more research, employing regulatory flexibility, and actively listening to the people stricken by these terrible conditions.

Neuroscience is an area of medicine where there is tremendous unmet need for safe and effective treatment, and for research that can guide and inform the development of new therapies. Although there has been great progress in basic and pre-clinical research for neurodegenerative diseases, we have yet to identify the key underlying molecular defects that give rise to many of these conditions.

The current limitations present significant challenges for drug development. This holds true for ALS. For instance, in ALS and many other neurodegenerative diseases, there are no easily-measured biomarkers that are reliable predictors or surrogates for the rate of disease progression in individual patients. Such tools would improve the precision with which drug response could be evaluated, leading to more robust and earlier insight to distinguish the more promising drugs from those that are less likely to succeed.

Researchers are continuing to make advances in

understanding the underlying causes of neurodegenerative diseases, and this holds promise for drug development.

As an agency, we are using every tool at our disposal to help facilitate the development of treatments for these diseases. We have long stressed the need to exercise regulatory flexibility in applying the statutory standards when it comes to medical products for serious diseases with unmet medical needs, while making sure that these are effective and have a favorable benefit-to-risk profile. This flexibility flows from the statute, and through our regulations and guidance.

In the meantime, we understand the need for access to therapies when people with life-threatening diseases cannot participate in clinical trials. This is why the agency grants almost all individual patient expanded access requests. However, an essential step in the expanded access process is the company's willingness to provide the drug. And there are instances when this doesn't happen, for reasons such as ongoing clinical trials, financial burden, or insufficient drug supply. We do all we can in these situations to help people who desperately need these drugs.

Finally, the capstone of all our efforts are the people who need therapy. Their experiences, perspectives, and priorities are a critical aspect of drug development. Patient-focused drug development enables the delivery of

therapeutics that have a meaningful impact on people's quality of life, and target what they consider the most important aspect of their diseases.

I look forward to discussing these and other issues with you today. We recognize the impact these devastating diseases have on patients and their loved ones. We share the sense of urgency. And, as an agency, we stand ready to make full use of our authorities in order to help bring new therapies to people with these diseases as quickly as possible. Thank you.

[The prepared statement of Dr. Cavazzoni follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Dr. Cavazzoni.

We are now going to move to member questions, and the chair recognizes herself for five minutes to do so.

First, to Dr. Cavazzoni, in your written statement you say that a treatment that provides meaningful incremental benefit would still be desirable. Now, many of the ALS advocates think that the statistically significant outcome in the Amylyx trial that showed a near three-point improvement was incremental, but meaningful.

Now, as we all know, these are individuals who are usually told they only have two to five years to live. And what I want to examine is -- because there is a discrepancy, I think, between FDA and incremental -- meaningful, incremental benefit, being desirable, and actually approving a drug that produces that.

So would you comment on that, and tell us how you define meaningful, incremental benefit?

[Pause.]

*Ms. Eshoo. You need to unmute.

*Dr. Cavazzoni. Thank you, Chair Eshoo, for that question. We generally don't comment on a specific drug program, as some of the information is sensitive.

Having said so, generally --

*Ms. Eshoo. But Doctor, in general, in general. I understand that you can't comment on specific drugs. I just

used that as an example. But in general, how do you define incremental?

*Dr. Cavazzoni. So, in general --

*Ms. Eshoo. See, I think that, you know, the context here is that incremental, in these cases, is small. But it represents a great deal of hope to people that are living with a death sentence.

*Dr. Cavazzoni. So, in general, we look at incremental benefit, and incremental gains from a -- from several points of view. The perspective of the patient is very important to us, because what we hear from the patient is -- it really guides us as to what they view as meaningful incremental gains.

And what we have heard from people suffering from ALS, for instance, is that improvement in symptoms, and improvement in quality of life is very important, in addition to lengthening of survival. And so we have actually reflected these perspectives in how we guide developers -- our programs for treatment for ALS, and this is actually reflected in our guidance on developmental drugs for ALS, where we point out that we -- developers should be looking at a variety of endpoints.

For instance, not only for --

*Ms. Eshoo. Let me -- I need to interrupt you, because I need to get another question in, and it deals with the

European conditional approval pathway. They have a different system. When they approve -- when the drug is approved, on the condition that they will -- be evaluated further while on the market. We don't do that in the United States. And this means that the Amylyx drug may be available to European patients two to three years before American patients.

So if FDA had a similar authority for a conditional approval pathway, would that give the FDA more flexibility in getting potentially promising therapies to dying patients sooner?

And if so, would the -- does the FDA seek that kind of legislation in Congress for a conditional approval?

*Dr. Cavazzoni. So thank you for that question. That is a -- it is a very important question.

The -- when it comes to approaches to expedite development of a drug for life-threatening diseases, we think we have a lot of tools at our disposal, and that the limiting factor in applying all of the tools that we have, such as accelerated approval, for instance, is really the lack of understanding of the biology of the diseases. And we are very eager to work with sponsors to identify some of the biomarkers, and the markers of the disease that would allow us to utilize our expedited pathway, including accelerated approval, in neurodegenerative diseases to accelerate the development.

*Ms. Eshoo. Well, my time is expired, and the chair now recognizes Mr. Guthrie, our ranking member, for his five minutes of questions.

*Mr. Guthrie. Thank you, Madam Chair, for the recognition, and the first question is for Dr. Koroshetz and Dr. Hodes.

As you know, the NIH BRAIN Initiative is intended to produce a revolutionary new dynamic map of the brain that can show how individual cells and complex neural circuits interact in both time and space. How will this initiative -- the question for you two -- how will this initiative improve our knowledge of neurodegenerative disease, and help researchers find new ways to treat, cure, and even prevent these diseases?

*Dr. Koroshetz. Well --

*Mr. Guthrie. Dr. Koroshetz?

*Dr. Koroshetz. Yes, thanks very much. So this is really -- I was talking about this, but I won't -- I will say basically three things.

One is that we now have the ability, after amazing discoveries -- try and get a census of the human brain. That is our transformative project that we are launching now. And that was enabled by technologies that allow us to look at single cells, and analyze what is inside those single cells. But instead of 400 cells over 6 months, we can do a million

cells in a few days. And that now is an amazing --

*Voice. It is amazing, isn't it?

*Dr. Koroshetz. -- study the brain of people with neurodegenerative diseases, and we will be able to tell what cells are missing. We will also be able to tell what is the difference between a sick cell and a healthy cell, as the disease progresses.

The second thing this will allow us to do, which is really amazing, is that inside these cells there are, like, genomic keys that open the door to the cell. And what we are trying to do is to find those keys for every specific cell, and then link them up to a genomic therapy that, when we give it to the person, it will only go into the cell that needs it. And that is -- that kind of precision targeting will be absolutely game-changing.

And the last one is that, as a neurologist, we see the patient, and we see what symptoms they have, and then we look in the brain and we see what kind of pathology we see. And we say pathology caused the symptom. But what is in between is the circuits. And we had no way of seeing those circuits. But now, with the BRAIN Initiative technology, we can see those circuits in action, which is really exciting. So the circuit, this function itself, becomes the target.

And for instance, just an example, there is a study of people who do not have any dementia, they are perfectly

normal, but their brains look like they have terrible Alzheimer's disease. So an example -- the pathology is fooling us. The circuits are still healthy. And so these kinds of things can be explored with the tools of the BRAIN Initiative.

Those are the three things that I would offer up --

*Mr. Guthrie. Okay, thank you, I appreciate that. I want to ask Dr. Hodes, instead of answering that question, that second question, you can emphasize -- you can go back to that one, if you would like.

But Dr. Hodes, as you know, caring for a person with Alzheimer's disease or other dementia poses unique challenges. Nearly all people living with dementia experience at least one neuro-psychotic symptom, which can include anxiety, irritability, agitation, depression, hallucinations, and delusions. And these are challenges, a leading reason that prompt -- family caregivers decide to place their loved ones in institutional care settings.

So the question is -- and you can respond to the other one, as well -- but do you believe that providing individuals living with neuro-psychiatric symptoms and dementia in their family with safe and effective treatments is an important priority?

But also, would you update us on the search for treatment options to address this unmet medical need?

*Dr. Hodes. Thank you, and a very important question. As I alluded to briefly, and can reinforce now, research -- ways in which to maximize quality of life, and care for those living with dementia is as current and imperative as our searching for the cure itself. And there are currently over 80 studies funded by NIA alone trying to understand which are the most effective of these interventions, so they can be promulgated.

Some already have. REACH is one, for example, that was a result of an NIA-sponsored trial some years ago that has been promulgated through the VA, and through Indian Health Service as one of the examples. But we are constantly looking for ways in which, through the pragmatic clinical trials I mentioned, randomized trials, every bit as rigorous as a drug trial, trying to look at the very best kind of intervention. And we are learning more and more about this every day.

So our ability to translate this to real care is on the horizon and happening now.

If I could just very briefly amplify on what --

*Mr. Guthrie. If you -- just some breakthroughs you see coming, yes, some breakthroughs you see coming.

*Dr. Hodes. Well, in terms of caregiver support?

*Mr. Guthrie. Yes, just in Alzheimer's research, yes.

*Dr. Hodes. Well, in Alzheimer's research, in general,

just a good point to start is amplifying what Walter Koroshetz described, the enthusiasm that I think we all share. This incredible ability to look at the levels of individual cells and circuits that we never had before begins with the basic science.

So these initial studies are done in normal brains, in animals, and then in humans. But it immediately provides the opportunity for breakthrough, as Walter alluded to, for diseases such as Alzheimer's. And now to find out what is -- what we have already learned, when we look at the genetics, the profiles of -- cell and molecular biology in brains of patients with Alzheimer's, from -- they are not all the same. So we are now poised, as never imagined before, to look at ways to intervene and target through some of the strategies Walter mentioned at a very --

*Mr. Guthrie. Dr. Hodes, I think I have let you run over time, so I am going to have to stop here. Hopefully, we will hear more as we go through. I yield back.

*Dr. Hodes. Thank you.

*Ms. Eshoo. The gentleman yields back. I thank you, Doctor.

The chair now recognizes the chairman of the full committee, Mr. Pallone, for his five minutes of questions.

*The Chairman. Thank you, Chairwoman Eshoo.

One of the strategies that has been discussed in witness

testimony today is bolstering expanded access, sometimes called compassionate use. Expanded access allows patients with serious or life-threatening conditions with no satisfactory alternatives, and who cannot enroll in a clinical trial, to access an unapproved investigational drug if their physician says that the potential benefit justifies the potential risk, and that providing access won't interfere with an ongoing clinical trial. And I have some questions about expanded access.

First to Dr. Cavazzoni, in 2017 former FDA commissioner, Scott Gottlieb, testified before this committee, and said that FDA approved expanded access requests 99 percent of the time. I wanted to know two questions.

One, is that still the case? And if so, why do some patients still have difficulty accessing drugs under the program?

And second, what reasons would manufacturers have for declining to participate in expanded access, if you would?

*Dr. Cavazzoni. Thank you for the question, Chairman Pallone. I can confirm that we are still approving the overwhelming majority of expanded access, individual patient expanded access applications. And between -- over the past 5 years we have approved close to 98 percent.

There are reasons for companies not making the drug, an investigational drug, available through expanded access. And

the first one, and most common, is the fact that there may be an ongoing clinical trial with that drug, and that the patients who are asking for expanded access may be eligible for that clinical trial, or they may be concerned about slowing down the recruitment of a clinical trial that could provide important answers on the drug.

For smaller companies, what we have also seen is that there may be some financial constraints in supporting an expanded access program. And sometimes we also see some issues with the limitations in the drug supply, when all of the drug supply has to be devoted to an ongoing clinical trial, for instance, or again, due to some financial considerations, particularly with the smaller companies.

*The Chairman. All right. Now, some have said that expanded access can improve research into neurodegenerative diseases, because more data would be generated from patients on the treatment. So let me go to Dr. Koroshetz.

Can you speak about NIH's view on whether data generated through an expanded access program could be useful for scientific research?

And how would NIH consider research proposals based on data generated from an expanded access program?

*Dr. Koroshetz. Right. So that is a very good point, to try to differentiate the finances of expanded access and the scientific value.

So for NIH, in a trial, the greatest value would be in continuing access to patients who are enrolled in the trial after they have finished the trial. That -- because then you have a comparator group, and you can check for durability of any result that was found. And then you can also do a crossover of patients who are on placebo and then get on active treatment. And you get information from that.

It is very hard to get -- unless there is a tremendous effect size, it would be very hard to get scientific value out of a broad expanded access, unless the treatment has a very big effect size. But if it is a smaller effect size, then you wouldn't be able to tell that there has been a change in the condition.

*The Chairman. Okay, can I ask -- I mean thank you so much. Let me go back to Dr. Cavazzoni.

Can you explain why a clinical researcher might choose to exclude a patient who has participated in an expanded access program from participating in a trial?

Is it possible to put safeguards in place to ensure that expanded access participation doesn't harm clinical trial enrollment?

*Dr. Cavazzoni. I cannot hypothesize why an individual researcher may decide to exclude a patient from a specific clinical trial. However, in general, studies routinely allow prior exposure to investigational agents, including

potentially expanded access, after a suitable period of time when the patient has been off that investigational agent. And there may be some situations where the developers may have concerns that the prior exposure to an investigational agent may have an impact on the conduct of the clinical trial, or the interpretation of the results.

When it comes to what we do at FDA, we are very sensitive to this, and we routinely work with sponsors to attempt to ensure that they do not use overly restrictive or unnecessary criteria to exclude patients who have been on investigational agents. And this is really part of our broader commitment to making sure that trials are inclusive when it comes to the diversity of patients that are included in the clinical trials, and the full scope of the manifestations of the disease, particularly in --

*Ms. Eshoo. The gentleman's time has expired. The gentleman's time has expired. The chair now recognizes the ranking member of the full committee, Mrs. McMorris Rodgers, for her five minutes of questions.

*Mrs. Rodgers. Thank you, Madam Chair.

Dr. Cavazzoni, FDA has been working on inclusivity of clinical trials. But as today's hearing is demonstrating, there is still a lot of patients desperate for access to drugs still in development that cannot get access. How do we appropriately address concerns about the need to broaden

eligibility for clinical trial participation?

And would you speak specifically towards the guidance FDA has provided, if any, about those including people with Down Syndrome in clinical trials designed to support drug approval?

*Dr. Cavazzoni. Thank you for that question. We have been putting a lot of thought in how to improve the diversity of representation in clinical trials. And as you have referenced, we have recently issued guidance to instruct or help developers on how to expand the eligibility to clinical trials, and to find ways to make sure that under-represented populations, including -- beginning with racial and ethnic minorities, are included in these clinical trials. And we are continuing to work to really make sure that we -- that developers are -- follow our guidance.

When it comes to the progress that we have done so far, we have seen over the past several years that there have been some gains when it comes to representation of women, racial and ethnic minorities in many therapeutic areas. There are certain therapeutic areas where there is still more work to do, including, for instance, trials of Alzheimer's disease. And we are very focused in working with developers to make sure that they deploy all the tools that are available to them, or even new tools that they may be able to identify to expand the diversity of the populations that are --

*Mrs. Rodgers. Mike isn't on. That might help. Okay.

Dr. Cavazzoni, thank you. I wanted to highlight the issue of individuals with Down Syndrome, because, as I mentioned in my opening statement, 100 percent of them are developing Alzheimer's, and yet they are not being included the way I believe they should, that we should embrace what we could learn from those with Down Syndrome, with that extra twenty-first chromosome, when it comes to research, and really including them in clinical trials. They develop juvenile leukemia at a higher rate, but no tumor cancers. Let's embrace what they could -- what we could learn from those with Down Syndrome for so many others.

Dr. Koroshetz and Dr. Hodes, individuals Down Syndrome experience a lifelong, chronic autoinflammation. While FDA just granted accelerated approval for anti-amyloid therapy, is NIH exploring alternatives, such as research to explore the use of therapies that modulate the immune system to slow down or even reverse Alzheimer's disease and other neurodegenerative diseases?

*Dr. Hodes. Yes, thank you for that specific question. As I alluded to, the diversity of targets that are now being involved in clinical studies, clinical trial, that has expanded, obviously.

So for, for example, in the more than 50 clinical trials now at NIA for drugs, the majority of them are looking at

targets other than amyloid and tau. Among them are the pathways -- inflammation and the immune system. This is coming from information -- science, as well as the nature of the pathology seen, so very much so --

[Audio malfunction.]

*Dr. Hodes. -- to the inclusion and the importance of including Down Syndrome as a population very vulnerable to Alzheimer's disease. It has been a pleasure working with you over the past years.

And, as you know, currently ongoing is the ABC, the Alzheimer's Biomarker Consortium for Down Syndrome, which is very rapidly putting together a cohort of individuals who are studied for the progression of the disease by biomarkers, and will provide a very important basis for their inclusion in intervention and clinical trials, as appropriate, as well.

*Mrs. Rodgers. Okay, thank you. Are there any efforts being funded at NIH or private entities to analyze neurodegeneration, brain inflammation, and other accompanying processes from birth to life?

And what about research to identify other early life events that may predispose individuals with Down Syndrome to Alzheimer's disease?

And would you just discuss further work in this space in 11 seconds?

*Dr. Hodes. Yes. Again, as you know, and under the

rubric of INCLUDE, where many institutes, including NIA, are participating, there is a multifaceted study looking at the role of inflammation as -- central nervous system, but also other autoimmune disorders, the cardiovascular disorders, which are a part.

So I think we have been very effective, as a consortium, across institutions, across all of NIH, in collaborating and focusing those efforts on the population -- critical to the population --

[Audio malfunction.]

*Dr. Hodes. And as you point out also, very informative to the components of the --

*Mrs. Rodgers. Thank you. Thank you for being with us, and for your work.

I yield back, Madam Chair.

*Ms. Eshoo. The gentlewoman yields back. The chair is pleased to recognize the gentleman from North Carolina, Mr. Butterfield, for your five minutes of questions.

*Mr. Butterfield. Thank you very much --

*Ms. Eshoo. Please unmute.

*Mr. Butterfield. -- Chair Eshoo, for convening this very important hearing. And thank you to our witnesses for your testimony today. Thank you for your dedication, and thank you for your brilliance.

This is an issue that we should be able to embrace on a

bipartisan basis. And so I want to begin to develop this with Dr. Cavazzoni.

Thank you for your testimony and your incredible work at FDA. You noted in your testimony that, although great progress has been made in treating and curing some conditions, you said the progress has not been even. Later today we will hear from patients and caregivers and researchers who will share what the human cost of this failed progress is.

FDA appeared to recognize the human cost when it released its 2019 guidance on ALS drug development. But since then it has denied approval for two ALS drugs. And so I would like to better understand how FDA is applying its guidance in practice.

One promising therapy, I think, was recently rejected by the FDA, even though it showed a 30 percent slowing in disability, and a 6-month prolongation in survival for a subset of patients. And so my understanding is that the basis of the rejection was a perceived need for a confirmatory trial. And so I am told that such a trial will take 3 to 4 years, during which time half of the 20,000 Americans currently living with ALS will leave us.

And so FDA said, in its 2019 guidance, that it understood the appropriateness of exercising regulatory flexibility for serious diseases with unmet medical needs --

end of quote. That is a long opening statement. Here we go. Here is my question.

Why hasn't FDA employed this flexibility for ALS treatment, when it has demonstrated its willingness to be flexible with the emergency use authorizations in other areas?

*Dr. Cavazzoni. Thank you for your question, and you are -- the questions that you raise are really very important, and core to how we view our work.

We are operating in a manner that is fully consistent with our guidance. Understanding that there has been a lot of hope that has been pinned on certain therapies, and that, unfortunately, they may have been disappointed -- disappointment with some programs. Our guidance, and the way we operate, recognizes that, first and foremost, there is a higher threshold for risk in patients who are suffering from diseases such as ALS, because they are so rapidly progressive and lethal.

And we also, as we look at how to guide developers, and how we interpret the data that they put in front of us, we take into consideration the fact that we -- there has to be a higher threshold for risk, and also that we may be in situations where we may have -- I have to accept some degree of uncertainty around the benefit in these particular diseases.

*Mr. Butterfield. All right, let me move on to the next question. This five-minute timeframe goes very quickly.

My staff, a few days ago, had the opportunity to speak with the director of the Duke -- that is Duke University -- ALS Clinic, which is right near my district. The director shared that he has taken care of over 3,000 ALS patients in his entire career, most of whom could not find a place in a clinical trial. And so, out of desperation, his patients are self-experimenting with treatments they buy from the Internet.

Not only are patients likely suffering financial and health harms from self-experimentation, but the research community suffers because this is not properly studied. I think everyone would agree that an access program with appropriate oversight and study would be preferable to self-experimentation.

I realize FDA cannot require a company to offer a product under expanded access, but can FDA incentivize participation, or leverage research generated from the expanded access program?

*Dr. Cavazzoni. We work very actively with sponsors to establish expanded access programs. And in fact, there have been instances where we have repeatedly asked sponsors to offer a drug under expanded access, and the sponsor has not been willing or able to do so.

And we also see the utility in data that is gathered from expanded access programs, particularly when it comes to rare diseases, where we try to accelerate the development by not requiring as large of a safety database that we would normally do so. And so we value the expanded access programs when those are put in place, as a way to also --

*Mr. Butterfield. Thank you. I am going to have to ask you to stop for a moment.

Madam Chair, I yield back. There is much more to go on this, but we will try it if there is a second round. Thank you, I yield back.

*Ms. Eshoo. The gentleman yields back. And thank you for your excellent questions, Mr. Butterfield.

The chair is pleased to recognize the gentleman from Michigan, Mr. Upton, former chairman of the full committee, and a member that we all have deep regard for.

You are recognized for your five minutes of questions.

*Mr. Upton. Well, thank you, Madam Chair, and -- for chairing this incredibly important hearing. And I appreciate the testimony by the witnesses, not only on this panel -- and I have read through the testimony of those that are coming on the second panel, as well.

I want to just remind my colleagues that when we embarked on 21st Century Cures, important legislation that every one of us then on the committee supported 53 to nothing

back in 2016, we worked with the FDA, we worked with the agencies, we worked with the patient groups. And we asked a lot of questions: What could we do to advance the cures for these diseases that impacts everybody?

You know, my neighbor next door, he died of ALS, a lot of friends with Parkinson's. We know people that are getting cancer and, hopefully, cured. That rate has, thank goodness, gone up.

And I would recommend the reading of Michael Milken's piece in the op ed page yesterday in the Wall Street Journal. He talks about where we can go for now.

And the chair was with me, along with Mr. Guthrie, with the President back in March, when he talked about ARPA-H, and that is an important thing. That is an element, a new element, that is going to be funded in the Labor H appropriation bill, and ultimately, will get to the President's desk.

And Diana DeGette and I are working again on a Cures 2.0 bill that will be included. But as part of 21st Century Cures, what we did was we also asked the FDA, what could we do to help you do your job better? How do we find the cures? How do we help you approve the cures earlier, so that we can deal with these folks, and not have them languish and die before their lives can be bettered or, hopefully, find a cure like we did with CF, cystic fibrosis, and some other things,

sickle cells -- and a remarkable achievement, in terms of what went on.

And so I know, Dr. Cavazzoni, you have been -- you have got an important role, and I appreciated your testimony, and I have looked at the testimony of the next panel that is coming, and read it, and I know -- you know, particularly the ALS community is so frustrated. You know, there is not a cure to better their lives. Can we extend them, so they can do some things that are certainly more functional, and provide the hope that, at some point, we will have a cure?

I think that is a frustration that all of us share with their group, and I know that, when I look at the testimony from the ALS Association, which is coming on the next panel, which probably won't be until late in the day, because we are going to have a whole series of votes, but they ask, rightly so, a number of questions.

The FDA must be fully funded, and fully staffed, and provided the regulatory authority, and that is -- we asked that question. We asked that question of then-Director Hamburg, and Janet Woodcock, and others: What can we do? And they gave us a dollar figure, and we did it. We actually increased it.

But I guess the question that I have for you on this panel is, what can we do now to give those folks who have ALS the hope that their lives will be frozen, will be better

while they are still here?

And I am just curious to know, is this really -- following up on my good friend, Mr. Butterfield's comments about the wonderful research that Duke has done, but other universities, as well?

What can we do to help you do a better job to provide the hope that these folks want? That is my question.

*Dr. Cavazzoni. Thank you for that question. And I am, you know, very, very sensitive to the -- how frustrated the ALS community are, and share the sense of urgency to bring therapies, to deliver therapies to patients with ALS.

When it comes to the tools that we have at our disposal, we have the same tools at our disposal when it comes to regulatory flexibility that have led to tremendous advances in oncology. Those are really the same tools.

Where we are experiencing some limitations and some challenges is in the fact that they are -- we don't have as good an understanding of the biology, the genetic underpinnings, the biomarkers in many neurodegenerative diseases. And those are the elements that have allowed us to fully deploy the expedited regulatory pathways that we have available, such as accelerated approval, such as breakthrough therapy, and so on, in therapeutic areas such as oncology, where we have made tremendous gains over the past 20 years.

And so as we -- as the understanding of the biology

improves, we are doing everything that we can to work collaboratively and proactively with developers of drugs with ALS and other degenerative diseases (sic) to advance their clinical trials, and to understand the data that we obtain through clinical trials, which -- sometimes is complex, and requires working very closely with the developers.

*Mr. Upton. Time has expired.

*Ms. Eshoo. I would just like to make a remark, and that is that, even though you don't have the biomarkers, you know what the outcomes are. And I think that that is an area that we need to hear more about from you. Maybe it is not a leapfrogging advance, but it is an advance. It demonstrates something, and that means a great deal to those that bear this God-awful disease. So I just want to get that down for the record.

The chair is now pleased to recognize the gentlewoman -- and that she is -- from California, Ms. Matsui, for her five minutes of questions.

*Ms. Matsui. Thank you very much, Madam Chair, for calling this very important hearing, as everyone can see by the expressions of the emotion that we have around the issue of neurodegenerative diseases. The reason why is we have so many friends and constituents who -- from all kinds of backgrounds -- have suffered in many ways, which have Parkinson's, Alzheimer's, ALS. We can go on and on. So this

is an issue area that is so critical for all of us. So I want to welcome all the witnesses joining us today as we try to untangle this, and try to find a path forward.

Now, last week I introduced the BENEFIT Act. It is legislation to ensure that patient experience and patient-focused drug development data can be considered as part of FDA's benefit risk framework for drug approval. Today's hearing is timely, as patient-centered research is essential to drug development for neurodegenerative diseases. The 21st Century Cures Act required FDA to report to Congress on the use of patient experience data and regulatory decision-making, and the first report was released just last month.

Dr. Cavazzoni -- and I realize you feel you are on a hot seat, but the FDA is so critical -- the report said that the variability in FDA's use of patient experience data may be reflected by the range of diseases it regulates. What can you tell us about FDA's use of patient experience data for neurodegenerative diseases, Dr. --

*Dr. Cavazzoni. Thank you.

*Ms. Matsui. -- Cavazzoni?

*Dr. Cavazzoni. Thank you for that question. We are very sensitive to the input of patients' experience in drug development, in how clinical trials are designed, and in identifying endpoints.

And so, to -- as an example, if we look at the guidance

that we have issued around the development of drugs for ALS, we not only provide a lot of information and advice to developers when it comes to the endpoint that they could use to study drugs for ALS, even in the absence of biomarkers such as, for instance, muscle strength, or function, or even breathing function, and so on, so that they have a host of potential endpoints that they can use to design clinical trials and find answers quickly.

And in addition to that, in the guidance, and as we work with developers, we also emphasize the importance of patient-reported outcomes, not only for ALS, but also for other neurodegenerative diseases, such as, for instance, Alzheimer's. And recognizing that the caregiver is also very important in -- when it comes to the lives of patients who suffer from neurodegenerative diseases, we also encourage the use of endpoints, or scales, or measures that allow us to also --

*Ms. Matsui. I am going to interrupt you, Dr. Cavazzoni. I wanted to also ask you about the conditional approval proposals, and I believes others have talked about this, the chairwoman, which have been put forward to allow approval of drugs before full safety and efficacy data is developed through phase three clinical trials, if relevant, early evidence based on early-stage clinical trials shows that there could be a positive therapeutic outcome from the

drug.

Now, can you explain how this standard is different from what FDA currently uses for full approval and accelerated approval?

And what are the risks of adopting a provisional or conditional approval standard?

*Dr. Cavazzoni. There are some similarities between, for instance, accelerated approval and a conditional approval pathway that exists in Europe in the sense that they both recognize that, when that pathway is used, there is still some degree of residual uncertainty around the drug's benefits.

Having said so, there is also some notable differences between the two. When we look at the tools that we currently have at our disposal, we really have an array of tools, starting with accelerated approval, that allow us to make determinations about benefit risk, and decide whether to approve a drug before we have, for instance, in some instances, have completed phase three trials. And there are some very good examples in oncology where drugs have been approved --

*Ms. Matsui. Okay, and could I just say this? I think what we are very interested in, as we talk to people about their particular situation -- and I am looking at the fact that many people don't have a lot of time and, quite frankly,

some of this depends upon the particular disease you have, and the pathway.

And so I would hope that we could focus a lot on how we might expedite these processes more safely, and look at some of the patient type experiences that we have had.

And with that, Madam Chair, I yield back.

*Ms. Eshoo. The gentlewoman yields back. The gentleman from Texas, Dr. Burgess, is recognized for his five minutes of questions.

*Mr. Burgess. I thank the chair, and I appreciate the fact that we have agency witnesses here today. We don't have nearly enough hearings involving agency personnel. And, for whatever reason, it is very, very difficult to get telephone calls answered from the agency.

So, Dr. Cavazzoni, I am -- forgive me. I am going to ask you a question, and I know your answer is going to be, "That is not my department,'' but people just have to know why. Why has it taken over eight months into the data safety monitoring board releasing the data on the Pfizer vaccine? December 8th or 12th was the emergency use authorization. Why has that not received either full authorization, or been withdrawn from the market? Why are we still left guessing here?

[Pause.]

*Voice. Patrizia, you are on mute.

*Dr. Cavazzoni. My apologies. Unfortunately, I did not come prepared to answer questions in this area today.

Having said so, I would be pleased to come back to you and your staff with answers to your questions.

*Mr. Burgess. Yes, I would like that very much. And it is very frustrating. We can't -- we call with questions. I have had a call into the CDC for several weeks, and we get no response. And we are in the middle of this pandemic. And your agency and our committee needs to work very closely, and it is -- right now I get the impression that it is not happening the way it should.

Now, having gotten that off my chest, Mr. Upton's remarks are similar to what I was going to bring up. I was on this committee, this subcommittee, when we worked through the 21st Century Cures Act. It really was a novel approach to the -- to that type of legislation. We had -- it was understood at the start that it would probably take more than one congress to work through and develop the bill, and understand the processes. We had hearings, briefings, field hearings. I personally attended 15 different field hearings around the country, hearing from people.

And it does -- in the Alzheimer's space, you know, as you can imagine, it has been intriguing for several years. It makes an appearance, and then it is withdrawn, and then goes through an advisory committee, and it was controversial,

and now it has received conditional approval. But -- and I would appreciate more information on this, but it seems like that is exactly what we talked about with Cures. We have a surrogate endpoint, and -- which is the, I guess, the development of amyloid or tau, and we have a drug to which to apply it. And the whole problem is how do we get to some answers before everyone expires.

I mean, it just seems to take so long, and that was the whole purpose of Cures: How do we reduce the time from lab bench to bedside? And I understand that I don't know everything that was involved with Aduhelm's approval, and then conditional approval, but it just seems like that followed the pathway that we had outlined in Cures in order to reduce the time from the lab bench to the bedside.

Now, in 2008 the ALS Registry Act was signed into law, with the goal of understanding and identifying ALS-associated risk factors. Granted, the registry is administered under the Centers for Disease Control. But are you at the FDA aware of any efforts from the FDA to utilize the data at the registry?

*Dr. Cavazzoni. I can't think of any specific instances right now. This is something that I would be able to -- would be happy to get back to you after the hearing.

*Mr. Burgess. Okay, and I would appreciate that very much.

And again, I would just underscore -- and brought up by Mr. Butterfield, and Chairman Upton -- that one of the most substantiative victories achieved in my time in Congress was the passing of the 21st Century Cures Act. And it did provide hope for so many families who had been suffering from a long, life-altering illness.

I just want to point out, during the work on the Cures, I felt very fortunate to be able to include a standalone bill to establish a national neurologic condition surveillance system. Prior to us passing the Cures Act there was no official structure in place to provide surveillance of neurologic diseases. So I am very grateful that that has been established.

Now we need to take the next step. We need to utilize that information, and deliver the benefits for our patients. Thank you, Madam Chair. I will yield back.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentlewoman from Florida, Ms. Castor, for her five minutes of questions.

*Ms. Castor. Well, thank you, Chair Eshoo, for holding this important hearing, and for your devotion of so much time, always, to cutting edge research. And thanks to our witnesses today for your important work.

I am committed to advancing treatments and cures for neurodegenerative diseases. In Florida about 580,000

Floridians aged 65 and older suffer from Alzheimer's. Over 1,300 Floridians are living with ALS. Florida has the highest percentage of individuals with Parkinson's in the country.

Now, in my neck of the woods, in the Tampa Bay area, we are very fortunate. We have a research university at the University of South Florida that is leading research on neurodegenerative diseases through the Department of Neurology. They -- we have a world-renowned USF Byrd Alzheimer's Center. They do a lot of important research that is family-centered, compassionate, in partnership with patients and advocates. They do the same with ALS patients. They have a clinic solely focused on ALS patients, with families and caregivers there. They really believe in the interdisciplinary approach.

And of course, we have a number of clinical trials with the university, community, industry, as well. So robust and consistent support for NIH and FDA is paramount here.

Dr. Cavazzoni, I want to ask you a little bit about recent guidance from FDA. Guidance to industry is very important to help direct work. It is my understanding FDA has released draft guidance for industry stakeholders seeking to develop treatments for ALS, that currently has no known cure, and very few approved treatments.

The guidance says that FDA will consider patient

tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy.

It also describes considerations for drug makers should -- that they should make at various points during drug development, and encourages industry to work with the FDA throughout the process.

Now, FDA does not often release disease-specific guidance. Why did FDA develop specific guidance for ALS?

*Dr. Cavazzoni. Thank you for the question. We have released a host of guidances that are sort of specific to certain diseases. And we do so in the instance for -- of ALS, for instance, when we recognize that there may be particular challenges in the development of therapeutics for those diseases. And certainly, neurodegenerative diseases are very much part of those situations.

We have worked on the ALS guidance, in collaboration and listening very carefully to the feedback from the ALS community, and what we heard from the community, and researchers, and treating physicians as to the aspects of development that were particularly challenging.

And certainly, when we look at the -- what we lay out in the guidance, we do make the point that we recognize that the tolerance for risks, when we are developing drugs for diseases such as ALS, is greater. And we do recognize that

in our thinking about the benefit versus risk, as we evaluate the data that are provided to us by sponsors, and are yielded by clinical trials.

*Ms. Castor. So the guidance says that developers should not unnecessarily exclude patients from trial enrollment based on characteristics such as age or disease stage, unless scientifically justified, and suggests that, even if they are testing a subset of patients for a primary analysis of effectiveness, they can include a broader population in the trial for secondary and supportive analysis.

How has industry responded to the guidance, especially when designing clinical trials?

*Dr. Cavazzoni. Well, industry has generally been receptive to this advice. Some of the challenges that has -- that sponsors have encountered is that -- in the fact that they are -- in the limitations, in some instances, in being able to identify biological markers for some of these populations.

So, for instance, we know that ALS has -- it is largely --

*Ms. Eshoo. The gentlewoman's time has expired, the gentlewoman's time has expired.

The chair now recognizes the gentleman from Virginia, Mr. Griffith, for his five minutes of questions.

*Mr. Griffith. Thank you very much, Madam Chair.

Dr. Koroshetz, a swimming friend of mine who has ALS recently participated in a National Institutes of Health study. He was very pleased with the way it was conducted, once it finally began. But recruitment for the study started about a year before it began, despite the study only needing 25 participants. I think we can all agree it should take weeks, maybe days to fill only 25 slots.

Tell me about your recruitment process, who is involved. How is information disseminated, such as to doctors and patients and to advocacy groups, so that they know that there is a study available?

And is there an appropriate sense of urgency at the NIH?

*Dr. Koroshetz. Well, there definitely is a sense of urgency, and everybody who knows ALS realizes --

[Audio malfunction.]

*Dr. Koroshetz. In general, ALS trials are actually better than even -- than most. The ALS community is a very tight community, we can't -- have very good ties with the ALS Association. And generally, you know, because they are -- the community is really looking for answers, we have, generally, not had trouble with ALS.

Now, you will talk to Merit Cudkowicz in the next panel, and she runs the platform trial for ALS. She could maybe have more -- on this. But my understanding is ALS is

actually doing pretty well, in terms of enrollment.

If you send me any information about the particular one you are mentioning, I would be happy to look into it.

*Mr. Griffith. Well, I would be happy to send you the information, but, I mean, you are saying that ALS is doing pretty good, and getting, you know, people into the studies.

*Dr. Koroshetz. Yes.

*Mr. Griffith. My friend's experience was it took him over a year before they got enough participants, and they only were looking for 25. That doesn't sound like we are doing good enough, and that we maybe need to do more.

It doesn't sound like you have any ideas. But look, we are here, trying to help.

*Dr. Koroshetz. Yes.

*Mr. Griffith. If there is something we need to be doing, if there is -- you know, you need authorization to advertise, as I sometimes hear for clinical trials, if you need to advertise, and we haven't approved language for that, then let us know, because we want to help. We want to try to solve this problem, because he is not doing very well, he is not doing nearly as well as I would have hoped.

*Dr. Koroshetz. Yes, yes.

*Mr. Griffith. But a year he waited for this study to get off and running. Now, he was very happy, once it got started.

Let me switch gears a little bit on that, and we will stick with you. When we are doing research on these types of diseases, the neurodegenerative diseases, and we are trying to recruit people from a wide variety of backgrounds, which I understand, but one of the things that is probably an impediment, which I know can be an impediment, is getting people who are not located in the D.C. area up to NIH.

So what are you all doing to make sure that we have participation from folks who live in rural areas, or maybe live away from this area, and it is more difficult for them to participate?

*Dr. Koroshetz. Yes, well, that is a really good question. And actually, the one bright side of COVID is that many of the trials had to move towards remote visits with the patients. So, again, you will talk to Merit about ALS trials later, but I think they learned that they could actually do things remotely, which is a tremendous advance for people who live far away, people who have trouble coming into the centers to be enrolled in trials.

NIH, actually, is in the very unusual position in which we can use NIH funds to transport people from anywhere in the country to NIH.

*Mr. Griffith. Well, and I appreciate that, and that was going to be one of my follow-up questions, is what can we do to facilitate using more telehealth?

Because, you know, if it is a blood sample that needs to be drawn, that can be done locally, and then shipped to the NIH, but I know you have to do some other things. And it may have to be an occasional visit, but the more we can do with telehealth, the better off all of our patients will be.

And again, I think I speak for both sides of the aisle and this committee, we are anxious for agencies like yours to tell us -- what do you need put into language in the law so that we can facilitate you all using more telehealth, and making sure that we are doing it right, so that we can get these studies, and get more participants in these studies. I do appreciate --

*Dr. Koroshetz. I 100 percent agree, yes.

*Mr. Griffith. -- you all --

*Dr. Koroshetz. One thing that might help, and we could talk to Merit later, is helping physicians in one state be able to work with patients in another state, without having to get a license. I know when I did telehealth, I had to have 15 different medical licenses for each state I worked in. One place --

*Mr. Griffith. And we have done that in special circumstances in the past. I will look into that. Thank you so much for your testimony.

Thank you all for being with us today.

I yield back.

*Dr. Koroshetz. Thank you.

*Ms. Eshoo. The gentleman yields back.

I would just add that the bills that we recently approved of with Mr. Hudson and myself, the additional funds for the -- you know, that will help, too.

And I want to encourage all of the witnesses to share with us up front what you need in order to make all of this work better. Don't be shy about it. That is what these hearings are -- it is one of the important aspects of the hearing.

The chair is now pleased to recognize the gentleman from Maryland, Mr. Sarbanes, for his five minutes of questions.

*Mr. Sarbanes. Thanks very much, Madam Chair, and I appreciate the opportunity. I want to thank the panelists for testifying today.

We have had others, I think, speak to this to some degree already in the hearing. But I wanted to come back and talk about the importance of inclusion and exclusion criteria that are used by developers in determining who participates in these various clinical trial studies.

In recent years, as you know, there has been a push to diversify study participants to better represent the populations that eventually may use an approved drug. The FDA Reauthorization Act of 2017 required FDA to hold a public meeting on clinical trial inclusion and exclusion criteria,

which was held on April 16th, 2018. A report was issued shortly thereafter.

Putting these inclusion and exclusion guidance measures together in a comprehensive way, and into effect for terminal neurodegenerative diseases, can present unique challenges, as you know. Researchers have to evaluate populations at different phases of disease progression, which is complicated, and determine how to maximize the clinical benefit that is brought to bear at each stage.

As FDA noted in its report, there is a tension between balancing the desire to minimize statistical noise, which can mask a finding of the effect for a certain population, on the one hand, and then the desire to generate data that can be applied to a broad patient population, on the other hand.

Dr. Cavazzoni, can you summarize why this tension exists, and what developers, in your view, should consider in order to balance tension, especially when it comes to neurodegenerative diseases, which we are discussing today?

*Dr. Cavazzoni. Thank you for the question. I acknowledge the fact that there is anxiety among developers in some instances, when it comes to broadening inclusion criteria in clinical trials. These -- inclusion of under-represented racial and ethnic minorities, or inclusion of some subset of the population that are affected with the disease, such as we heard earlier, Down Syndrome and

Alzheimer's.

We think that we can -- developers can find ways to appropriately represent the subgroups that are affected by the disease, while also be able to conduct clinical trials in a timely fashion, without seeing those clinical trials slow down.

And in addition to the guidance that we have issued, when we meet with developers we talk about tactics, such as having in place the appropriate outreach to a certain geographic area, or establishing a network of treating physicians, who may be able to refer clinical trial participants, and -- as well as, you know, making sure that we deploy -- to the earlier conversation -- important tools, such as decentralized clinical trials.

And we have issued guidance on decentralized clinical trials during COVID, and we are working on a go-forward guidance, recognizing that one of the reasons for -- some sub-populations that have been under-represented in clinical trials, cannot access clinical trials, it is because they cannot travel there, as we have just heard. They live in rural areas, and so on. And therefore, it is particularly important that we encourage developers to use decentralized modalities, including telehealth, digital health technology, as a way to capture endpoints in a way that doesn't require people who suffer from neurodegenerative diseases -- so maybe

on a wheelchair and debilitated -- to travel to an investigative site, but rather, have those procedures done remotely, using telehealth when possible.

And so we think that we can get to a point where we can have greater representation, and appropriate representation of all the sub-groups, while not slowing down the drug development and the timing of clinical trials.

*Mr. Sarbanes. Thank you very much, I appreciate your testimony.

I yield back.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentleman from Florida, Mr. -- I am sorry -- Bilirakis for his five minutes of questions.

*Mr. Bilirakis. Thank you, Madam Chair. I appreciate it very much. I thank you for holding this hearing, a very important hearing. I give thanks for holding the hearing, so we can learn more about the challenges involved with these neurodegenerative diseases, such as ALS, which is a brutal disease that, sadly, has no known cure, or any real treatment.

I was particularly saddened to learn this past week of the passing of my constituent and good friend, Doug McGinnis, a combat veteran who was diagnosed with ALS over 15 years ago. He was an incredible lawyer, Madam Chair -- I knew him very well -- and managed to fight back for many years before

the disease again progressed. Unfortunately, since he received experimental treatments -- and that prolonged his lifetime -- from outside of the United States, he was barred from clinical trials here in the U.S., and ultimately he couldn't access the treatments that were effective for him, sadly.

Both he, his wife, and my good friend -- and also a constituent -- Gary Desati, has been at the forefront of the critical fight against this disease. And I agree we must act, and do more.

So my question is for Dr. Cavazzoni -- I am sorry -- Cavazzoni. We have heard and will hear the concerns from the ALS community that the heterogeneity and rareness of the disease and others, such as Huntington's disease, can complicate participation in clinical trials and access to investigational therapies.

In Doug's case, these included adult stem cell treatments that proved effective for him, in particular. Again, he had several treatments outside the United States.

How can we better improve the drug development process, so that patients with varying stages of neurodegenerative diseases are able to participate in clinical trials?

*Dr. Cavazzoni. Thank you for the question. And first, let me say how sorry I am about the passing of your constituent after a battle with ALS.

*Mr. Bilirakis. Thank you.

*Dr. Cavazzoni. I am very sad to hear that.

When it comes to the ability to access drugs, despite the heterogeneity of diseases, ALS is a good example of a rare disease where we know that there are certain forms that are genetic, and where we have actually been able to underpin the genetic mutation that then allows for development of very targeted drugs.

On the other hand, the 90 percent, or 85 to 90 percent of ALS is actually sporadic, meaning that we have not identified a specific genetic mutation or molecular underpinning, and that poses some challenges when it comes to development.

On the other hand, the way we have continued to advance the development, even if we -- in many instances in these diseases we do not have a full understanding of the biology -- is to work with developers, and with the disease community, who identified modalities that can still allow patients to be evaluated in clinical trials.

For instance, going back to the work that we have done with ALS and the guidance, we have identified a host of clinical endpoints that, even without an understanding of the molecular biology of the disease, or having biomarkers, can allow us to adequately and quickly evaluate a drug and determine whether it can be advanced, and whether the

benefits and risk profile is positive. And these tools for ALS include -- or these endpoints include endpoints such as function, breathing -- tracheotomy, muscle strength, and so on, because we really want to make sure that developers can use multiple approaches to evaluating these potential therapeutics.

*Mr. Bilirakis. Madam Chair, I have a question with regard to Parkinson's disease and Alzheimer's, but I know we don't have a lot of time, so I will have to submit them for the record. Thank you very much, I appreciate it.

*Ms. Eshoo. I thank the gentleman for his questions. And do submit your written questions to our witnesses.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. The chair now is pleased to recognize the gentleman from Vermont, Mr. Welch, for his five minutes of questions.

*Mr. Welch. Thank you very much, Madam Chair. I want to ask about three areas: one are migraines and headaches; two is ALS; and three, Alzheimer's.

Director Koroshetz, often times we talk about headaches, and it is way, way worse than that. Nearly 50 million Americans, as you know, suffer from migraines. Forty-six of my colleagues, bipartisan, have written to the -- in support of the HEAL Act.

My question to you is, could you tell me what the NIH is doing to help the millions of Americans who are suffering from headache disorders?

And how can the NIH work to engage more researchers in this field, considering the incredible impact on so many Americans?

Thank you.

*Dr. Koroshetz. Thanks for the question. Yes, headache is the leading cause of missed work in the U.S. It causes a lot of suffering. We fund research trying to get at mechanisms by which the headaches occur, and we have had some amazing successes. So, you know, in my career, you know, there wasn't very effective drugs. Now we have triptans and the new drugs, the CGRP antagonist, which came out of

research on the connection between the nerves and the blood vessels.

Industry has been really good at picking up on any kind of discoveries that come out of science. And so the Lundbeck prize in neuroscience actually went to the three people who discovered this CGRP mechanism.

Now, truth of the matter is, in clinical practice we do have a great shortage of people who concentrate in pain and headache. It is a very difficult field to go into. Unfortunately, we have fewer people than we need. And the HEAL initiative, which is -- has a focus on building non-addictive pain therapies, has a lot of programs out now to do research, including on headache, and to build new research capacity, younger people, headache pain, any types of pains.

*Mr. Welch. Thank you very, very much.

Director Cavazzoni, could you explain the actions that the FDA has taken to expedite development and approval programs available to bring new treatments to ALS patients as quickly as possible?

*Dr. Cavazzoni. Thank you for the question. We have been working closely with developers to advise them on how to design clinical trials, and -- including identifying endpoints for clinical trials, how to recruit for clinical trials in a way that allows those trials to deliver answers as quickly as possible, depending on the endpoint.

And so we are very engaged with developers, as we always are, in -- particularly when it comes to development of therapeutics, where there is a large, unmet medical need. And we guide them on the, really, the details on the clinical trials, the endpoints that it could be using that may yield faster answers.

And I am going to give an example of ALS. While we know that clinical programs have been looking at the impact on a potential therapeutic survival, we have heard from people suffering from ALS that what matters to them is also improvement in symptoms, improvement in quality of life. And so we work with developers to really identify an array of ways to evaluate the drug that could really yield the answers that we know are meaningful to people suffering from the disorder.

*Mr. Welch. Well, thank you both very much. I so appreciate the work you are doing and your organizations are doing. I want to end by just making a comment.

You know, Alzheimer's is just devastating. The drug Aduhelm -- there is a lot of controversy about the approval, but the price is unreal. I just want to say this, because we get a drug, and let's hope it works, but if it is so priced that you can't afford it -- and this one is -- the pricing power that Biogen had, they set the price at $55,000. There is six million Medicare-eligible people who suffer from

Alzheimer's. If just one-third of those folks on Medicare took that drug, it would cost $110 billion, and that is more than the Medicare Part B program spends on all medications for all patients.

So I really appreciate the work you are doing on research, but we have to have reasonable pricing so it is affordable for individuals, taxpayers, and for -- and I yield back. Thank you.

*Ms. Eshoo. The gentleman yields back. Seeing no Republicans available for questioning, or committee Democrats, I will recognize the gentlewoman from Illinois, Ms. Kelly, for five minutes of questions, and then make some remarks about impending --

*Mr. Cardenas. Madam Chair, this is Cardenas.

*Ms. Eshoo. -- votes that we have.

*Ms. Kelly. Thank you, Chairman Eshoo --

*Ms. Eshoo. Oh, I am sorry. I think that -- Robin, I think we need to go to Mr. Cardenas for five minutes, and then let's see if we can squeeze you in, as well.

The gentleman from California is recognized for five minutes of questions.

*Mr. Cardenas. Sorry about that, Madam Chairwoman, and I could see myself on the screen, but I -- maybe it wasn't connecting to the committee. Thank you so much --

*Ms. Eshoo. There you are, there --

*Mr. Cardenas. I appreciate --

*Ms. Eshoo. There you are.

*Mr. Cardenas. Okay. I appreciate this opportunity. Thank you to all the panelists for your expertise and your advice that you are informing us today.

I would like to cover various issues when it comes to clinical trials, for example. Outside of the inclusion/exclusion eligibility criteria, a number of external factors may preclude individuals from participating in clinical trials. These can include geographical limitations, financial burdens, transportation difficulties, and the ability for caregivers to assist patients in enrolling in a trial and participating.

In our second panel today we will hear testimony from a witness who has -- who was faced with all of these issues. One of our witnesses, Yvonne Latty, describes in her written testimony that she had to help her mother with Alzheimer's disease, commute from the Bronx to Manhattan every week, while she maintained a full time job. To top it off, the clinical trial barely compensated participants enough to cover the cost of a cab from her mother's home to the research site.

As Ms. Latty notes, these issues are systemic, and the Federal -- and federally-funded Alzheimer's disease research centers tend to be in the wealthiest neighborhoods, to add

insult to injury, for people who would love to be part of these trials, but live on the other side of town. And it is clear that, if we are going to discover new treatments that are available to the widest possible patient population, we need to do more to break down these barriers and expand access to clinical trials.

Dr. Cavazzoni, what guidance has the FDA provided to developers in how they should consider these non-clinical barriers, including financial barriers?

*Dr. Cavazzoni. This is an area where we are putting a lot of thought, and we are putting a lot of work into this, because we recognize that it is critical to increasing the representation of underserved communities and under-represented racial and ethnic sub-groups.

During COVID we very quickly issued guidance on how developers could use decentralized clinical trial approaches to make it easier for patients to participate in clinical trials, or stay in clinical trials during the pandemic. And those modalities entail using technology, telehealth, digital health tools, and also include encouraging developers to design clinical trials in a way that they are as simple as possible, that don't require multiple unnecessary visits, such as the situation, you know, that can be very cumbersome, as you described in the caregiver who was -- had to go to a -- through the Bronx --

*Mr. Cardenas. Thank you, Doctor. My time is limited. I would like to get a question in to Dr. Hodes. Thank you so much.

The ability of a caregiver to assist the patient and accessing a clinical trial can be critical, especially for older adults and those with Alzheimer's disease, for example. Has NIH evaluated the role that caregivers play in facilitating patient access to trials, and what can be done to support caregivers so more patients can participate?

*Dr. Hodes. Thank you for the question. You know, absolutely, in many -- certainly Alzheimer's, as disease progresses it is critical that there be provision made for a caregiver or someone to accompany the person living with dementia. And this is a part of the study, it is a part of the design, it is a part of what we can fund.

Your point well taken, too, though, about outreach, and doing our best -- sites located as close as possible to affected communities. To that extent, we have established a standing infrastructure of clinical sites, so we don't have, for each clinical trial, to redesign and re-identify those sites.

The use of remote -- is another important area, as just mentioned. And in some areas, at a national level, I recognize we haven't had Alzheimer's disease research -- in all parts of the country where the disease is most prevalent.

Just recently we funded four pilot centers, in previously unrepresented areas in Nevada, New Mexico, Alabama, and Tennessee, all of these designed to accomplish what you said, to try to put the clinical science as close as possible to affected populations, allow for companions when needed, and do as much as we can remotely to reduce the burdens of participation in trials.

*Mr. Cardenas. Thank you, and health equity is something that is very important to every single person on this committee, and I am sure it is on -- it may not be on the minds of every American, but I think that every American would agree that everybody deserves not only equal access, but also equal care. So thank you so much, and I look forward to seeing you in the future. And once again, thank you for being here today.

My time has expired. I yield back, Madam Chair.

*Ms. Eshoo. The gentleman yields back. It is my understanding that Dr. Ruiz is with us, and I recognize him for five minutes for his questions.

*Mr. Ruiz. Thank you very much. Thank you for holding this important hearing today.

As a physician and chair of the Congressional Hispanic Caucus, and the son of farm workers who grew up and practiced medicine in the medically underserved Coachella Valley area in California, I am happy to hear so many members talk about

the importance of diversity in clinical trials.

Factors such as gender, race, ethnicity, age, or lifestyle play an important role in how our bodies respond to the different medications and therapies. And what is more, the disproportionate impact of the COVID-19 pandemic on communities of color has highlighted the vital importance of including diverse participation in clinical trials.

Addressing the social determinants of health, and creating greater health equity has long been one of the top priorities of the Congressional Hispanic Caucus. And for the past several months I have been working with fellow Hispanic Caucus member Senator Menendez on important legislation aimed at improving diversity and inclusion in clinical trials through supporting patient engagement of communities of color in decentralized clinical trials, and developing solutions to better recruit racially and ethnically diverse populations.

NIH and FDA's engagement will be key in improving outcomes and the participation of communities of color in clinical trials for neurodegenerative diseases and beyond. The first question is to Dr. Cavazzoni.

How do you determine if the clinical trial data you receive in the drug application is representative of the U.S. population?

And when, if ever, do you require a sponsor to increase the size of your clinical trials in order to accurately

understand if there are different outcomes and different demographic groups?

*Dr. Cavazzoni. So we have issued guidance to sponsors to encourage them to make sure that the entry criteria for clinical trials are as broad as possible, and to encourage them to ensure that there -- the -- there is representation of racial, ethnic, and other sub-groups that are relevant and represented in that particular disease.

When we talk to sponsors about the design of clinical trials, this is very much top of mind. And we discuss with sponsors modalities and approaches to make sure that the clinical trial population is as close as possible in representing the scope of groups that suffer from the disease.

This is an area that is very important to us. We have made gains over the past few years, as shown in the clinical trial snapshot that we published a while ago. And we --

*Mr. Ruiz. Thank you.

*Dr. Cavazzoni. -- understand that we need to continue to focus.

*Mr. Ruiz. Thank you, thank you.

*Dr. Cavazzoni. Sorry.

*Mr. Ruiz. Given the nature of neurodegenerative diseases, how can greater use of decentralized clinical trials improve the experience for all patients, and make

trial participation more accessible for more diverse communities?

*Dr. Cavazzoni. So we think that using decentralized trial approaches can be really important tools in facilitating the participation and the inclusion of patients, particularly patients in underserved communities, in neuroscience and neurodegenerative diseases, particularly in diseases that are debilitating, such as the ones that we are discussing, that are dependent on caregivers going with the patient to a clinic or a clinical site. We think that these decentralized modalities that use telehealth, that simplify clinical trials, that make it easier to collect data from the patient's home or for, let's say, a lab technician to go to the patient's home to collect the blood test --

*Mr. Ruiz. Thank you.

*Dr. Cavazzoni. -- they are critical in ensuring --

*Mr. Ruiz. Thank you. I have 40 seconds left.

I would like to ask Dr. Hodes from NIH what your perspective on -- in terms of the importance of diverse participation for those therapies being developed for neurodegenerative diseases, and what you think about improved community outreach to diverse -- to increase diverse participation in those clinical trials.

*Dr. Hodes. So hugely important, not just for all of the moral and ethical principles, but because we already know

risk factors differ across parts of our population. The Alzheimer's disease itself is heterogeneous. So, for example, cardiovascular and other contributions will -- an absolute imperative.

I see time running, but as far as outreach, the new technologies will help. So, rather than the current situation, where we may have to bring people into a site that has access to a PET scan, we have the ability to use blood biomarkers to -- takes one of our restrictions and constraints away.

We also put into place a system in real time for tracking each individual accruing to a study for ethnic, demographic characteristics, so we can track not just on an annual report, but in real time, and see if we are on track in each study, and the collection of those studies, in meeting the goals.

*Ms. Eshoo. The gentleman's time has expired.

Colleagues, we are going to -- and witnesses, we are now going to break, because we have seven bills on the floor that we have to vote on. So we will take a recess. I think that we will come back at -- well, we will take Robin.

Let me just make this announcement. We will take Robin Kelly, and then we will recess, coming back at approximately 3:30, 15 minutes after the last vote is taken. Hopefully, votes will end sooner than that. So I encourage members and

witnesses to return in a timely way.

We will take one more member, Congresswoman Robin Kelly, and then we will recess. I think everyone needs a break, anyway. So the gentlewoman from Illinois has five minutes for her questions, and then we will take our break.

*Ms. Kelly. Thank you so much, Chairwoman Eshoo, and Ranking Member Guthrie. I really wanted to talk about clinical trials, and, you know, there is always a concern about how they reflect the diversity of our population. So we need to ensure that clinical trials are reflective of the racial disparities in neurodegenerative diseases.

According to the ALS Association, Black patients are 2.5 years younger than White patients at the time of symptom onset, and are up to one year delayed in receiving an ALS diagnosis. This is one of the many stats that highlight the need for increased diversity in clinical trials.

Dr. Koroshetz, what guidance has NIH provided to sponsors to ensure that demographic diversity in clinical trials is reflective -- excuse me -- of disease disparities, including race, ethnicity, and gender?

*Dr. Koroshetz. Thanks a lot. So at NIH, the trials that we run, we are obliged to report what the population is on a yearly basis, and we examine those. And if it has fallen short, we put in, you know, changes to improve the diversity of the participants.

We also find -- particularly relevant here -- there is actually research to try to understand what is the best way of detecting these conditions in different populations, because, as you mentioned, there is a problem there. And as these treatments come along, the worst thing you want is for the diagnosis to be delayed, because the treatment is going to be best early on.

So we do something called -- there is a program called Detect Cognitive Impairment, which is to try and figure out how to know when someone is developing these neurodegenerative diseases. And that is done in many different populations, for the exact purpose that you raised.

*Ms. Kelly. Would there be any additional benefit to having sponsors work with NIH to establish clear, measurable diversity goals in the funding application, and to have those goals be publicly available and enforced throughout the trial?

*Dr. Koroshetz. You know, I -- well, my understanding is that NIH -- we do what we have to do, and we do what you say, but we don't have any -- I don't know that we have any leverage on what the industry folks do.

I mean, that -- the FDA might be able to say what their levers are in that space, but we don't have any levers there.

*Ms. Kelly. But we do need to improve the clinical trial and drug approval process --

*Dr. Koroshetz. Yes.

*Ms. Kelly. -- continuing to fund basic research to understand how these devastating brain diseases work. This will ensure that we have a continuous pipeline of novel therapies.

Dr. Hodes, what are some promising areas of research for neurodegenerative diseases, and how can we increase the likelihood that this research translates to novel therapies?

*Dr. Hodes. Well, for Alzheimer's disease, in particular, as noted, we have come in the last few years to recognize that there are multiple pathways on a molecular, cellular level, that contribute to Alzheimer's as a clinical syndrome. And we have made great progress in translating that basic information already into clinical trials that target components of them. So in some individuals it may be that the vascular component is dominant. In others, it may be an inflammatory component. In others, errors in folding of proteins.

And so, ranging from drugs, to small molecules, to individual and combination behavioral therapies, as is necessary in diseases as complex and devastating such as this, we are targeting multiple such pathways with the notion that -- a personalized or precision level, we are going to find differences not just in racial --

[Audio malfunction.]

*Dr. Hodes. -- individuals in designing the optimal therapy.

*Ms. Kelly. Thank you so much, and I will yield back the balance of my time. Thank you.

*Ms. Eshoo. The gentlewoman yields back. The chair will now recess the committee, and resume at approximately 3:30 this afternoon.

[Recess.]

*Ms. Eshoo. [In progress] resume and be back in order. To all the witnesses, to say I apologize on behalf of all of the committee, subcommittee members, and myself really doesn't begin to describe it.

I just leaned over and said to the ranking member that I have learned something. The week that precedes heading into a major break, I don't think I will ever schedule a hearing again, because we have absolutely no control over what is going to take place on the floor.

So apologies to everyone, especially our witnesses that have flown across the country to be in the room to testify, and sitting in a wheelchair, waiting. I just -- I -- you know, our deepest apologies.

So now, back to where we left off, it is -- the chair now has the pleasure of recognizing the gentleman from Oklahoma, Mr. Mullin, for his five minutes of questions.

He is not ready? All right, all right. Then we will go

to Dr. Joyce.

He is? He needs to -- Mr. Mullin, you need to unmute. I can't hear.

I think that we will go to the gentleman from Pennsylvania, Dr. Joyce, for your five minutes, sir.

*Mr. Joyce. Thank you for yielding, Madam Chair. And to this panel of witnesses, your testimony today, on a long day, but an incredibly important issue.

Neurodegenerative diseases devastate the lives of those diagnosed. It impacts their family members and all around them. It is critical that we are putting forward the proper set of policies that will foster the research and the development of cutting-edge therapeutics, and cures that will stall these diseases. We need to have that impact. My first question is for Dr. Cavazzoni.

My home state of Pennsylvania has been a global pioneer in the fields of cell and gene-based therapies, which could offer incredible help to patients with neurodegenerative diseases. Does the FDA have the necessary resources and the necessary workforce expertise to ensure timely review and approval of these new medicines for years to come?

*Dr. Cavazzoni. Thank you for that question, and I will assume that you would like me to comment broadly on cell and gene therapies, and not specifically for neurodegenerative diseases, although I am certainly happy to touch on that.

So this area is an area that is really exploding, when it comes to research and a number of programs that are coming to the FDA for review. And the review is done not by my center, but the Center of Biologics. And so, certainly, this is an area where we need to continue to be able to invest in a highly specialized workforce that will allow us to keep pace with both the volume and the scientific advances that we see in cell and gene therapy.

Understanding that this area is also particularly important for advancing new therapies for neurodegenerative diseases, and in order to do so, we will need resources, as well as -- we will need to be able to recruit the right scientists and personnel and experts, and, you know, be competitive with the private sector.

And to this I would like to really extend -- acknowledge the tremendous support by Congress by passing the -- by giving us the H.R. Cures (sic) authorities, which is the hiring authority that really allows us to be much more speedy and competitive with the private sector in recruiting highly-specialized scientists, such as the ones that we need to review applications, and work with sponsors who are developing therapeutics in gene and cell therapy.

*Mr. Joyce. Dr. Cavazzoni, we are going to be hearing from our second panel of witnesses that the FDA has not fulfilled its commitments to provide regulatory flexibility,

or consider patient tolerance for risk and the life-threatening nature of diseases when making regulatory decisions about drugs to treat ALS, as outlined in the agency's September 2019 guidance for ALS clinical trials. What is your response to this?

*Dr. Cavazzoni. Thank you for the question. I think it is important to differentiate the -- how the fact that we are, in fact, operating in a manner that is entirely consistent with the ALS guidance that we have put in place when it comes to what we ask, and -- the sponsors to do, as they develop clinical trials, and design clinical trials, and conduct them.

Now, that guidance is really about how to develop drugs for ALS. However, at the end of the day, our decisions are based on the data that are derived from those clinical trials. And sometimes --

*Mr. Joyce. With our remaining time, do you feel that guidance is necessary, and is it reliable? Because I can't wait to hear the patients comment on this.

*Dr. Cavazzoni. We think that the guidance is very important for developers. At the end of the day, we have to make decisions on the basis of the strength of the data that is derived from those developments, and those clinical trials that may well have been designed in complete compliance and according to the guidance, however sometimes we are

disappointed by what the clinical trials give us, in terms of results, and we are left with data that are sometimes either very complex to understand, or sometimes insufficient for us to make a determination that the drug can be approved.

*Mr. Joyce. My time has expired. Thank you, Madam Chair. I yield.

*Ms. Eshoo. The gentleman yields back. The chair now recognizes the gentleman from Oklahoma, Mr. Mullin, followed by the gentleman from Utah, Mr. Curtis. And I am taking two Republicans in order, because Ms. Schakowsky is waiving on to the committee.

So we will hear from both of you first. So, Mr. Curtis, you are recognized.

*Mr. Mullin. Mullin, Mr. Mullin.

*Ms. Eshoo. Oh, I am sorry, Mr. Mullin.

*Mr. Mullin. Yes, I am not letting John get in front of me. He always cuts.

*Ms. Eshoo. Are you all miked up?

*Mr. Mullin. Yes, I am ready to go.

*Ms. Eshoo. All right.

*Mr. Mullin. All right, thank you so much, Madam Chair, and thank you for our witnesses that are here. I just wanted to throw out some questions to Dr. Cavazzoni.

There are numerous documents from the FBI (sic) that discusses the importance of exercising regulatory flexibility

when it comes to approval for ALS therapies. Has -- how has the FDI -- FDA exercised --

*Ms. Eshoo. Mr. Mullin, excuse me, can you --

*Mr. Mullin. Yes?

*Ms. Eshoo. Mr. Mullin, excuse me, I am sorry. Can you speak up? Because we are having a hard time hearing you, and we don't want to miss a word.

*Mr. Mullin. Oh, I am so sorry. Hold on.

*Ms. Eshoo. Okay.

*Mr. Mullin. Is that better? Can you guys hear --

*Ms. Eshoo. It is a little better. We want it even --

*Mr. Mullin. Is that better?

*Ms. Eshoo. Yes, just speak up.

*Mr. Mullin. Okay. I am turning my mike up all the way, is that better?

*Ms. Eshoo. Okay.

*Mr. Mullin. Can you hear me now?

*Voice. We can hear you.

*Ms. Eshoo. We can hear you, thank you.

*Mr. Mullin. Okay. There are numerous documents from the FDA that discuss the importance of exercising regulatory flexibility in the approval of ALS therapies. Do you know how the FDA has exercised regulatory flexibility when it comes to reviewing clinical trials with ALS?

*Dr. Cavazzoni. Well, we exercise regulatory

flexibility as we review the data from all life-threatening diseases, including ALS, and the -- our ability to fully exercise regulatory flexibility within the confines of, you know, our statutory standards is -- at the end of the day, is dependent on the data that is in front of us, and what the clinical trial results are telling us.

And so there are times when the -- despite the fact that we are very committed, and very willing to be as flexible as we can within our standards, the data are not sufficient for us to be able to exercise the extent of regulatory flexibility that we would want to be able to do in situations such as ALS, where there is such a huge unmet medical need.

*Mr. Mullin. There is -- the issue that you have is we feel like it is very possible that the drug will work well in some ALS patients and not others, just kind of like chemotherapy treatments work well for some cancer patients, and some others.

And what the fear is, is that we are sometimes waiting on the FDA to have approvals, but yet the ALS patients are just saying, listen, we will try whatever. I mean, if it is working on some patients, and even though it may not be working on all patients, they are -- the ability to try -- we passed a bill for pediatrics that said the right to try, to allow pediatric cancer patients the right to try drugs that were available. And I think that is what ALS patients are

wanting, too.

*Dr. Cavazzoni. Well, these are very important points. I think it is important to distinguish the access, the importance to provide access to investigational therapies through expanded access programs, or right to try, versus the importance of being able to study drugs in controlled clinical trials --

*Mr. Mullin. Sure.

*Dr. Cavazzoni. -- in a way that would allow us to understand whether they work, and their -- whether they are sufficiently safe. And so we try to balance that need by working with sponsors to put in place clinical trials that have the best chance to be able to give us answers, including answers about sub-populations within ALS. And I recognize and I agree that this is a very heterogeneous disease, as many rare diseases are.

And in parallel to that, we work with sponsors to facilitate access to treatments through expanded access. And to that effect, obviously, we try to do everything that we can to facilitate those programs.

*Mr. Mullin. Well, I have visited with some of my constituents that have had -- responded well to some of the ALS treatments that they participated with, with clinical trials. And then, you know, of course, some of them would love the opportunity to do that.

And I just wonder if the FDA is doing other things to ensure that treatments that are available to patients that they have seen some success with are available to other patients that would like to try it, because I know we have had several reach out to us and say, "Hey, we have spoke to constituent A, and they have responded well on -- in this trial, but we have tried to get involved in the trial, and we are being denied.'' And I am just wondering if the FDA could be more flexible on that.

*Dr. Cavazzoni. Well, we try to be as flexible as we can within the -- our authorities. So, for instance, we work with sponsors, and we encourage them to have open label extensions in their clinical trials after the controlled phase of the trial has ended, so that all patients can move into that open label extension, and have access to the drug.

And we also encourage sponsors to make the drug available through expanded access after the trial is completed, or even only after the controlled phase, the placebo controlled phase of the trial is completed. Ultimately, we need the sponsors to be willing to work with us. And obviously, we engage them regularly on these matters, because we really understand the tremendous urgency and unmet medical need.

*Mr. Mullin. All right. Well, I am out of time. If Congress -- if we can be helpful to you in any way, if there

is any barriers that is in place that is keeping you from being able to do that, let us know.

With that I will yield back. Thank you, Madam Chair.

*Ms. Eshoo. The gentleman yields back. The chair is now pleased to recognize the gentleman from Utah, Mr. Curtis.

*Mr. Curtis. Thank you, Madam Chair, and I am pleased to be here, and this is an important hearing. I think you are going to hear in my questions a theme that we have heard throughout the day. I would like to start with Dr. Cavazzoni.

My colleagues and constituents back home often communicate to me that the FDA needs to be less risk-averse, and they cite the inability to access tutorial treatments under expanded access. A right to try is one reason why.

Now, I have here my notes, "without undermining patient safety,'' but I am going to put a big asterisk by that, because our patients are not exactly worried about their safety, right? They are worried about living. And so, with that in mind, is there more that Congress can do to make the FDA and pharmaceutical community more comfortable offering these drugs to patients under expanded access and right to try?

It feels to me like there is some hesitancy because patients might not always be in the best health. They may not be the best clinical pick, but they are denied a

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potential for something lifesaving, because of this risk-averse nature. So my question to you is what can Congress do to add to the comfort level of both the FDA and the pharmaceutical companies, so they are more willing to take more risk?

[Pause.]

*Mr. Curtis. Dr. Cavazzoni, that is to you.

*Dr. Cavazzoni. My apologies, Congressman --

*Mr. Curtis. Okay.

*Dr. Cavazzoni. I did not unmute myself. When it comes to --

*Mr. Curtis. I understand.

*Dr. Cavazzoni. When it comes to clinical trials, we work with sponsors who design clinical trials that have the best chance of developing --

*Mr. Curtis. So I am going to cut you off, Doctor, and I don't mean to do that, but, you know, we have limited time. That is really not my question.

My question is, these people are desperate for an opportunity to try something, and there is an aversion to risk on both the -- and I understand that aversion, right? I mean, that is natural. I mean, their reputations are at stake, the reputation of the FDA is at stake. How do we protect, as Congress, how do we protect them, so they are

more willing to take risk?

*Dr. Cavazzoni. My -- the -- I would like to make the point that, in fact, every day, when we work with sponsors and with clinical trials for drugs for ALS, we take into consideration the fact that there is a much higher tolerance for risk in people who are afflicted by this disease, and we take that into consideration as we review the data.

So, for instance, we do have a higher threshold when it comes to safety. We also are open and have, in many instances, accepted less safety information than we would normally accept --

*Mr. Curtis. Once again, I -- and I just have so much I want to ask you, so please excuse me for interrupting you. I really would like you to go back and consider that question, because I am -- I just know that your nature, the nature of doctors, is to not take risk. And I think we need a different paradigm here, as we look at this.

Let me ask you again, and perhaps any of the witnesses that would like to answer this, I have noticed and been touched by, almost without exception, all of my colleagues who have asked questions today know somebody back home, a family member, a neighbor that is afflicted either by ALS or Down Syndrome or MS.

Of course, I am no different. ALS has ravaged my neighborhood, and I currently have a very, very good friend

suffering from ALS. He has been fortunate, because of some of his resources. He has been able to travel worldwide to receive some of these treatments. So many are not. He frequently discusses how patients are unable to receive many treatments under right-to-try that are under clinical investigation for which he can -- if he is willing to travel, and spend more than the average person is able to do -- access.

I get it. The complexity of treating certain diseases can be a challenge, especially to ensure sufficient trial participation. Additionally, it is hard to predict how individuals may react to an experimental drug.

Is there more we should consider doing to get patients into clinical trials without undermining the integrity of the trials, and harming patients?

And I am referring specifically to Congress, right?

I know that you are doing your job. What can we do to expedite this?

*Dr. Cavazzoni. I think that having more -- having a greater push when it comes to understanding the biology of disease will be very important in advancing the therapy for ALS.

Continuing to support us, as we continue to focus on expanding the eligibility criteria for clinical trials will be very important, because we want to have as many patients

as possible being able to access clinical trials.

And also, continuing to support us in our efforts to engage with sponsors to make drugs through expanded access more available to patients --

*Mr. Curtis. Thank you. Yes, Doctor, I am going to --

*Dr. Cavazzoni. -- be very important.

*Mr. Curtis. Please, I am going to lose my time. I want to make one point, and that is something that you brought up, which is cause. We spend a lot of time, and we have talked a lot time today about treatment. But I am not convinced that we exactly know the cause, if it is environmental, if it is not environmental, and I would just like to emphasize how important your work is in that area.

Thank you, Madam Chair, I yield my time.

*Ms. Eshoo. The gentleman yields back. The chair is now pleased to recognize the gentlewoman from Delaware, Ms. Blunt Rochester, for five minutes for her questions.

*Ms. Blunt Rochester. Thank you, Madam Chairwoman and Ranking Member Guthrie. And thank you to the distinguished panel before us today on neurodegenerative diseases.

As was said by Mr. Curtis, almost all of us in this hearing has been personally touched. I lost a friend and also a loved one to ALS. I had a grandmother and great-grandmother who suffered from dementia, and recently a long-time neighbor who died from Alzheimer's disease, and I have

seen firsthand the devastating impacts these diseases have on our loved ones, and the toll that they take on our working families.

As you all have noted, Black Americans are about 2 times more likely, and Latinos 1.5 times more likely to develop Alzheimer's than non-Latino, White Americans. At the rate we are going, by 2030 nearly 40 percent of all Americans living with Alzheimer's will be Latino or Black. Black and Latino Americans living with dementia are also less likely to receive a timely diagnosis, more likely to report experiencing racial discrimination along their patient journeys, and less likely to be enrolled in cutting-edge Alzheimer's and brain health research.

I want to highlight this last point, because I think it is important. Latino and Black Americans make up less than 10 percent of all clinical trial participants in active Alzheimer's research. And, as I just mentioned, in less than 10 years 40 percent of Americans living with Alzheimer's will be Latino or Black.

This is why I introduced a bipartisan bill with my colleague, Congresswoman Herrera Beutler, H.R. 3085, the ENACT Act, to increase the participation of these under-represented populations in Alzheimer's and other dementia clinical trials, by expanding education and outreach to these populations, encouraging the diversity of clinical trial

staff, and reducing participation burden.

Dr. Hodes, I am grateful for the technical assistance that your team has provided on my bill, the ENACT Act, and I look forward to our continued collaboration. As you know, the National Institute of Aging currently funds 31 Alzheimer's Disease Research Centers at major medical institutions across the United States. However, an analysis has shown that the geographic distribution of the nation's 31 federally-funded ADRCs skews toward the most wealthy neighborhoods. Would you agree with that characterization?

*Dr. Hodes. Let me agree with the extreme importance of what you said, including diverse -- in our trials, and doing what we can to make that happen. And the location and sites for the trials is critically important, I agree. I had mentioned earlier in this hearing that, even at the gross level -- the states, large regions where we do not have Alzheimer's Centers, and we have corrected that, in addition -- four states in this past year, to try to extend.

You are right, because the academic research centers are often situated in major cities, this leads to the unintended but serious consequence of limiting to those people who have direct access to the studies there. We are working very hard to get around that, and newer technologies are helping. For example, remote contact with individuals for assessment of cognition. Looking forward to the day when we can replace

the PET scans, which have to be done at centers, which can make the radio isotopes, with blood tests which will extend what we do.

Putting registries in place -- we track for every study, not just by an annual report, but essentially real time, how many people were recruited in each study, what their demographics are, and rapidly turn around to correct things if those are not living up to standards.

But with your help, as well, increasing the visibility in communities to help us in recruiting for studies individuals who are -- who mirror the population, including those, as you noted, who are at the highest risk of all.

Grossly unsatisfactory, currently. These are among the things we are doing, with help of you and others, to help make this difference in the immediate future.

*Ms. Blunt Rochester. Yes, one of the things that our bill would do is actually increase the number of ADRCs in areas with higher concentrations at places like historically Black colleges and universities, Hispanic-serving institutions, tribal colleges, and other under-represented populations. And so further, our bill would provide funding so that the new research centers could establish and operate diagnostic and treatment clinics, which we believe are important.

Do you believe that funded research centers with clinics

in areas with higher concentrations of minority groups could help them to better connect with diverse population, and enhance recruitment?

*Dr. Hodes. Well, I mean, we certainly are looking for ways to do just that, to -- local contact with individuals, more local access to research, studies, and trials, absolutely.

*Ms. Blunt Rochester. My last question, I have run out of time. We will follow up with you, but I wanted to ask specifically about how we can improve engagement with under-represented populations in research, and some of the things that you believe are necessary to do that. So we will follow up with you in writing, and thank you.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Blunt Rochester. I yield back, Madam Chair.

*Ms. Eshoo. The gentlewoman yields back. The chair is now pleased to recognize the gentleman from Texas, Mr. Crenshaw, for his five minutes of questions.

[Pause.]

*Ms. Eshoo. Mr. Crenshaw, you need to unmute.

[Pause.]

*Ms. Eshoo. All right, I --

*Mr. Crenshaw. Does that work now?

*Ms. Eshoo. Yes, there you are.

*Mr. Crenshaw. Okay.

*Ms. Eshoo. Yes, I can hear you --

*Mr. Crenshaw. Sorry about that, thank you. Thank you, Madam Chair --

*Ms. Eshoo. You can proceed, please.

*Mr. Crenshaw. -- thank you, Dr. Cavazzoni, for being here with us.

I want to ask you, when you make determinations on drug approvals and emergency authorizations, would you ever use data or studies that have been rejected in peer review?

*Dr. Cavazzoni. If I understand your question correctly, you are referring to peer review in clinical journals. And when we look at the data and consideration about approval, we look at the totality of the data that is presented to us. So we don't necessarily exclude data on the

basis of where they were published, or whether they were published, the data provided to us by the sponsor. And we also look at everything else that we can find in the public arena, including published journals --

*Mr. Crenshaw. Sure. I mean, this isn't a trick question, honestly. I don't think the FDA has relied on large decisions, and relied on a single study that has been rejected in peer review, right? I doubt the FDA has done that. It is not a trick question.

*Dr. Cavazzoni. Well, I don't take it as such, Congressman. I cannot think of an instance where this may or may not have played out in our deliberation. The point that I was trying to make is that we look at all of the data that is presented to us, and whether it has been published or not is --

*Mr. Crenshaw. I appreciate that. I appreciate that. Let me move on. I have got to make a point, because it is big in current events right now, that the CDC is using a study that was rejected in peer review in trying to justify their new mandates. The CDC cited a study that was rejected, and only included symptomatic patients, and evaluated a vaccine, AstraZeneca, that is not allowed for use inside the -- in the U.S.

The FDA, where you come from, has supported data that shows that the COVID vaccines that we approved here in the

United States prevent transmission, and are effective against the Delta variant. Is that still true?

You, know, you are just -you are from the FDA. And so that is, you know -- you are the only person we have here, so that is why I am asking.

*Dr. Cavazzoni. Yes, I didn't come prepared to speak to vaccines today. And we have a whole center that --

*Mr. Crenshaw. Okay, okay.

*Dr. Cavazzoni. -- is focusing on that --

*Mr. Crenshaw. Okay, but you have -- this is very much in the public sphere. You have had conversations about this with CBER, right?

*Dr. Cavazzoni. I would be very happy to have our colleagues at CBER and vaccine experts follow up with you, and answer your questions in writing. I would prefer to have the experts address your very important question.

*Mr. Crenshaw. You are a physician from the FDA, I consider you an expert.

Let's move on. The FDA is also responsible for moving forward with incredible, innovative work, especially from our biotech community in Houston. And amongst these innovators are stem cell therapies. And I think that is a -- that is pretty relevant for the current conversation about neurodegenerative diseases.

And we have seen, in specific cases in Houston, where we

have been able to move regenerative cell stem therapies under the RMAT pathway laid out by Cures, passed by this committee. We are finding that the work is being stymied by some of the unintended regulatory burdens surrounding the current RMAT pathway. And I understand that you don't manage that division directly, but, since I have you, don't you think -- can you at least say this, that autologous stem cell treatments can provide a significant therapeutic benefit?

*Dr. Cavazzoni. The stem cell treatments are part of an array of potential therapeutic modalities. And ultimately, whether they can be helpful or not depends on the data that is generated by the clinical trials and the studies that look at these therapies.

And so, you know --

*Mr. Crenshaw. Well, you know --

*Dr. Cavazzoni. I certainly do not --

*Mr. Crenshaw. Well, I am kind of philosophical. I know you are going to hedge, and you are going to -- one philosophical question that I think we would really like to address here is the purpose -- the mandate, the purpose of the FDA. Is it focused on safety?

I think you can standardize safety pretty well. I think the FDA focuses on that pretty well. But are you doing that at -- but are you also focusing on efficacy to such an extent that you can't really standardize it?

With something like stem cell therapy, which is very clearly safe, is the FDA getting in the way of it, trying to standardize the efficacy of it in a very unreasonable way?

Is it -- was it worth looking at a paradigm shift on that?

*Dr. Cavazzoni. When it comes to diseases with unmet medical needs, we take an approach where we want to be as flexible as possible, understanding that there is a higher tolerance for safety.

And we also -- in a situation like when we use accelerated approval, for instance, we also accept, when in the appropriate instances, the fact that there may be some residual uncertainty about efficacy, and this is actually an inherent element of the accelerated approval pathway, which we have used in many situations and -- for unmet medical needs, such as, for instance, oncology, rare diseases, and infectious diseases.

*Mr. Crenshaw. Okay, thank you. I yield back.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentlewoman from Washington State, Dr. Schrier, for five minutes for her questions.

*Ms. Schrier. Thank you, Madam Chair, and thank you so much to the panelists for coming today, and also for your patience with our crazy schedule today.

Neurologic diseases impact our communities and our

families. And I am so glad to know -- relieved to know -- that so much research is happening in our institutions to find cures and treatments for these sometimes really devastating diseases.

My state of Washington also houses some research powerhouses in the space, from what we call ISCRM, the Institute for Stem Cell Regenerative Medicine at the University of Washington, working on stem cells and neurological disorders, to the Paul Allen Institute, which was just awarded a $40 million NIA grant to define the human brain's vulnerability to aging and degeneration at the cellular level, in partnership with UDaB and Kaiser.

Now, this week I read an NPR article highlighting some similarities between Long COVID symptoms and those of early Alzheimer's, and raising the question about whether there could be a common pathway. For example, genetic studies, evidently, are showing that some of the same genes that increase a person's risk for getting severe COVID-19 are also associated with an increased risk of developing Alzheimer's. And this is incredibly scary, partly because Long COVID affects young people, including children, and also because we are already seeing this explosion of Alzheimer's cases in the Baby Boomer generation. And to add to that would just be devastating for patients and families.

So Dr. Koroshetz, I was wondering if you could tell me

if we know, you know, anything more about this. Can you enlighten us a little bit with any more research into this space, and maybe applicability for children, and whether we see these kinds of manifestations in children with Long COVID?

*Dr. Koroshetz. Okay, well, it is definitely an important question, and we hope to get data coming in from what we call the RECOVER study, which Congress has appropriated funds for us to -- we are going to be studying tens of thousands of people who had COVID, and try and understand what these persistent symptoms really are, including children, pregnant women, people from diverse backgrounds. So we are going to have more information. We know very little now.

I would say that the cognitive problems that people with persistent symptoms have are different than what you would see in Alzheimer's disease. They are much more like what you would experience if you had the flu, and you know, you just can't think right, or you had a concussion. It is more that kind of attention/concentration issues.

There is one study, where they looked at the risk of dementia in, you know, millions of health care records, and they do see an increase that they think may be related to COVID. The question there -- and Dr. Hodes may opine -- is whether or not people who are having trouble, whether COVID

could have tipped them in a little bit further into the dementia/Alzheimer process. But I think that is still a hypothesis.

*Ms. Schrier. Yes, of course. Everything about this virus is so new. Thank you for that.

And rather than hypothesizing, I am going to hop, just because of timing, to my next question. I am going to pivot again to children.

As a pediatrician, I interface most often in the neurologic space with autism and with seizure disorders. And I was just wondering -- I will give this to you, as well, Dr. Koroshetz -- if you could just touch on the state of research into pediatric neurologic diseases, specifically etiologies, causes of autism, if we have any more information there, and also any new treatments for epilepsy.

*Dr. Koroshetz. Right. Well, I guess a lot to unpack there, but I would say that what we have learned from the genetic studies is that there is an overlap between autism and epilepsy, very commonly, and also with developmental delay. And so that is getting at kind of what are the problems that occur, as the brain is developing in a young child, or even in a fetus. And we have some clues. And the question is how to go from those genetic clues to treatments.

I would say, in the epilepsy space, there are some very new genomic techniques that are now coming out, because we

know what the different mutations are, and they are very mutation-specific. So we are very hopeful that more precise therapies will help, especially these young children with severe epilepsy and mental disorders, cognitive disorders.

*Ms. Schrier. Thank you very much. Those are my questions. Thank you for your research, and I yield back.

*Ms. Eshoo. The gentlewoman yields back. The chair is now pleased to recognize the gentlewoman from Arizona, Mrs. Lesko, for five minutes of questions, followed by our very patient waiver-on, Ms. Schakowsky. And then we will go, thankfully, to the next panel.

So, Congresswoman Lesko, you are recognized.

*Mrs. Lesko. Thank you, Madam Chairman.

Dr. Koroshetz, has NIH ever used Federal funds to pay for non-FDA-approved medicines for individuals not in a clinical trial?

If so, under what conditions, and who or what agency made these decisions?

*Dr. Koroshetz. So NIH pay for non-FDA-approved medicines in a clinical trial. Only --

*Mrs. Lesko. Not in a -- so has NIH ever used Federal funds to pay for non-FDA-approved medicines for individuals not in a clinical trial?

*Dr. Koroshetz. I do not think so, no.

*Mrs. Lesko. Thank you. Another question for you, sir,

is, if an expanded access program were available, and the medicine purchased with Federal funds, what kind of program would have to be created to make it a fair program, in terms of who benefits?

*Dr. Koroshetz. Well, that is a tricky question, because I think we are talking about drugs that have not been proven to have benefit.

So, as has been mentioned, there is a great need for patients who are suffering with these deadly disorders to try something. And so I think that the benefit there would be to have them feel as though they are getting access to things that might help, even though the chances are slim.

I think that the issues there are that they could be so slim that they are either zero or harmful, and I think we also have to consider the fact that the treatments that we have been seeing, I would say, are not, you know, powerhouses.

And so what we want is multiple shots on goal. We want multiple different things to be tried. And so we need patients who would enroll in these new trials. The ones we have seen so far just are not that impressive.

*Mrs. Lesko. Thank you, Doctor. And my next question is for Dr. Cavazzoni -- sorry if I say your name wrong.

You know, this is -- many people seem to be surprised by the FDA's approval of aduhelm, considering that the

recommendations from the advisory panel were not really robustly in favor. And so, my question is, can you walk me through why the treatment was approved?

*Dr. Cavazzoni. Thank you for the question.

First, let me say that we greatly value the input from all our advisory committees, including the input that we receive from the Neurology Advisory Committee related to Aducanumab. So we looked at the data from this program over many, many months. And, after exhaustive and detailed review of the data that was provided in the application over the course of these many months, we had a discussion within FDA with experts, and also took very careful stock of what we heard from the advisory committee.

And putting all of that together, we concluded that the data fully met the criteria for accelerated approval, which is an expedited approval pathway that Congress gave us in 1992, and has been used successfully over the past 30 years to bring therapies faster for a condition, whether it is -- an unmet medical need, such as oncology, infectious diseases, and some rare diseases.

The accelerated approval pathway has not been used as extensively when it -- in neurodegenerative diseases. In this case, in the case of Aducanumab, the data really made us very comfortable that all the criteria for accelerated approval had been met. And we view this as an incremental

step, not only for Alzheimer's, and for bringing a potentially beneficial treatment for Alzheimer's, but also an incremental step in finding ways to leverage the expedited pathway that we have at FDA to bring therapies for neurodegenerative diseases faster for patients who are desperately needing them.

*Mrs. Lesko. Thank you, Doctor. My time is almost out, and so I yield back.

*Ms. Eshoo. The gentlewoman yields back. Maybe I should know a heck of a lot more about this, but I am struck by the irony on -- of the conditions under which the Alzheimer's drug was approved, understanding that it had limited help to patients, which is one of the reasons that we are having the hearing today to try and -- you know, to examine what FDA is doing, and bring about the same kind of limited hope, but yet it is hope, and it is help for the ALS community. So I just pose that, because I -- but think that there is an irony here.

The chair recognizes the gentlewoman from Illinois, Ms. Schakowsky, whose constituent has been in the hearing room since we opened the doors at 11:00 this morning, and traveled across the country -- except he has been waiting in a wheelchair. So the gentlewoman is recognized. She is waiving on to the subcommittee, as she has many times before, always welcome here.

*Ms. Schakowsky. Thank you, Madam Chair.

Dr. Cavazzoni, some time ago one of my oldest, long-term friends, a dear friend, made a decision to set a date to end his life. He moved to Canada. He had ALS. And he made a decision that was representative of having no hope. He chose death. Well, you, Dr. Cavazzoni, have brought, through the wonders of science, some hope to people, a person in this room. Because of this decision that was made, the 2019 FDA guidance, there is some hope now.

But my understanding is that, when I ask you to produce the name, the individual who has actually been able to benefit from this 2019 guidance, that there really isn't anybody that has been able to access that so far, that there are people all over this country who -- there is this glimmer of hope, but it is still out of reach.

If I sound upset -- because my constituents are here, I have been getting calls from their friends all over the country, who are begging for a bit of hope. You are going to hear them, and I hope you will stay to hear them. I know that, you know, once we move to the next panel, you can leave, but I really beg you to stay and listen to their testimony.

Could you tell me the people who have actually been able to benefit? Because my understanding is that it has been quite impossible to be able to access the two drugs. There

are two drugs that are there now, and maybe my friend, Art, would have been here to benefit from that. Can you answer me? Are there people you can tell us -- give us a list of names?

*Dr. Cavazzoni. Well, first, I really want to say how sorry I am to hear about the story of your friend, and it is really tragic, and I really empathize with the suffering that people with ALS have to go through every day. I cannot mention -- I don't have the names of people with ALS who may have been --

*Ms. Schakowsky. A number, how many?

*Dr. Cavazzoni. -- in trials and --

*Ms. Schakowsky. How many? Are there people --

*Dr. Cavazzoni. Yes, I am sorry, I don't have that information with me.

I would like to address your point about the guidance. The guidance is critically important, because it provides advice for developers so that they can put in place clinical trials and development programs that have the best chance to provide --

*Ms. Schakowsky. This is now --

*Dr. Cavazzoni. -- in a timely fashion.

*Ms. Schakowsky. Excuse me, I -- the guidance is about flexibility. And what I am not understanding is, when you have people who actually could help advance the science, this

is one contribution they could make, whether or not it extends their lives. Why we wouldn't do this -- because the option is death. And it is in your power. I mean, what a blessing that is. It is in your power.

And so I am begging you, I guess, I am, to try to give some hope that there will be some accessibility, due to this flexibility in the guidance. Is there any more that you can do?

*Dr. Cavazzoni. I really hear you, and I can tell you that we are working every day to find ways to accelerate the development of therapies, and to be as flexible as we can in how we work with sponsors, how we help them put in place clinical trials, and also as flexible as we can in how we look at the data that is derived from those clinical trials, understanding that, when we are dealing with diseases such as ALS, there has to be a higher threshold for risk, and also greater tolerance for some residual --

*Ms. Schakowsky. Well, I don't know what --

*Dr. Cavazzoni. -- around the --

*Ms. Schakowsky. You know, I don't know, and I know my time is up. I don't know what flexibility is, then, when people are standing by, willing to contribute to the science and make discoveries that could help others, and perhaps extend their lives.

So I yield back.

*Ms. Eshoo. The gentlewoman yields back. This concludes our first panel. And Dr. Hodes, Dr. Koroshetz, and Dr. Cavazzoni, thank you for your testimony. Thank you for your patience. Thank you for the work that you are engaged in. You, obviously, heard a lot of frustration and very direct questions from members today. We have an enormous challenge together, as I said in my opening statement. I believe that we can not only make progress, but, as we are making progress, that we bring hope to the patient population who are in dire need of hope.

And members will be submitting written questions to you. We ask that you answer them in a timely way.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. And again, we thank you for being with us.

Now we will hear from a second panel of witnesses today. Dr. Cartier Esham, the executive vice president of emerging companies, and senior vice president of science and regulatory affairs at the Biotechnology Innovation Organization -- we all know it by the short name of BIO.

It is really an honor to have Dr. Merit Cudkowicz. She is the director of the Sean M. Healy and AMG Center for ALS, as well as the chief of the neurology department at Massachusetts General Hospital, and the Julianne Dorn professor of Neurology at Harvard Medical School.

Dr. Jinsy Andrews is the director of Neuromuscular Clinical Trials at the Neurological Institute of New York, and the associate professor of neurology at Columbia University, Vagelos College of Physicians and Surgeons.

And thank you, Dr. Andrews, for traveling to Washington, D.C. to testify in person.

And last, but certainly not least --what? Oh, I see, yes. Oh, I am -- I have another page.

Mr. Brian Wallach and Sandra Abrevaya are the co-founders of I AM ALAS (sic).

Thank you, Brian and Sandra, for traveling to Washington, D.C. to testify before our committee.

Ms. Yvonne Latty is a journalist and college professor at NYU, as well as a caregiver to her mother, Ramona Latty,

who has advanced Alzheimer's disease.

And Ms. Kala Booth is a Huntington's disease patient and caregiver. She is also a constituent of the ranking member of our subcommittee, Mr. Guthrie.

And now I will recognize Mr. Guthrie to offer a few words of introduction.

*Mr. Guthrie. Thank you. It is great to have Kala here from Cecilia, Kentucky, Kala Booth. I talked about her earlier in my opening statement, which seems like such a long time ago, but -- so I have kind of told your story, Kala, if you weren't able to listen, and look forward to hearing it from your own words, and appreciate your courage in being here today.

And also we have another Kentuckian, Dr. Esham, who I think, I found out earlier, went to high school with Thomas Massie in Vanceburg.

So welcome, as well. Two good Kentuckians here today, and some other wonderful people, so thank you very much. I yield back.

*Ms. Eshoo. The gentleman yields back. I am going to go first to Dr. Cudkowicz, because she has to leave us.

And I thank you for your willingness to testify, for saying yes to me when I called you. It is an honor. And I am sorry that the day has dragged on the way it has. It is something out of our control, but we wanted to complete our

work today, and thank you for staying with us. You are recognized for your five minutes of testimony. And thank you, again.

STATEMENT OF MERIT CUDKOWICZ, DIRECTOR, SEAN M. HEALY AND AMG CENTER FOR ALS, CHIEF, NEUROLOGY DEPARTMENT, MASSACHUSETTS GENERAL HOSPITAL, JULIANNE DORN PROFESSOR OF NEUROLOGY, HARVARD MEDICAL SCHOOL; CARTIER ESHAM, PH.D., EXECUTIVE VICE PRESIDENT, EMERGING COMPANIES, SENIOR VICE PRESIDENT, SCIENCE AND REGULATORY AFFAIRS, BIOTECHNOLOGY INNOVATION ORGANIZATION; JINSY ANDREWS, M.D., DIRECTOR OF NEUROMUSCULAR CLINICAL TRIALS, NEUROLOGICAL INSTITUTE OF NEW YORK, ASSOCIATE PROFESSOR OF NEUROLOGY, COLUMBIA UNIVERSITY VAGELOS COLLEGE OF PHYSICIANS AND SURGEONS; BRIAN WALLACH, CO-FOUNDER, I AM ALS, ACCOMPANIED BY SANDRA ABREVAYA, CO-FOUNDER, I AM ALS; YVONNE LATTY, CAREGIVER; AND KALA BOOTH, HUNTINGTON'S DISEASE CAREGIVER AND PATIENT

STATEMENT OF MERIT CUDKOWICZ

*Dr. Cudkowicz. Thank you, Madam --

*Ms. Eshoo. Unmute.

*Dr. Cudkowicz. I have unmuted. Can you hear me now?

*Ms. Eshoo. Yes.

*Dr. Cudkowicz. Thank you, Madam Chair and members of the House subcommittee, for inviting me to testify today.

Since 1994 I have cared for thousands of families living with ALS. As a clinical trialist, I designed and led many ALS trials, including the recent trials of AMX0035 and

NurOwn. I am grateful for longstanding support from both the NIH and the FDA for my research.

We are at a major therapeutic turning point in ALS. There have been huge advances in understanding the underlying biology of ALS, and this has led directly to several exciting drug targets and positive phase two and three trial results in people. Yet patients can't get access to these treatments.

We must act now to be both global leaders in the science and therapy development, but we also must be global leaders in regulatory approaches by the FDA to help all those living with ALS today.

There are two pieces of legislation before you, at least two, that can define success and options for tens of thousands of people living with ALS and other serious neurodegenerative disorders. I beg you and ask you to approve them.

The first is the ACT for ALS, which will support expanded access to ALS investigational therapies for people with ALS who do not qualify for trials. More than half of the people with ALS do not qualify for trials. At the Healy Center for ALS at Mass General we have 130 of our patients receiving 9 different treatments in expanded access. These patients were not eligible for any trials. This was their only option.

EAPs can be designed to also learn about ALS. For example, in one of our EAPs we learned how to best dose the treatment using biomarkers. In another, we found that people's breathing was getting better. One person noted that they could swim in the pool again. Another person found that they could be off their mechanical ventilator for a few more hours a day. Expanded access absolutely does not interfere with clinical trials or drug development; it can help it.

The second bill is the Promising Pathway Act that would allow for conditional approval of promising treatments in phase two and three. We need this faster pathway for approvals for treatments in ALS. This is already happening in other serious illnesses, like cancer, and it is happening for ALS in other countries, but not in the U.S. This is why we are here today.

Progression in ALS is dauntingly rapid. After diagnosis, median survival is two to three years. Again, this is getting more common. The worldwide number of people with ALS is expected to rise more than 40 percent in the next decade. There is an urgency to act.

There was no hope before, but there is hope now. Thousands of people are studying this illness. There is 160 companies in it. We understand some of the biology. We have good targets, and we have positive treatments. This is, again, a major therapeutic turning point.

We partnered with a small company, Amylyx, to develop the AMX0035 drug, and we showed last year -- a year ago we published this in New England Journal of Medicine -- that this drug slowed disease progression, and it prolonged survival. This is a combination of two old drugs. We know the safety of these two drugs. And while this drug, AMX0035, is under review in Canada for full approval, and it is going to be submitted to EMA in Europe for provisional approval, there is no option for provisional approval here, in the United States. This means a drug developed and tested here will likely be approved elsewhere first. That is not good.

We have also heard reports from people in the NurOwn trial of improvements in function. We don't usually hear this. There were also some important biomarkers, and better responses in people who were earlier in the disease. We need continued dialogue with the FDA about how to move those type of treatments forward.

Our goal is to make sure everyone with ALS has options, whether that is in the trial or expanded access. And no one should be told there is nothing to do.

We are seeing pharma companies go to other countries for their phase one and two studies. They claim that the regulations are less onerous in Canada or Australia. We are starting to see drugs approved faster in other countries. My request is that we continue to be world leaders in regulatory

science and the approaches to accelerate therapy in ALS and other serious disorders. We need to do that.

We are the leaders in the science. Working together, and creatively, and flexibly, we are going to find the cures for ALS and help our patients, and tens of thousands of people. Thank you.

[The prepared statement of Dr. Cudkowicz follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Dr. Cudkowicz, thank you for your most welcome testimony. I think the sun has gone down -- well, it has, it is about a quarter to seven -- but listening to you made me feel like the sun was rising. So thank you for your marvelous testimony. And I think that you are going to have a lot of questions from members, a lot of feedback. And we sincerely look forward to working with you.

And thank you for underscoring the legislation that you support, and why, and how it will help move the needle. So thank you.

And I know that you need to leave. We are -- you have our lasting gratitude.

Okay, so now who is next?

The chair now is pleased to recognize Dr. Cartier Esham -- I hope I am pronouncing your name correctly --

*Dr. Esham. Yes.

*Ms. Eshoo. You have five minutes for your testimony, and welcome.

STATEMENT OF CARTIER ESHAM

*Dr. Esham. Thank you. Can everybody hear me?

*Ms. Eshoo. Yes.

*Dr. Esham. All right, well, good evening, Chairwoman Eshoo, Ranking Member Guthrie, and members of the Health Subcommittee. My name is Cartier Esham, and I am the chief scientific officer at BIO. And thank you for the opportunity to share our insights on the state of innovation for medicines to treat neurodegenerative diseases.

We are the largest trade organization representing biotechnology companies, and our members range from entrepreneurial companies developing their first product to Fortune 500 multinational companies. We regularly publish reports to help us assess the health of the pharmaceutical pipeline across different diseases, so we can identify and remove barriers to providing next-generation cures and treatments to patients and their families. I am going to highlight three such analyses, with a focus on neurology, with the goal of providing insights to this very important conversation.

In 2021, we counted 653 clinical development programs from medicines to treat neurological diseases, 43 percent of which are for neurodegenerative diseases. By comparison, there are 2,798 oncology clinical development programs.

There have only been a total of 39 FDA approvals for neurological treatments in the last decade, compared to 123 for oncology. Analysis of fiscal trends provides us with tremendous insights as to whether incentives are misaligned, or there are other scientific or development barriers in any given disease area that need to be resolved.

We focus most of our fiscal analyses on emerging companies as they are responsible, alone or in partnership with larger biopharmaceutical companies, for over 77 percent of the clinical development pipeline.

Over the past 5 years, we have seen an increase in venture capital in neurology, setting a record of 1.7 billion in 2020, a fourfold increase from 2012. While important, it is important to put these numbers into context; in 2020, venture capital invested 7 billion in emerging oncology companies.

We have also seen a recent increase in the number of neurology companies to go public, which is an important way to generate investment dollars. There was not a single neurology company that went public in 2012. However, in the past 5 years we have seen 18 emerging neurology companies go public. But again, to provide context, in that same time period 75 oncology companies went public. Thus, while investment in neurological disease is increasing, it is not at the level we would like to see or need.

When we look at clinical trial success rates from 2011 to 2020, we found the overall success rate across all diseases is 7.9 percent. Neurology clinical development programs have a 5.9 percent success rate. However, there are important and informative differences in success rates when you look at modalities in disease categories. For example, development programs with patient selection biomarkers have a twofold higher success rate.

Looking quickly at Alzheimer's, a very complex, very biologically complex, chronic disease, scientists have identified more than two dozen genes known to correlate with increased risk of Alzheimer's. However, despite the identification of gene mutations associated with Alzheimer's, many unknowns remain. For example, there are individuals who do not have Alzheimer's-associated gene mutations that still develop the disease. Conversely, other individuals may have fibrillary tangles, but do not exhibit dementia.

Our 2019 report on the state of innovation for Alzheimer's found that venture capital funding of U.S. companies with lead programs in Alzheimer's was 16 times below oncology funding. The field saw 87 programs suspended from 2008 to 2019. However, this year marked the first approval of a disease-modifying drug for Alzheimer's. And we do continue to innovate. Our report identified 74 disease-modifying clinical-stage Alzheimer's programs in the pipeline

that are using 10 different strategies involving 30 distinct molecular targets.

Additionally, our analysis of the pre-clinical pipeline found that 23 of the 122 pre-clinical programs had unique targets not currently in the clinic. But to deliver on these innovations and overcome historical odds for neurodegenerative medicines, creative solutions are required.

As our scientific understanding of disease evolves, so must the way we develop and review these medicines. Policies supporting patient-centric, efficient, and effective clinical development and review will encourage investments into new treatments.

Additionally, continued funding of basic research to advance our understanding of the biology of neurodegenerative diseases, advance our ability to understand and to develop novel endpoints, and understand how to interpret those endpoints will arm developers with new targets and approaches to attack this complex disease.

BIO and its member companies view innovation as key to helping patients with neurodegenerative diseases. Advances in science, more choices for patients, and a policy environment that stimulates investment in R&D are necessary to achieve this goal. And we look forward to working with Congress to develop and advance important legislative solutions to achieve this shared goal. Thank you.

[The prepared statement of Dr. Esham follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you very much for your testimony, Dr. Esham.

The chair is now pleased to welcome and to recognize Dr. Andrews for your five minutes of testimony, and it is just so embarrassing that you have had to wait all day. We are very honored to have you here, and we apologize, and we thank you, and I am happy to finally recognize you.

STATEMENT OF JINSY ANDREWS

*Dr. Andrews. Thank you, Chairwoman Eshoo and Ranking Member Guthrie, and members of the committee. Thank you so much for the opportunity to testify on the challenges and opportunities of ALS research and development. My name is Dr. Jinsy Andrews, and I am the director of neuromuscular clinical trials at Columbia University. I am also a volunteer board of trustees member for the ALS Association. I also receive NIH funding for clinical trials, and I serve as a part-time staff physician at the James J. Peters VA Hospital, caring for veterans with ALS. My testimony today are my own personal views, and not of the VA.

First, I want to thank the committee for persevering through a very long day, and I would like to also thank the members of the committee and the House for passing the consolidated appropriations bill during the break between this hearing's panel. The ALS community deeply appreciates this, and increasing funds to the NIH, including ARPA-H and other Federal research programs, are critical for ALS and other neurodegenerative diseases.

I also urge you to increase funding for the DoD ALS Research Program.

I am here today to ask for your help because the ALS research and development is not moving fast enough, as we

heard today. The ALS community needs your help to ensure that the FDA accelerates drug development, approval, and access to effective new ALS treatments. When we all work together, we have seen the ability for regulatory flexibility and speed. Congress should urge the FDA to use their existing regulatory authority to move much more quickly on ALS drugs.

Specifically, the ALS Association has urged Congress to pass the ACT for ALS Act to provide increased access to experimental treatments for people with ALS, while funding new research. The ALS Association has also urged Congress to increase Federal funding for research, ALS research, and to develop a conditional approval pathway modeled on the successful experience of the European Union.

I have cared for people with ALS, and conducted clinical trials for over 15 years in both an academic and industry setting. In 2013 I attended a public hearing for ALS held by the FDA, where many people with ALS at that time shared that they are willing to take higher risks, that time is a luxury that they just don't have, and that they had limited access to experimental treatments. Many of those patients, including the ones that I cared for, have since died. Time is of the essence. People with ALS urgently need effective new treatments.

The FDA should be fully funded, fully staffed, and

provided the regulatory authority they need to be fast, effective, and transparent for ALS clinical trials and drug approvals. Making approval decisions about promising therapy is never easy, especially in fatal diseases. But year after year, people with ALS have shared with the FDA, with Congress, and basically anyone else who will listen, that they are willing to accept greater risks, that anything that retains function, that provides more time, is meaningful to them, and that access to new treatments, including ones prior to FDA approval, is a top priority, because right now there is no cure for ALS.

There are also opportunities for manufacturers to make ALS clinical trials more efficient, more impactful, and more respectful for people with ALS. That includes expanded access to experimental therapies, which is not often provided by the pharmaceutical companies that are in the ALS space, typically because they are small, or they don't have resources. And in contrast, big pharma companies that may be able to provide expanded access don't invest in ALS programs until they are de-risked. All clinical trials should be accessible to people with ALS, by including open label extensions and expanded access, which, if it is designed appropriately, could collect data regarding safety and tolerability.

Additionally, I am going to emphasize what Dr. Cudkowicz

emphasized: providing expanded access to patients outside of a clinical trial can be accomplished without impeding the completion of a clinical trial in ALS. We have done this, and we are doing this by offering expanded access to patients who are not clinical trial eligible. We stagger the enrollment of clinical trials in offering expanded access, and clinical trial participants should be assured that they have access to the experimental therapy after they have completed their participation in the formal clinical trial.

This -- there is a perception out there that ALS is rare, but we have all shared stories today about how we have been touched by neurodegenerative diseases, so I don't have to explain much more than that. It is important for us to act now. Thousands of people with ALS are dying today, and don't have options. Anyone, any one of us, are at risk of developing ALS or a neurodegenerative disease. Our veterans who served this country are twice as likely to develop ALS than the general population.

When someone is told they have ALS, they have a zero percent chance of survival. Pancreatic cancer even has a five percent chance of survival. Let the people that get diagnosed with ALS not have to face what people with ALS are facing today: a lack of access to treatments. You have the power to change that.

And especially I want to thank the committee for the

opportunity to testify and, of course, thank the panel before us, that we are able to participate in this important hearing today. Thank you.

[The prepared statement of Dr. Andrews follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Dr. Andrews, thank you. I think all of us more than welcome your testimony. And the clarity and the passion that you delivered it is really welcome here.

Did you have any -- just very quickly -- recommendations on the legislation that is at hand, and what you would say about it?

*Dr. Andrews. I have to agree, and I am going to say that almost all of the ALS community agrees.

As Dr. Cudkowicz mentioned, these pills that are on the floor can make transformational change, help preserve clinical trial integrity, and help access to experimental therapies. And actually, in those cases of access, in expanded access, we can actually gain data to help understand the disease, and improve our understanding of the biology for the future, for more effective treatments down the line.

*Ms. Eshoo. Thank you very much. And we ask that -- I am sure there are many members that are going to submit written questions to you, and we will look forward to hearing back on those, the questions being answered by you on a timely basis. So thank you very, very, very much.

The chair is now so pleased to recognize our two guests that have been with us since the doors were unlocked this morning.

You knew that it was going to be a long day, you had no idea that it was going to be all day and part of the night.

We are blessed to have you. We thank you for traveling across the country. I said to you when I greeted you this morning that I thought you were both profiles in courage, and that you are.

So, Mr. Wallach, welcome again, and thank you.

And Ms. Abrevaya, it is more than an honor to have you, and we look forward to your testimony now.

I should -- I wanted to add, because I don't want him to leave, he left before, and I didn't recognize our colleague, Mr. Quigley from Illinois. He is one of the -- he is the Democratic lead on the legislation that Congressman Jeff Fortenberry from Nebraska -- they have worked so hard on that bill. I look forward to this committee considering it.

We want to thank you for the work that you have done, and thank you for being here for the second time today. But I didn't get to introduce you and acknowledge you. You scooted out before I could say something before.

At any rate, it is your five minutes. And if you go over time, the chair is not going to lower any gavel.

STATEMENT OF BRIAN WALLACH, ACCOMPANIED BY SANDRA ABREVAYA

*Ms. Abrevaya. Thank you so much. Well, we would be here all night and into the morning, because this is a critically important hearing, and tens of thousands of ALS patients have been waiting just for this moment. And we are so grateful to be here.

So Chairwoman Eshoo, Chairman Pallone, and Ranking Members McMorris Rodgers and Guthrie, thank you for the opportunity to testify before you today.

*Mr. Wallach. My name is Brian Wallach. I am 40 years. I have been fighting ALS for four years.

*Ms. Abrevaya. I am Sandra Abrevaya. I am a caregiver. I am Brian's wife. And, as you will hear today, I will be his voice. We have two young daughters. One turned six two weeks ago, and our second daughter, she turns four on Saturday.

Professionally, I have served as a staff member in the House, in the Senate, in a Federal agency, and Brian and I together served as staff members in the White House. At the time that Brian was diagnosed, he was 37 years old, and he was an assistant United States attorney.

*Mr. Wallach. This is our closing argument for our lives.

*Ms. Abrevaya. This is our closing argument for our

lives.

As you just heard from the panel's expert ALS clinicians, we are all aligned. ALS, while currently a 100 percent fatal disease, is no longer hopeless. Today there are more promising therapies that are slowing or stopping ALS in people, not in animal models, in people.

So the question we all need to answer today is the one I am so tremendously grateful that so many members, perhaps a record number of members, asked in a unified voice today: How do we get the tens of thousands of ALS patients, alive and dying today, using the tools and the science that currently exist, therapies that can keep patients alive to be here, to see cures?

And I am excited to tell you that the answer is abundantly simple: make the FDA act with urgency and regulatory flexibility. It promised in its 2019 guidance to approve the drugs that are stalled right now. It is abundantly simple, and it is within your power.

Despite what you heard from the FDA this morning, it has never historically required a biomarker to approve an ALS therapy. Instead, FDA has used two outcome measurements to approve therapies in the past: survival length and the ALSFRS scale, which measures a patient's ability to do things like walk up the stairs or cut their own food.

I think it is extremely important for this committee to

know the data, the facts. I can tell you, Brian and I have done our homework. Radicava is a drug that was approved for patients in 2017, and the FDA cited that it slowed patients' progression on the ALSFRS scale. The trial for AMX0035, one of the two drugs being stalled now, also showed that it did the same thing, it slowed progression on the ALSFRS scale. And, I might add, it gave patients an average of six-and-a-half months longer to live, when compared to the placebo.

Interestingly, AMX turns out it is headed for speedy approval in Canada and Europe. And it is based on the very same data that the FDA had a year ago. It certainly begs the question of why didn't FDA approve this a year ago?

The trial for the second therapy being stalled is called NurOwn, and that trial showed that, for those patients who started the trial with a score of 35 or higher on the same ALSFRS scale and received the drug, their score at the end of the trial was 2 points higher.

We heard again and again today, "We need science, we need data.'' I am telling you what the data was. It is publicly available. For patients who entered the trial with a 35 or higher, they scored 2 points better than the placebo. You can go back and look at Radicava on the FDA website. That is the exact same type of success rate that Radicava had when it was approved in 2017, which begs the question, why has this therapy, NurOwn, which is successful for a subset of

the patients in the trial, not being approved?

Moreover, after that NurOwn trial, several patients have been able to access it through a small, expanded access program, and a number of them have seen it halt their progression, or improve their function.

*Mr. Wallach. Phil Green.

*Ms. Abrevaya. Phil Green is a friend of ours who can now buckle his seatbelts and take his own pills. I can tell you Brian can't do either of those things, and we just turned 40.

For a clear explanation of expanded access than I think we were all provided with today, I would encourage you to go to FDA.gov. On that site you will see very clearly that, just as Dr. Andrews articulated, in order to be eligible for expanded access, on their website, "patient enrollment in a clinical trial is not possible.''

Let me be super clear. Expanded access in no way endangers a clinical trial.

Second, it was great to hear the FDA this morning say they are so supportive of expanded access for patients. If that is true, I would ask the FDA to publicly announce their support for ACT for ALS, which will fund expanded access programs. As Dr. Andrews also said, again, you will see the ALS clinical community and the ALS patient community is all aligned, uniform. Expanded access is not affordable for the

small biopharma companies that are currently in the ALS scene. We need the funding in ACT for ALS. So if anybody in this room wants to see patients get access to expanded access, you have to do that by giving it funding. And ACT for ALS is the vehicle to do so.

The FDA's recent decisions are all the more shocking, in light of their own September 2019 guidance, which, again, I am so grateful that so many members brought up today. However, it said it would exercise flexibility and urgency and, sadly, what we have seen is even less urgency, and less flexibility. They have asked the two drugs I have repeatedly mentioned, AMX0035 and NurOwn, to run another large placebo-controlled trial prior to any approval. That means these therapies won't be approved for four years.

Let me remind you, when you are diagnosed with ALS, you are told you have two to five years to live. So if this won't be on the market for four years, every single ALS patient, including us, will be dead before having access to either therapy.

Congressman Upton asked an excellent question of the FDA today: How can Congress help?

*Mr. Wallach. FDA did not answer his question.

*Ms. Abrevaya. FDA did not answer that question. So we, as the patients who are dying, whose lives are on the line, we will answer it for you.

One, urge FDA to approve AMX0035 today.

Two, urge FDA to approve NurOwn for the over-35 subgroup today.

Three, pass ACT for ALS, which funds expanded access, today.

Four, pass the Promising Pathways Act to provide a conditional approval pathway for rapidly progressing fatal diseases, even beyond ALS.

I beg of you. There are tens of thousands of patients who are watching this from their homes, wheelchair bound, some of them on life support, watching this today. Their hope is in this hearing. Some of them have waited and postponed their decision for suicide to see this hearing. I don't think you understand what this hearing means to us. Please do not let another generation of ALS patients die in pursuit of the perfect. Please let this be the first generation to survive.

*Mr. Wallach. We want to live. You have the power to make that possible.

*Ms. Abrevaya. We want to live. You have the power to make that possible. Thank you.

[The prepared statement of Mr. Wallach follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. I think that there is a sound building across the country of applause from the entire ALS community, listening to you offer your testimony and your message to this committee. We are so in debt to you. We thank you for your clarity. We thank you for your courage, and thank you for the patience that you had to exhibit today. And I don't think there is a -- let me put it this way, in a positive way, that every single member of this subcommittee is moved by what you said, and that we are determined to pursue exactly what you set out in your testimony. So thank you, thank you, thank you, thank you.

All right. Next we have Ms. Yvonne Latty, and we welcome you, and we thank you for being willing to testify. We apologize to you, as well, for having to spend a day and part of the night waiting to testify, but I am really pleased to recognize you now for your five minutes of testimony.

STATEMENT OF YVONNE LATTY

*Ms. Latty. Okay. Chairwoman Eshoo, Ranking Member Guthrie, and distinguished members of the committee, thank you for the opportunity to tell my family story during today's hearing.

I am a journalist and a college professor at New York University, but I sit here before you as a daughter. My mom, Ramona Latty, a Dominican immigrant, has advanced Alzheimer's disease, and lives in a nursing facility in the Bronx. She is 88, and I am her only living child.

This disease is rampant in my community. In general, Latinos are 1.5 times more likely than non-Latino Whites to develop Alzheimer's disease. My chances of getting the disease are also slightly elevated, because my mother has it. The health issues that plague our community -- high blood pressure, heart disease, diabetes, and stroke -- make us more vulnerable. The statistics for the African American community are even worse. They are two times more likely to get the disease than White people.

But this disease is not who my mother is, even though it has taken control of her life. My mom was born in Santo Domingo, a city on the coast of the Dominican Republic. She grew up poor in the -- she grew up poor. In the eighth grade she had to drop out of school to take care of her brother, so

that her mother could work. My mom was a big dreamer, who wanted more, so she wanted out of Santo Domingo, where she worried she would live a life with no work, no money, and no hope.

In 1950 my mom immigrated to New York. Coming to America was her dream come true. She worked in factories and went to beauty school. She met my dad, Albert, a child of Jamaican parents, at a beauty parlor in Spanish Harlem, where she worked. They were married nine months later, and had two daughters, me and my big sister Margie. My dad and my sister have both died. And so it has been the two of us for a long time.

About six years ago my mother started to show signs of dementia. She was losing things, and was confused. Then she began to hallucinate a boy who lived on top of her refrigerator. I discovered she gave all her money away to mail-order psychics who promised her riches. We spoke every day, sometimes multiple times a day. I found myself thinking about her all the time, worried. So we turned to her doctor, who suspected dementia, and referred us to a neurologist.

I remember the day we went to his office in the Bronx, where Black and Brown people packed the waiting room. After a series of tests, he told us dryly that she had Alzheimer's disease. He gave me some URLs, told me to Google it, and sent us on our way in less than 10 minutes. It was clear he

had no time for us. He barely looked at my mom. I went home and cried.

This is not uncommon in the Latino community. Despite a higher risk for Alzheimer's, Latinos and Black Americans face steep inequities in accessing a formal diagnosis. According to a recent study of Medicare beneficiaries, Black Americans and Latinos were less likely to receive a timely diagnosis, when compared to non-Hispanic whites.

But I was ready to fight this disease. I switched neurologists, and the new one referred her for a clinical trial to help with the hallucinations. While Latinos make up roughly 17 percent of the U.S. population, they make up less than 2 percent of the participants currently enrolled in Alzheimer's research funded by the National Institute of Health.

Clinical trial enrollment represented hope against a disease that is often seen as a death sentence. I was thrilled that she was going to be part of one, and hopeful that it could help her, but it was grueling. She lived in the Bronx, and I live in Philadelphia. I had to get her to New York Presbyterian Hospital in Washington Heights every week for six weeks. She had to visit a series of doctors, and have psychological exams before the medicine was administrated. We barely had enough compensation to cover an Uber from the Bronx to reach the research site.

Research accessibility in communities like the Bronx is a systematic issue. According to an analysis by the University of Wisconsin, the geographic distribution of the nation's 31 federally-funded Alzheimer's Disease Research Center's marquee research sites skews toward the most wealthy neighborhoods.

Balancing her research participation and my full-time job was another challenge. I was teaching, and had to ask my coworkers to cover me so I could be at every appointment. I was able to make it work because my employer offered paid family and medical leave and flex time. The millions of Americans are not so lucky.

Paid leave is an urgent health equity issue for dementia caregivers. According to a national survey of unemployed dementia caregivers, less than half have access to paid family and medical leave policies like me. More than half of caregivers who utilize paid family and medical leave benefits reported it resulted in better emotional well-being, compared to the 23 percent of caregivers who didn't have access to these benefits.

Having this flexibility was critical as my mother's care became more complicated. She had to take the medicine at a certain time, but she couldn't take it on her own. Plus, she only had a part-time aide, and so I had to scramble for help. It was exhausting. And in the end, she got the placebo

version of the trial drug. After all that, the treatment hadn't done anything, and there was not much else they could do but wish us luck and send us on our way.

Despite the initial engagement, and our interest, we were never contacted again about opportunities to participate in a clinical trial. Things continue to get worse. Soon the boy above the fridge was joined by a new hallucination: ICE. I would get frantic, late night calls that a black ICE van was circling the block around her apartment, and she would beg me to help her. They were coming to deport her, she said. I tried to tell her they couldn't take her away, she was a naturalized citizen.

Finally, her aide found her wandering in the street one morning. She was no longer safe. She needed 24-hour care, and I had to place her in a nursing home. It was the hardest thing I ever had to do in my life.

So now, after living through a pandemic, in which every floor of her nursing home was infected with COVID-19, and I had no physical contact with her, after a year in which my mother further declined, she is now non-verbal and can no longer feed herself. And every day I wait for the call that says she is passing.

I am asking your committee to think of her, me, and so many others like us who journey through this disease. So here is what I am respectfully asking on her behalf: Improve

equity and diagnosis and detection of Alzheimer's to expand treatment and care options for families; improve equity in Alzheimer's clinical trials to deepen our understanding of the disease in high-risk communities; establish a paid family and medical leave policy to help families navigate work and medical care; support a national Alzheimer's prevention goal to give hope to families.

Without the committee's action and society's commitment to brain health equity, Alzheimer's will be the last chapter in the lives of more and more Americans. It is time to change the way this story ends. Thank you.

[The prepared statement of Ms. Latty follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Ms. Latty. I hope you realize how powerful your testimony has been, and that, even though we kept you waiting all day, that none of that time that passed really diminished the power of your testimony, and the story of your mother, and you, as her daughter, is the story of so many Americans in our country. And I look forward to the day where the policies that you articulated that are needed are actually put into place by the Congress, because it would just serve the American people so well, as they struggle. These are 24-hour struggles on a daily basis in people's lives.

I had the, I think, the privilege to take care of my parents, and it was a huge responsibility, and I was working, and everyone else in my family was working, as well.

But there were so many things that you brought up that others have, that I didn't have to carry the burden of. These are huge burdens.

And this is by no means -- I think some people think of these services as handouts. I say go walk in your shoes for 24 hours. So thank you for walking in your shoes into our lives today at the committee.

And now I would like to recognize Ms. Kala Booth. As I said earlier, she is a Huntington's disease patient and a caregiver.

We are prepared to hear your five minutes of testimony.

Thank you for your extraordinary patience.

STATEMENT OF KALA BOOTH

*Ms. Booth. Thank you. Good evening, and thank you for the opportunity to share my family's story, and the story of so many HD families. My name is Kala Booth. I am 34. I am the fourth known generation in my family to have Huntington's disease, but only the second to be officially diagnosed. I am a patient, I am a caregiver, and, more importantly, I am a voice. Today I am a voice for the HD families who do not have one.

Over the years I have taught myself to emotionally disconnect. This allowed me to be able to separate the Huntington's disease from the person. Twice I have watched a broken system turn a devastating situation into an almost unbearable one.

Huntington's disease is a rare, inherited disease that causes degeneration of the brain. It affects each patient differently. The symptoms are different. The progression time is different. But what is not different is it is fatal, and there is no cure. Unlike other neurological diseases, symptoms of HD typically develop in the prime of a person's life, their forties. These years are typically a person's highest earning income years, the middle of raising families, or planning for retirement. However, HD disrupts all of that and physically, emotionally, and financially drains families.

In the late 1990s, early 2000s, when I should have been creating memories with my papaw, I was emotionally disconnecting from him. HD had turned this previously gentle man into someone who beat my mamaw black and blue, someone we always needed to keep a phone nearby, in case we needed to call 911.

Before HD, my papaw was a man who stepped in as a father figure for my dad, a man who drove across country to wherever we were stationed. A broken system would send my papaw to Central State Mental Hospital, a broken system that didn't have the ability or facilities to care for someone with HD, because he could be a danger to himself and the staff. A broken system ended with my papaw passing away, and my mom spending five years in court, battling to settle those bills.

Fast forward to 2015, the third generation, a second path, and another interaction with a broken system. My mom, Marsha, is what you would describe as a ray of sunshine, the type of person to never say a harsh word. My mom decided, when my papaw was diagnosed with HD, that she didn't want to be tested. She wanted to live her life to the fullest. And when it was God's time, He had a plan. My mom had hope, hoped she didn't have the disease, hoped there would be a cure. But honestly, she didn't want to be a burden, and she sure didn't want to have to take an MRI.

But man, if we had only known how valuable those results

would have been. November 2015, my mom's HD started manifesting as paranoia. The less she slept, the worse it got. Eventually she ended up in a psychiatric ward, receiving treatment for what doctors thought was schizophrenia. Thirty days it took to get her home. Thirty days we drove to Louisville to see her for one hour. Thirty days I watched my dad's heart break each time we had to leave her.

They didn't understand she was experiencing the progression of HD. Over the next few years, her health slowly declined. She went from being a top real estate agent in the county to needing help calculating figures. She was no longer able to drive. She is losing control of her swallowing, and she has mentally declined to childlike behaviors. So my dad and I always make sure to be nearby.

November 2019, we applied for her Social Security disability income. It was declined. We appealed. It was declined. We hired a lawyer and, in March of 2021 a broken system finally awarded her SSDI and Medicare coverage.

A fourth generation, and new approach. In 2018 I chose a more hands-on approach. I wanted to have all the facts and all the options. There was a fear of medical insurance finding out. There was a fear of life insurance finding out. So after I got all my affairs in line, I was able to do genetic testing off the record. The results came back. I

had HD.

I was tired, and living in fear. And after the battles my family had faced, I decided it was time to help make a change. I now have an amazing team of doctors and nurses on the record. I participate in clinical trials, and I help with advisory boards. And I am here to help fix a broken system.

I urge Congress to take the following steps to help patients and families living with Huntington's disease.

Pass the Huntington's Disease Parity Act this year. The HD Parity Act eliminates the Social Security Disability Insurance and Medicare wait periods. As you can see from my family's story, HD families often spend years securing a disability determination, then are forced to wait another six months to receive SSDI cash payments. And two years for medical care coverage is unacceptable. This policy must be changed.

Expand the focus of the NNCSS to include Huntington's disease, and require the FDA and NIH to work with companies that are researching HD cures to design trials that recognize the uniqueness of HD -- that the disease onset and progression is different from any other diseases. The HD community needs more research and cures as possible.

Thank you.

[The prepared statement of Ms. Booth follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Ms. Booth, for your important testimony. And again, on behalf of all of the members of the subcommittee, we apologize for keeping you waiting all day and into the evening. But you enriched our hearing with your testimony, and we very much appreciate it.

We now have -- we have completed the testimony of our witnesses on the second panel, and will move to member questions, and I will recognize myself for five minutes to ask questions.

To Dr. Andrews, as a researcher on the front lines of ALS, what do you need from Congress and the FDA to continue to innovate on clinical trial design?

*Dr. Andrews. I think it is very important to urge FDA to use its existing regulatory authority, and abide by the 2019 FDA guidance when reviewing clinical trial results in the context of the disease that they are reviewing for.

It is important to note that something like ALS, that has a zero percent chance of survival, if something shows a clinical benefit in retaining function, and slowing disease progression, and extending survival, yet is safe and well tolerated, the traditional framework that we typically -- that is typically used by the FDA doesn't work for a fatal, degenerative disease like ALS. In doing so, this can spur innovation and interest of other pharmaceutical companies to come in the space.

When we get stuck in these types of situations, it actually drives people away from that disease, and we lose that interest. So I think, in that way, the two bills we talked about, and urging some regulatory flexibility, and abiding by the FDA guidance that was finalized in 2019 can help that process along for clinical trials.

*Ms. Eshoo. There is something that kept coming up that the witness from the -- Dr. Cavazzoni kept mentioning, and that was biomarkers. And it seems to me that the FDA kind of stood on that, "Well, we have to have biomarkers, we have had biomarkers and other,'' you know, drug development, and all of that. It seems to me that the needle is stuck there.

And can you cast some light on this, because I pointed out in a comment, after what was stated, that it was -- there seemed to be a real irony when there are results, even though they are limited, but they are desperately needed, and we don't move in that direction, but again, back to the biomarkers. Can you enlighten us on this?

*Dr. Andrews. Yes --

*Ms. Eshoo. Please.

*Dr. Andrews. -- thank you for that question. It is a very good one. And it is important to understand. It is true that, in ALS, we don't fully understand the biology. And if we did, we could cure it today.

*Ms. Eshoo. Exactly.

*Dr. Andrews. However, when we are talking about biomarkers, that is not what a patient feels or functions. We have to understand that biomarkers will develop if we continue to do clinical trials and collect serum, spinal fluid, urinary samples, and understand the biology. So that is why continuing Federal funding for ALS research is critical, in parallel to helping gain access to experimental therapies for those living with the disease.

We can do both. You know, it is such --

*Ms. Eshoo. This sounds like the European model to me.

*Dr. Andrews. So --

*Ms. Eshoo. In a way.

*Dr. Andrews. This is --

*Ms. Eshoo. Is it?

*Dr. Andrews. -- part of the reason why the ACT for ALS Act can help in this situation. It is difficult for us, as Americans, to see potential therapies get faster review and approvals because regulatory review processes abide by different legislations. This could help harmonize us globally, and keep us leaders of developing, innovative therapies for these types of conditions.

*Ms. Eshoo. Thank you very much.

To Dr. Esham, how can we get more companies to participate in expanded access?

*Dr. Esham. Thank you, Chairwoman, for the question.

In terms of expanded access, generally speaking, you know, each clinical development program and each company do have unique and multiple factors they have to evaluate, including the ethical and resource capacities to stand up programs that include establishing rationale and criteria about how to make decisions about which should be granted, and on which basis they would be denied.

There are other factors, such as the questions around the ability -- the capacity to scale up supply, as well as thinking through any impact on clinical trial enrollment. So it -- there is not a one-size-fits-all relating to each clinical development program, or each company, as to how they approach expanded access. And the goal, the primary goal remains to get medicines approved, so that they are available to all patients.

I will note just quickly -- I don't want to cut time, but the requirement for companies to provide information on expanded access that was passed in Cures, there may be something to think through there, to make sure that more people are aware about how to find expanded access programs. So that is something maybe we can think through, and work with you all on.

*Ms. Eshoo. Thank you very much. My time has -- I have exceeded my time.

The chair now is pleased to recognize our wonderful

ranking member of the subcommittee, Mr. Guthrie, for your five minutes.

*Mr. Guthrie. Thank you, Madam Chair. Thanks to everybody for being here.

And Kala, I know that, when we talked earlier this week, I was talking about how important it is that patients and advocates come before Congress. It is vitally important. I think people get the impression that we are up here, more walled off. And, as from the testimony of the Wallachs and Abrevayas, it moves us, and it really does -- hopefully, will inspire most of us to act.

In the most important meeting I have had in 12 years here, I can tell you the -- and we have, what, 8 or 10 a day? And the one that I could point to as my most moving was a 9 or 10 year old. Her name was Shelby Enzer. I will say her name, her mom was Kay Enzer, the dad was Mitch, and her brother was Tanner. And she came here as a 9 or 10-year-old with ALS, and she said, "My father cannot hug me anymore, but I am here because I want to make sure no other little girl goes through what I am going through.'' And God rest his soul, a wonderful, wonderful man, and just a great family. And it -- I have always been an advocate for it, because they showed up.

I didn't have personal experience with ALS. Unfortunately, a lot of us have personal experience with at

least one of the ones we are talking about today. And Alzheimer's is one that I have in my family.

So it is all important, and thanks for being here, and sharing your stories, and making a tremendous effort to be -- whether you are on Zoom, or whether you came here today, the tremendous effort to be here. It is important. I am glad you are here.

So, Kala, when we talked earlier this week you mentioned your past involvement with a hopeful clinical trial for HD, and shared some exciting news of that this week. Your mother had her first appointment for a clinical trial. Can you describe the significance for you, personally, of having the opportunity to participate in a clinical trial, and now your mother?

And can you share with us some of the changes you would like to see happen to better reflect the needs of the HD patient community?

[Pause.]

*Mr. Guthrie. Kala, you may be on mute, if you are --

*Ms. Eshoo. Yes, you have to unmute.

*Ms. Booth. Can you hear me?

*Mr. Guthrie. We hear you now --

*Ms. Eshoo. Yes.

*Mr. Guthrie. -- yes.

*Ms. Booth. Being part of the clinical trial gave me

purpose. It helped me find my path. I think God wants me to help others in joining the -- put that into action. Knowing that I have HD brings a lot of challenges, and I had to make a lot of tough decisions before most people my age. However, enrolling in a clinical trial helped me see that I can help a lot of people with HD, and those at risk. Families are hoping for treatments to delay the disease, or even cure HD.

Clinical trials give me hope. The clinical trial I was in had so much positive talk to be a breakthrough treatment to help me, my family, and so many other families. The trial didn't work out, but now my mother is enrolled in her first clinical trial.

Once HD does damage to your brain, it can't be fixed. So the sooner you get treatment or a cure is better.

As far as what can be done, being part of the trial, and working with my local center of excellence, I have learned that the FDA has been a good partner with the HD community and its researchers. However, I would like the FDA to think about ways it can work with the communities to recognize the difference that exists from patient to patient, so that we aren't missing out on treatments that could help HD patients.

*Mr. Guthrie. Thank you. My friend, Adam Kinzinger, a member of this committee, is working on -- with Social Security that you talked about. And it sounds like your family had a difficult time getting your mom's disability

application approved, and that it felt like the system was uninformed, or didn't understand HD. How did that impact the experience with your family?

*Ms. Booth. So the disability process was very difficult and frustrating. It took 16 months to finally get my mom's application approved. She was denied two times, and it wasn't until we hired a lawyer that she was finally approved.

Luckily, because we involved a lawyer, the judge backdated her eligibility to receive her SSDI and Medicare right away. However, I know, from other HD families who cannot afford a lawyer, it takes much longer to get approved, and then the waiting periods still apply. Many individuals and families, including mine, try to support the HD patient, so that they can work as long as they can, and try to prolong progression, maintain income, and health insurance through their employer. So by the time that they have applied for a disability, they really need it. Making them wait years to get through the process, and even longer wait times, is unacceptable.

HD is devastating physically, emotionally, and financially. Not receiving the SSDI payments or access to the Medicare immediately is an added hardship that HD families should not have to endure. That is why I am asking Congress to pass the HD Parity Act. HD families need your

help.

Most people have not heard of Huntington's, and even those who have don't really understand it. That was our experience with going through the SSDI process. While we learned that HD is on the Social Security Administrative Compassion Care List, it did not seem that anyone understood HD, or applied compassion to my mom's case. For HD patients, their limitations may not be obvious to someone who is physically disabled. The first symptom that many HD patients experience are cognitive and behavioral. Uninformed staff and judges deny the application, because they don't understand the way HD impacts a person.

For people like my mom, who do not want to get tested to confirm they have HD, actually makes the disability process even more challenging. Disability staff and judges need to be better educated about how HD -- to ensure patients get their disability termination quickly.

I would recommend requiring the SSA to consult with HD Center of Excellence. The providers and staff at the Center of Excellence are true experts. However, even if it only takes six months for an HD patient to get through the SSDI process, the existing wait time still delays the Medicare coverage for two years, and cash payments for five more.

*Mr. Guthrie. Thanks, Kala. I think I have run out of time to ask questions, but -- and thanks for answering that.

I know that Representative Kinzinger appreciates your answer, and I will yield back.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the chairman of the full committee, Mr. Pallone, for your five minutes of questions.

*The Chairman. Thank you, Chairwoman Eshoo, and let me really thank everybody for testifying today. As the chairwoman said, this was really incredibly informative.

I mean, we have heard from some of you, you know, in the last few months, but the testimony today really makes a difference in our understanding, I think, of where we need to go.

So I just wanted to mention, obviously, there was a lot of -- from patients that find -- there has been a lot of information from patients that finding access to a clinical trial can be extremely difficult, based on age cut-offs, cut-offs based on disease progression, and other factors. And the FDA has even spoken about the tension in designing trials so more people can participate, while understanding the clinical benefit.

In the FDA's guidance for developers of ALS treatments, the agency advised that more patients could participate in clinical trials if developers broadened the criteria, allowing for one group to be considered for a primary analysis, and a broader group to be used for a secondary and

supportive analysis.

So I wanted to ask three of you, starting with Dr. Esham, to your knowledge, Dr. Esham, how has industry responded to this, guys? Is greater guidance from the agency needed in this space?

*Dr. Esham. Thank you, Chairman Pallone. I don't know that I can answer that question with specificity, but I will say, in general, when you think about guidance, I know that the 2019 was welcome, as it was -- had been some time since that -- any guidance had been updated.

And in an area like this, in such a serious and life-threatening disease, it is important to keep an iterative process that includes engagement between the regulators, the patients, the medical community, and the biopharmaceutical industry, to make sure that the guidance is keeping pace with the needs and understanding of science, generally speaking.

I also just quickly want to point out -- I don't want to take up all of your time, but as to the question of inclusion and exclusion criteria, I think there is, in addition to what you are raising in the space, there is a larger conversation really looking about how we think through inclusion and exclusion criteria, based on what we have learned during the pandemic. And I know a lot of our member companies are really re-examining how we should be thinking through that to ensure that there is not bias.

And then, in terms of trial design, if we brought in that, how can we make sure -- how can we use all the modern computational tools at our disposal in today's time and in tomorrow's, only to increase -- to really improve how we are able to analyze data across sub-populations or, particularly in diseases with heterogeneity and outcomes.

So there is a lot of interesting work going on, and we are certainly ready to advance all of those concepts.

*The Chairman. Well, thank you. I want to get to Mr. Wallach and Dr. Andrews, as well. Let me ask Mr. Wallach.

I know your organization has done a lot of work to track available clinical trials and their exclusion criteria. How would you assess how developers are doing in implementing that portion of the guidance, and how could they do better?

*Mr. Wallach. I think it is fair to say --

*Ms. Abrevaya. I think it is fair to say --

*Mr. Wallach. -- that developers have taken that guidance to heart.

*Ms. Abrevaya. -- that developers have taken that guidance to heart.

*Mr. Wallach. But it takes two to tango.

*Ms. Abrevaya. But it takes two to tango.

*Mr. Wallach. And FDA has not taken the guidance to heart.

*Ms. Abrevaya. And FDA has not taken the guidance to

heart.

*Mr. Wallach. So what I mean by that --

*Ms. Abrevaya. So what I mean by that --

*Mr. Wallach. For the NurOwn trial --

*Ms. Abrevaya. For the NurOwn trial --

*Mr. Wallach. They had more patients --

*Ms. Abrevaya. They had more patients.

*Mr. Wallach. -- further --

*Ms. Abrevaya. Oh, the NurOwn trial had more patients that were further progressed in the disease than any trial had before.

*Mr. Wallach. And that was used against us.

*Ms. Abrevaya. And that was used against the company when they sought approval.

*Mr. Wallach. We need to have both players -- and implement the guidance.

*Ms. Abrevaya. So we need both players to be true to the guidance, and implement.

*The Chairman. All right. Thank you. Let me just -- I know this time is almost gone, but Dr. Andrews, can you offer any insight into how trials could be better designed to allow for more inclusion?

*Dr. Andrews. Yes. Our field -- actually, in collaboration with the FDA, have designed something called the platform trials, actually, which Dr. Cudkowicz leads.

And it has broadened the inclusion exclusion criteria to allow more patients, or people with -- living with ALS to participate in clinical trials.

The issue is -- I think it is true that manufacturers are trying their best to broaden the inclusion exclusion criteria. Many of the drugs that we are testing are trying to slow down disease progression. And so often, previously, the inclusion exclusion was very stringent to get very early onset or early-stage disease, which meant that more than half of people living with ALS were not eligible, and that is what led to this kind of lack of access. And there was no other ways to gain access to experimental therapies, no expanded access, no open label extensions.

And so that, I think, is changing across the field. But, as Brian and Sandra mentioned, it will take -- in order to design clinical trials that are more inclusive, we will have to employ technology. So there are ways to stratify populations, and identify subsets of populations that you think might respond better to that particular drug, but we need the help of our regulatory colleagues to understand how to employ that in a clinical trial.

Second, if there is a pre-specified sub-population that would be your analysis, your primary analysis, they have to accept that, so that we can include a more broader population.

And so there are ways to design it, but we have -- we need kind of to work together with our regulatory colleagues to ensure that that would be acceptable to them.

*The Chairman. All right. Thank you so much. Thank you.

Thank you, Madam Chair.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentleman from Virginia, Mr. Griffith, for your five minutes of questions.

*Mr. Griffith. Thank you, Madam Chair. I appreciate it.

Dr. Andrews, I am going to start with you. In regard to ALS, you know, it is supposed to be relatively rare -- not as rare as Huntington's, but relatively rare. And yet I know four or five people that have had it. Is there any research that you are aware of that is going on with, like, a geographic outbreak?

I mean, at one point in time, in about a four or five-year period, I had three people that I knew who had, in their earlier part of their life, had all lived within probably a half mile of each other. Is there any work going on on geographic outbreaks of ALS?

*Dr. Andrews. That is a very good question. Historically, in ALS we have identified populations and specific geographic areas like Guam, for example, that had

high rates of ALS, due to environmental exposures. And over the course of study, there have been many epidemiological studies looking at environmental exposures and toxins that may increase your risk of ALS.

It is, actually, from the ALS Association's standpoint, one of the priorities in studying risk factors, and that is why the funding to the CDC National ALS Registry is critically important to identify those clusters.

One of the most important risk factors we have already identified and acknowledged is the service in -- by our veterans. Military service increases your risk by two times the general population.

*Mr. Griffith. Yes, do -- is the thought today in -- and I know this may not be directly your area, but is the thought today that it is -- it actually causes it, or may just be a trigger for the onset of ALS?

*Dr. Andrews. I think that is still yet to be determined. But there are definitely exposures that have been identified as associations.

*Mr. Griffith. And I am sorry, I was talking about exposures to some kind of an environmental --

*Dr. Andrews. Yes, those -- there have been associations that have been identified, and warrant further research, and that could be helped by the ALS Registry.

*Mr. Griffith. Now I want to completely switch gears,

and go to Huntington's. But I am going to ask you a question, because it is something I think we need to be looking at, and I don't know the answer, and you probably don't, either. But I am going to ask the question, because it gives me a good platform.

You said, in regard to ALS, if we knew what caused it, we could cure it today -- we could cure it today if we knew -- understood what caused it. With Huntington's, we know what causes it, and yet we are still not able to cure it. You got any comment on that?

*Dr. Andrews. Well, I can only speak to ALS as my specialty --

*Mr. Griffith. Yes, ma'am.

*Dr. Andrews. -- but, you know, as I said, there are -- ALS also has -- in the minority of patients -- has a genetic contributor to their disease. And there are technologies that can be targeted and deployed for genetic diseases.

*Mr. Griffith. Thank you. I am going to go to Ms. Booth. Ms. Booth, if you would unmute, I could ask you a couple of questions.

[Pause.]

*Mr. Griffith. If you are with me, what I want to know is, the clinical trial that you were involved in, and now the clinical trial that your mother is involved in, are those for drugs to treat Huntington's, or --

*Ms. Booth. They --

*Mr. Griffith. Yes?

*Ms. Booth. Can you hear me?

*Mr. Griffith. Go ahead. Yes, ma'am.

*Ms. Booth. So let's slow the progression now. There is nothing to treat right now. But it is to slow the progression of it now.

*Mr. Griffith. So you don't know of any kind of genetic work that they are doing to maybe figure out how to solve the problem?

And I bring it up because one of the big successes NIH has had recently is with sickle cell, where they were able to completely change the genetic makeup in the blood cells. Now, I know Huntington's would be more complicated, but I was just wondering if you knew of any work that involved dealing with changing the gene that causes this, particularly if we can catch it before its onset.

*Ms. Booth. I am not familiar, but that doesn't mean it is not the right answer.

*Mr. Griffith. No, no, I understand, I appreciate that. I asked -- I have been interested in Huntington's for some time, because there was a family, now there are two families that I am aware of in my community that have Huntington's, one of whom, the first family, was -- I was good friends with the children of that family, and knew the mother who died of

Huntington's.

This was all -- of course, a lot of this happened before they had testing available. Your mother, who didn't want to be tested, but always had a happy attitude until recently, with the onset, I am just curious if any of the data that you have seen working with the association indicates that there is a higher rate of suicide for those people who do get tested and realize they have the disease.

*Ms. Booth. I think there is a higher rate of suicide, because there just isn't -- there is no cure, and there is -- like, the only two medicines out there are to treat chorea. Other than that, it is, you know, other drugs treating the symptoms.

So they get to the point of, like, the hopelessness, or it gets to the point that, you know, the brain is, like, causing, you know, mental illnesses and stuff.

*Mr. Griffith. Yes, ma'am.

*Ms. Booth. So there is a lot higher rate of suicide in HD patients.

*Mr. Griffith. And my time is up, but I am going to ask the chair, just so I can tell you, just for a couple more seconds, as a result of your testimony I have instructed my staff to sign me on to H.R. 2050, which is one of the requests that you made. And thank you for your testimony.

*Ms. Booth. Thank you so much.

*Ms. Eshoo. The gentleman yields back. The chair is now pleased to recognize the gentlewoman from California, Ms. Matsui, for your five minutes of questions.

*Ms. Matsui. Thank you very much, Madam Chair, and I want to thank you very much for convening this hearing. This has been one of the most wonderful, enlightening hearings that we have had in the Health Subcommittee.

And I want to also thank the patients, the caregivers, and advocates, because your testimony here really does help us, as we look to make sure that we are doing everything we can to address the diseases that are involved in what you are having to do to deal with every single day.

And for me, I just really feel that each one of us could be involved in our own families, and we know that. And to hear even the testimony of the caregivers, that is something that all of us, in whatever way, know that it could be something that we will be involved in at some time.

So let me just say this. I would like to follow up on an earlier discussion from the first panel on the use of patient experience data in drug development and applications to FDA.

Dr. Esham, what steps do developers take to collect patient experience data, and how is that communicated to FDA?

*Dr. Esham. Thank you for that question. So, you know, as you are very aware of, as part of PDUFA VI and 21st

Century Cures, there was a tremendous effort to really set the framework to establish a systematic approach to incorporating patient experience data into the entirety of drug development and drug review.

I would say we are making tremendous strides in collecting patient experience data that are very -- on a much more regular basis, provided as part of the application. That could be in terms of primary endpoints, secondary endpoints, as well as things like patient preference studies, which provide context about how to think through benefit and risk. So all of that is advancing, but we want to advance it a lot more. And so, again, there is still work to be done.

Another requirement was for when patient perspective data is submitted as part of the package, and reviewed, the FDA is required to report on that fact. We would like to see that reporting to provide more context so that we can gain insights, not just that it was reviewed, but what impact did it have on the review decision-making. And that, itself, will help more of us understand how to develop stronger -- collect the strongest possible patient perspective data to continue to inform regulatory decision-making.

We also want to advance the ability to put this information in the label, so that it can be communicated to the patients, their families, and their physicians. So these are things that I think we still want to improve, as we move

forward and continue to develop more --

*Ms. Matsui. Could I also ask you that --

*Dr. Esham. Yes?

*Ms. Matsui. Now, FDA has indicated it may consider patient experience data differently for different disease types. Do developers similarly use patient experience data differently?

*Dr. Esham. I am sorry, I am not sure I completely understand the question.

*Ms. Matsui. Well, the FDA has indicated they will consider patient experience data differently for different disease types. How about the developers, do they use patient experience data differently, also?

*Dr. Esham. I don't know that it is different, it probably depends on the -- you know, again, if you are trying to support, say, a benefit risk decision, whereas some of the patients on this panel have talked about the value of being able to improve quality of life, your daily functions, patient perspective data would be very -- is very important, and it will focus on that question.

So I don't know that it is different, as much as there might be different questions that are trying to be asked, if that makes sense.

*Ms. Matsui. Okay. Let me change here.

Mr. Wallach, thank you for your testimony. In your

testimony you discuss your view that FDA could do more to consider patient experience in conducting a risk benefit analysis. So what is the best way for FDA to approach this challenge, given that experience -- inputs from patients may vary?

*Mr. Wallach. The best way for FDA --

*Ms. Abrevaya. The best way for FDA to --

*Mr. Wallach. Approach.

*Ms. Abrevaya. -- approach patient-reported outcomes --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. -- to proactively work with drug sponsors to incorporate --

*Mr. Wallach. New technologies.

*Ms. Abrevaya. -- new technologies that allow us, as patients --

*Mr. Wallach. To provide information --

*Ms. Abrevaya. -- to provide information that was never available before.

*Mr. Wallach. And that information --

*Ms. Abrevaya. And that information, as Dr. Andrews mentioned, can help us understand if a therapy --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. -- is helping us retain function, which is everything.

*Mr. Wallach. So being more forward-leaning --

*Ms. Abrevaya. So being more forward-leaning is the key here.

*Ms. Matsui. Well, thank you so very much, because I believe very much that the patient experiences is really very, very important as we look ahead to how we may address these issues in a more holistic way.

So, Madam Chair, I yield back. Thank you very much.

*Ms. Eshoo. The gentlewoman yields back. The chair is pleased to -- always be pleased to recognize the gentleman from Florida -- from Georgia, Mr. Carter, our resident pharmacist.

*Mr. Carter. Thank you, Madam Chair.

And let me begin by thanking you for being here, and thanking those who joined us on -- virtually, for your testimony. Let me just say that your presence here, that your presence virtually, and that your advocacy brings a human touch to ALS, to Huntington's, and that is extremely important. I echo the remarks of my colleague, Representative Guthrie, when I say that it is important for you to be here. It is important for us to understand.

As Chairwoman Eshoo said, I am a pharmacist, and I practiced pharmacy for over 32 years, and I will tell you that, through research and development, I have witnessed nothing short of miracles in the way of medicine. And it has been extremely important that I continue to encourage

companies and the United States Government, the Federal Government, to invest in research and development. Because, as I say, I have witnessed nothing short of miracles in the years that I practiced pharmacy. And it is extremely important, and it gives hope. It gives hope to all of us, and it gives it to you. So please understand that I am -- I support you.

Dr. Esham, I want to ask you. In your written testimony you suggest that investment in therapies and cures for chronic diseases have been in decline, or is low, relative to the rate of disease in patients. You even report that funding for Alzheimer's therapy was 16 times lower than oncology funding, despite estimates that the disease will impact 13.8 million Americans by 2050, and cost $1 trillion, annually.

My colleagues across the aisle have worked to pass legislation in H.R. 3 that would upend investment in new cures, due to revenue reductions from their proposed international pricing index. The Council on Economic Advisers estimates that legislation would stop over 100 new drugs from coming to market over the next decade.

Obviously, we all want to decrease prescription prices, no one more than I do, having been on the other side of the aisle, on the prescription aisle. This has been one of my primary focuses since I have been a Member of Congress. But

I just don't think that this is the way -- this is the approach we should be using.

And I wanted to ask you, Dr. Esham, are you concerned that such revenue reductions as I described here would further limit new research into therapies and cures for ALS and other neurological diseases?

*Dr. Esham. Yes, I think that is a fair statement. I mean, as you point out, and as my testimony points out, this is a -- it is a difficult endeavor, fraught with failure, and heavily reliant on venture and public market investment.

We are committed to working with Congress on policies to help remove or alleviate fiscal burdens to patients, but sweeping policies that create more uncertainties relating to the ability to get returns on investment for the less than one percent of the programs that actually make it to the market will unquestionably have a negative effect on future investment, and impact future innovation.

*Mr. Carter. And as you say, these are risky investments that these companies are making. We all understand that.

Listen, I have seen drugs get all the way up to the final stage of development, and then have to be pulled. And they -- and companies understand this. Look, I am not trying to give the pharmaceutical manufacturers a free pass here. They need to do a better job with prescription pricing. But

at the same time, they do play an important role, extremely important role in research and development in what they invest in that. And that is something that we have to continue to encourage.

Dr. Esham, you also discussed in your testimony that the first-ever disease-modifying ALS drug moved beyond phase three clinical trials for the first time ever this year. But, unfortunately, 87 programs were suspended over the past decade. What do you attribute this long-term lack of success to?

And what are the biggest barriers that we face in getting drugs to treat neurological diseases approved?

*Dr. Esham. Sure, and that is a complex answer, but I will try to just hit the highlights.

Again, you know, Alzheimer's is a -- it is a complex disease. And, as I pointed out, there are, you know, over two dozen, you know, genes that we have identified now associated with Alzheimer's.

I will say a lot of the failures in Alzheimer's that is different than the generality across diseases, they have a lot of failures in phase one, where you are really doing, like, early safety studies. They are pretty much on par with phase -- during phase two, in terms of transitioning from phase two and initial efficacy and safety studies to phase three. But phase three has where -- has been the real brick

wall. And so this is a really exciting time to see the first disease-modifying program get approved.

And again, when you think about what accelerated approval did for cancer, it is a great -- it will allow us to gain further understandings, and we do think it will have a positive impact on investment.

But there are other pathways, as I mentioned in my testimony, that are in the pipeline that we also have -- hold great promise.

*Mr. Carter. Right, right. But research and development is extremely important. And again, I want to thank you for being here, and I want to thank those who are participating virtually for being here. You bring a face, you bring a voice to what otherwise is just a disease. But it is real, and it impacts real people. And we must commit to continuing research and development to come up with cures.

Thank you, Madam Chair, and I yield back.

*Ms. Eshoo. The gentleman yields back, and I want to express not only my condolences to you, Congressman Carter, but that of all of the members of our subcommittee. Congressman Guthrie leaned over and just told me that you lost your father. So you have our sympathies. Those of us that have lost a parent, or both parents, know how difficult it is, how very, very hard it is. Really, our lives are never the same again when we lose those that shaped us,

brought us into this world and shaped us. So we hold you in our prayers and our thoughts. You are a good friend to all of us, and we really value you here. So God bless.

The chair would now like to recognize the gentlewoman from Florida, Ms. Castor, for your five minutes of questions.

*Ms. Castor. Well, thank you, Madam Chair, and thank you to the witnesses. I, too, have learned a lot over the course of this very long day, but especially from Yvonne and Kala and Sandra and Brian. You all are speaking on behalf of millions of other Americans who don't have the ability to be here and appear before a congressional committee. So thank you for doing that, and thank you for sharing your very personal challenges.

Ms. Esham, Dr. Esham, you know, I have read now a former FDA commissioner said, when it comes to expanded access, that often times it is the unwillingness of drug manufacturers to provide, or sometimes it is just the plain ability of the drug company to provide a certain drug.

You also cited, in an answer to a question, that it is difficult sometimes to scale up supply. You also said there are impacts on clinical trials. Does BIO have an official position on how manufacturers should approach expanded access, or is it just too divergent across diseases?

*Dr. Esham. We do have principles on expanded access that largely reflect the points to consider that I outlined

in my earlier answer to the question.

And further, we do have a firm position that the -- for our member companies to comply with the Cures statute, to make sure that, if they have an expanded access, they provide the information on their website about whether they have a program and, if they do, ensure that there is information that helps patients navigate contacting and working with the expanded access programs that are available.

*Ms. Castor. Okay. Ms. Latty, you provided a very important voice on behalf of caregivers, so thank you for that. You have a number of recommendations for the Congress: improve equity in diagnosis, improve equity in clinical trials.

But we have got to do so much more for caregivers. I note that you also recommend paid medical and family leave. The United States of America is the only country, developed country, that does not provide family medical leave. And it would just seem, in this day and age, in this country, that we could support our families across America with paid family leave.

There -- I note -- I looked it up, while we were waiting -- just over the course of COVID-19, about 865,000 women have left the workforce, 260,000 men. So, boy, the burden is -- we know it falls on women, they are doing double duty.

But can you talk a little bit about what caregivers need

today, and your view of family and medical leave?

*Ms. Latty. I feel like caregivers need a lot of support. When you have a family member who comes down with any one of these horrible diseases, your whole life is completely unended. And often times, like for someone like me, I mean, like, this sort of -- I had a sandwich generation, where I had kids in high school, then I have my mother, I am still working full-time. It was just really out of control.

So you really need some sort of a paid leave, you need bosses who will understand that you have to take time off sometimes, because things are going on at home with your mother or your father. You need doctors who are a lot more supportive.

I mean, it is the one thing I learned from my mother's journey, is, especially with low-income people, with people of color, the doctors are not focused on something as simple as kindness.

But in many cases, caregiving does fall on daughters. And often times we are caught between our children and our parents. And so having a policy of paid family medical leave could make a huge difference, and take off so much pressure, and it also means that a lot of women wouldn't have to leave their jobs.

I mean, if I didn't have the job I had, I would have had

to stop working, because -- especially when my mother was first diagnosed, it was just complete chaos with the hallucinations, and I didn't know what was going on. And there were just tons and tons of appointments.

So I really -- I kind of like just beg you to please, please help us, help women like me, help men like me, parents like me, daughters and sons like me.

*Ms. Castor. Thank you. Thank you very much. I yield back my time.

*Ms. Eshoo. The gentlewoman yields back. It is a pleasure to recognize the gentleman from Utah, Mr. Curtis, for your five minutes of questions.

*Mr. Curtis. Thank you, Madam Chair. Before I jump into my questions, a couple of observations.

One is how delightful it is to be part of this discussion, in which it would be hard to find a sliver of difference between Republicans and Democrats on the committee. And it is nice to be here, united with all of you together tonight.

The second observation is the clear difference between our two panels. And it felt a little bit like a lot of resistance in our first panel, and a lot of empathy and sympathy here, in our second panel. And I would kind of like to explore that just a little bit.

And maybe, Dr. Andrews, if I could start with you, like

everybody else here tonight, I have a close friend that is dealing with ALS. I -- we talk about geography. I have a particular neighborhood that seems to be plagued with ALS.

And this dear friend has had access to a number of treatments because of his resources to be able to travel around the world and obtain these. And he frequently discusses how patients are unable to receive many treatments under right-to-try and expanded care, and we have talked about that a lot tonight.

But I kind of want to talk to you about barriers, and maybe why, some of the root causes of this. I mean, clearly, we understand the complexity, right, of these clinical trials, and the needs of these pharmaceutical companies. But you mentioned price, right, as one barrier. And I think we have heard that message loud and clear.

I am curious. In your opinion, is there another barrier that we have not really talked about, which is what I would call the reputation?

So if somebody enrolls in a clinical trial that is maybe further along in the disease, or has other complicating issues, and the likelihood of a good outcome is less, could there be a perceived, like, resistance to that, because it is going to reflect somehow on the reputation of their drug?

And I am wondering if there is anything Congress could do to help the pharmaceutical companies with transparency,

where that data wouldn't necessarily need to be public. Or is there another way that we can help them with that perhaps barrier that they might have?

And is that a barrier, in your mind?

*Dr. Andrews. I think it is important to note that some of the barriers we have already talked about heavily, mainly with resources, both financially and drug supply from the manufacturer's standpoint, both expanded access mechanism and right-to-try are contingent on manufacturers being able to provide the product. That is the first thing.

The second, in the instance of expanded access, which is used more often than right-to-try -- and I know right-to-try was meant to make things a little bit easier to access, but there are still hurdles like provision of drug, monitoring of safety at a clinical site, so there might be additional regulations within a hospital system or an academic center that requires additional paperwork through the ethics committees or the institutional review boards.

Resources at the clinical site also are essential to be able to provide expanded access. Often these are not funded. If a sponsor is able to provide the investigational product, often the clinical sites don't get any reimbursement for use of facilities, or use of any kind of --

*Mr. Curtis. Can I jump in on you?

*Dr. Andrews. Yes --

*Mr. Curtis. Only simply because it is such a limited time. So what I am hearing from you is still resources is the --

*Dr. Andrews. Yes.

*Mr. Curtis. -- single biggest barrier --

*Dr. Andrews. Very much so.

*Mr. Curtis. -- that you are seeing.

I am aware that there was some experimentation with long-distance or remote trials. Is that something that we should expand further, and how big a deal is that?

*Dr. Andrews. I think this is a very big deal, especially for ALS and other, actually, neurodegenerative diseases. As you heard from the advocate with Alzheimer's disease, access to clinical trial sites are very difficult. And so anything that we can do -- and I will name some specific issues with it, because it has been highlighted during the COVID pandemic, when I have had to conduct clinical trials through the pandemic, with limited access to our clinical trial sites because of fear of transmission of the virus.

One is trying to ship investigational product to patients. Sometimes that can be difficult across state lines, if you are trying to treat people in a large catchment area.

The second is issues about regulations of principal

investigators or physicians who are doing the clinical trial, trying to assess safety and monitor the patients, and the patients may be across state lines. So trying to make it so that it is easier for patients to participate in clinical trials in that way.

So shipping of drugs across state line, practice of medicine, and research.

*Mr. Curtis. Okay, as so quickly it happens, I am out of time, Madam Chairman. I thank you. I yield.

And thank you very much for the answers.

*Ms. Eshoo. The gentleman yields back. The chair is delighted to recognize the gentlewoman -- and that she is -- from Delaware, Ms. Blunt Rochester.

*Ms. Blunt Rochester. Thank you so much, Madam Chairwoman.

First, I want to say thank you all for your patience. It has been a very harrowing day here, but it was really important for me to be present, and I am so grateful. I am so thankful for you taking the time, and sharing.

And I think it was Kala, and then I heard Mr. Carter, and I heard Ms. Castor use the word "voice,'' that you are the voice of millions. And, as I sat here, I recalled losing my father-in-law to ALS, and we didn't even know for months what was wrong with him. And it just really reminds me how important our work, in a bipartisan way, is to the American

people, and to the families.

And so I also want to thank Ms. Latty, as she talked about her mother. I thought about my mother, and how it was her mother who had dementia, and her mother's mother, who would wander. And just the challenges, watching my great-grandmother. And I just -- I wanted to stay, I had a few questions, of which I can submit in writing, but I wanted you to know how grateful we are for you standing up, and speaking up, and speaking out, and I thank my colleagues, as well, for their leadership on these issues.

I -- Ms. Latty, you mentioned in your testimony -- you mentioned the bill that I led, the ENACT Act, which is really about expanding clinical trials for Alzheimer's. And I was hoping that maybe you could talk a little bit about how we can -- first of all, were there provisions in my bill that would have helped your situation?

And how can we strengthen engagement with communities of colors, and -- color, and working families to make sure that there is an interest in research and clinical trials?

That is my question to you, and I will start there.

*Ms. Latty. I don't think there has been much of an emphasis or energy in reaching out to Latino and Black communities, explaining that there is help. There is not a lot of compassion. It is a lot of -- lots of people in waiting rooms. You get moved in to a doctor who doesn't care

about you, gives you the diagnosis, and then your relatives take care of you until you die. I mean, that is what I saw.

And I think that it is really, really important to start thinking about how you communicate with these communities, what kind of messaging, what kind of pamphlets, what kind of websites, hand-outs, posters to make the community feel safe, and make them feel that there is hope. Because that was the one thing that I saw, that just no one seemed to care.

I mean, the only reason I got as far with my mom is because, you know, thanks to my mom, I got a college education, and I learned to advocate for myself and for her. But if I was not me, we never would have gotten into a clinical trial. We never would have changed neurologists. And God only knows what would have happened to my mom. You know, the journey is already really bad. It would have been worse.

*Ms. Blunt Rochester. Thank you.

*Ms. Latty. So I think messaging, messaging, messaging, and reaching out to the community is really important.

*Ms. Blunt Rochester. Thank you. And also, I know the barrier, as well, in terms of where the research is done, and making sure that we break down some of those barriers.

I also -- when Kala was speaking about Social Security disability -- I think today or yesterday was intern day. And I recalled I was the intern for our current senator in 1988,

and I went on to be a case worker, working on Social Security disability. And this is maybe a commercial for families, that our offices have caseworkers that can help navigate Social Security disability. That was one of my jobs. And especially for those who might not have the resources, that is a commercial.

And then, Dr. Andrews, I was also curious about your mentioning COVID, and the impact of COVID. And specifically, the two things that you talked about, whether those issues are -- in terms of state -- going across state lines, maybe we can follow up with you afterwards on whether those are state or Federal problems that are barriers. We would love to follow up with you afterwards.

I want to end by saying thank you so much, Madam Chairwoman, again, for your leadership, and making this not just about data, which is important. Science is important, but people are more important.

So thank you all, thank you very much, and I yield back.

*Ms. Eshoo. The gentlewoman yields back. Thank you for your beautiful remarks.

It is, again, a pleasure to recognize the gentleman from Pennsylvania, Dr. Joyce.

*Mr. Joyce. Thank you, Madam Chair. Thank you for this important hearing. We are approaching 10 hours that you have been here, and yet your impact, by coming here to the

people's house, is so important.

Mr. Wallach, I will never forget your words. I want to present a question to you, and you have presented challenges to us today. If you had to choose between the problems that we have addressed, would you look for more innovation, more accessibility, more flexibility, or more urgency in response?

[Pause.]

*Ms. Eshoo. Can you turn your microphone on? We don't want to miss one word.

*Ms. Abrevaya. Yes, the flip answer is that he would choose all of the above. But --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. But the most important thing to patients alive today --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. -- that they have access to promising therapies that are moving through the clinical trial -- today.

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. Oh, we look at the European Union --

*Mr. Wallach. And the conditional approval pathway.

*Ms. Abrevaya. -- and the conditional approval pathway.

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. And that we have a conditional approval pathway for animals in the U.S., but not for human beings.

*Mr. Wallach. It begs the question --

*Ms. Abrevaya. It begs the question --

*Mr. Wallach. -- of why we aren't doing everything we can --

*Ms. Abrevaya. -- why we aren't doing everything we can --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. -- to get therapies to people who are dying, and to have the science --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. Oh, to have the chance to live to see a possible cure.

*Mr. Joyce. Thank you for an honest and courageous answer. I am going to take that answer and pivot to Dr. Esham.

Dr. Esham, the clinical trials process can be long and incredibly resource intensive, and especially with the delays that COVID has caused for patients in the clinical trial process, which really exacerbated what Mr. Wallach just stated. And he is nodding in affirmation of that.

Are there actions that can be taken, or policies enacted to redesign clinical trials to account for the interruptions that have been caused by the COVID pandemic?

*Dr. Esham. Thank you for that question.

We, at the very onset of the pandemic, we worked with --

very quickly with our member companies to continually engage with the FDA to make sure that we understood how to document any disruptions or any missing data that may have occurred, due to revamping operations during the outset of the pandemic.

We currently are operating under the assumption that the FDA did put out guidance very quickly, and put out iterative guidance over the course of the spring and early summer. So we were operating under the assumption that that issue should not result in undue delays in programs. But that is an area that we are monitoring very closely.

*Mr. Joyce. Thank you for addressing what Mr. Wallach put forth. These delays are so important for these people. Time is of the essence. Time is limited.

Do you feel, Dr. Esham, that there should be other steps, such as allowing increased patient access, which Mr. Wallach just talked about, for investigational drugs outside of the clinical trials, and that we should be mindful of -- to account for the disruptions that have occurred in this pandemic?

*Dr. Esham. Again, thank you for that question. And again, we are supportive of the fact that there is the -- that expanded access is a tool in the toolbox that can -- where companies can provide -- can make a decision to provide that medicine, investigational medicines, via expanded

access.

But I do -- if I may, I just want to underscore some of the other revelations that I think are also important in this -- in the entirety of this conversation, and that is, again, some of the things we learned under the pandemic, and that is how can we bring the trials, the actual clinical trials themselves, closer to the patients, and in a way that reduces burdens on patients?

So, in addition to expanded access, I just want to make sure we are also focusing on improvements to the ability to enroll people in clinical trials, based on tools and designs, such as decentralized trials, telehealth, all of those types of things, in addition to the expanded access conversation.

*Mr. Joyce. I think that innovation is so important. My time has expired, but again, thank you, Madam Chair, for this incredibly important hearing today, and thank you for being here at this late hour. I yield.

*Ms. Eshoo. The gentleman yields back, and now the chair is pleased to recognize one of the new members to our committee, and a marvelous addition to the Health Subcommittee, the gentlewoman from Minnesota, Ms. Craig, for your five minutes of questions.

*Ms. Craig. Well, thank you so much, Chairwoman Eshoo. And let me just say that I am new to this committee. This is my second term in Congress. And this has been one of the

most impactful subcommittee hearings, committee hearings, that I have been a part of, as a member.

You know, I know, because we meet with our constituents regularly who have devastating neurodegenerative diseases like ALS, Alzheimer's, or Huntington's, that this is just a devastating set of disease states. While I know there have been huge advancements in our research and understanding of brain illnesses, I know there are limited treatment options, and absolutely no cures.

I will add that I know the impacts on families, as my own family watched my grandfather suffer with Alzheimer's for a number of years before his passing.

You know, in Minnesota we are so fortunate to have world-class health care systems and research centers like the ALS Clinic in Hennepin Healthcare. It is the first certified Center of Excellence in the State of Minnesota, and it provides ALS patients with the most cutting-edge treatments that are only available in a research setting. So your words today are incredibly important to me.

Still, my constituents suffering from those illnesses and their caregivers do not have the luxury of time. And if there is anything that you have made clear to Congress here today, it is that point.

I want to say to our witnesses, and to those in our communities watching tonight, your message has been received

by this Congress. I am so proud of the bipartisan nature of our work on these issues on this particular subcommittee. Congress, NIH, FDA, and industry, we must work together to make sure that we are doing everything we can to improve patient access to lifesaving treatments and, ultimately, to cures.

I want to start with Mr. Wallach. Just your presence here is so commended. Thank you for your patience. Thanks for sharing your story, and advocating not just for yourself, but for everyone who can't be here.

I would like to ask you, from your perspective, what do you think FDA should do better to incorporate the patient experience and perspective into their decision-making?

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. It took FDA 6 years to write the 2019 guidance that we talked about today. So, at some point in time, you begin to wonder whether the words are matched by reality.

*Mr. Wallach. So one thing -- FDA can do --

*Ms. Abrevaya. So one thing I think that FDA can do --

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. -- to dramatically expand the emphasis, and in including patients in their processes, and finding ways to actually expedite therapies in terminal diseases -- when the risk paradigm is obvious to all.

*Ms. Craig. Mr. Wallach, I promise you that my team and I will make sure the FDA sees the answer that you just gave me to that question. You and all of our witnesses here tonight have really touched every single one of us. And for the pieces of legislation that you have all asked us to review, I commit that my team and I will do just that.

I just want to close this out, Ms. Latty, by giving you the last word here. We know that health disparities exist in this country, especially for Black and Brown Americans. Can you talk a little bit more about your experience, and how you believe -- what we should focus on to begin to close this gap?

*Ms. Latty. Wow, that is such an important question. I think that there has to be more money put in an effort for Black and Brown people to participate in clinical trials. I think there needs to be more outreach. I think we need better medical care. I think we need paid family leave. I think there needs to be more visibility, which is one of the reasons why I am so committed to doing this. I think people need to see my community, both my Black and Brown community, and see us as people that are going through this disease in far higher rates than any other group. I think there needs to be more compassion and understanding, but I think that the government needs to focus on finding a cure for Alzheimer's disease. And I think, by helping Black and Brown Americans,

you help all Americans.

*Ms. Craig. Ms. Latty, thank you so much.

And Chairwoman Eshoo, thank you for your graciousness in giving me a few extra seconds. With that, I yield back.

*Ms. Eshoo. Any time. And now I think we have exhausted the -- I have recognized all the members of the subcommittee, and I can recognize the gentlewoman from Illinois, Ms. Schakowsky, who is waiving on to our subcommittee.

You are recognized for your five minutes of questions.

*Ms. Schakowsky. Thank you so much, Madam Chair. So I have been here -- I am in my twenty-second year in the Congress, unlike Angie Craig, a little bit longer. But I also feel that this is one of the most impactful hearings I have heard, and I think it could be a real game-changer, the kind of intensity I hear from my colleagues.

I want to say to people who are listening -- you said that there are hundreds, if not thousands of people who are being -- who are advocates, and who are -- have ALS -- that I remember the AIDS epidemic, and it -- AIDS was a death sentence, also. And actually, it was a population of people -- mostly gay men, at first -- that weren't especially popular, necessarily. And yet the community organized, and was out there, and fighting, and noisy, and organized groups of supporters and partners to make things happen. And I

think that you probably recruited a lot of partners, not just ALS, but all the diseases that we were talking about today. I think there is a lot more intensity of interest.

I learned, actually, from Mr. Wallach that MS diagnosis -- that ALS is diagnosed as much as MS. Is that true?

*Mr. Wallach. That is --

*Ms. Abrevaya. That is true.

*Ms. Schakowsky. So my guess is, also, that the more money -- that there is more money that goes into MS. People live longer, et cetera. And it -- you know, we may disagree now across the aisle, but I feel like it is because, in some ways, Big Pharma gets to pick winners and losers, and maybe the fact that ALS patients don't live as long, it may not be as useful.

However, I think the government and taxpayers, American taxpayers, put a lot of money into the research and development, and trials, and all that kind of thing. And hopefully, as Members of Congress, we are going to be able to direct more resources, and more availability, and accessibility, which, as you pointed out, Mr. Wallach, I think is one of the most important things -- accessibility, especially -- as a result of what you have said today.

And I want to thank all of the witnesses, really. This has been quite a remarkable hearing. The testimony has been so incredibly moving. And I mean that in the most active

sense, moving. And I think that we have a lot of assignments that are out there now of what -- the kinds of things that we can do, and that we need to do, and that you will find, in a short period of time, I think, that you have really made a difference.

I would actually just like to see if you have any final words, Mr. Wallach, that you want to leave with us, or if any of the other witnesses have a brief -- I have got a little over a minute left and, you know, just a few closing comments -- I would be welcome -- I would welcome them.

*Mr. Wallach. Thank the committee --

*Ms. Abrevaya. I really wanted to thank the committee for this hearing, for seeing all of us --

*Ms. Eshoo. Put your microphone on, so we can hear it all.

*Ms. Schakowsky. And put it close to her.

*Ms. Abrevaya. Oh, maybe I need to be closer.

For hearing all of us, for seeing all of us, and for acting on all the requests we have made, as advocates, today.

The committee, this Congress, has the chance to end diseases that were once hopeless.

*Mr. Wallach. [Inaudible.]

*Ms. Abrevaya. We hope you have the courage to see this through.

*Mr. Wallach. And we look forward --

*Ms. Abrevaya. And we look forward --

*Mr. Wallach. -- to celebrating --

*Ms. Abrevaya. -- to celebrating the end of these diseases with you.

*Ms. Schakowsky. Well, thank you. I am so proud to have you as constituents of mine. I am honored. And I thank all of the witnesses. And, you know, we are not powerless here to make a difference, and to partner with you to make them in the right direction.

So thank you, Madam Chair. I really appreciate it.

*Ms. Eshoo. The gentlewoman yields back. And last, but certainly not least, we will close out the questions of members today with the ranking member of our full committee, Mrs. McMorris Rodgers.

I am glad you could make it back.

*Mrs. Rodgers. Well, I heard just the tail end of that, and I just want to say thank you for being here. Thank you for your compelling advocacy, for sharing your story.

I was talking with Jan earlier -- well, she has talked to me a couple of times, actually, about this hearing, and just what a long day this has been, and the fact that you made the trip, you traveled here. That is not easy, to be here and to share your story. And it is powerful, it is powerful.

And we have all been impacted by you, and others that

have received this devastating diagnosis with ALS. And I have worked in years past, but I think this is really an opportunity for us to come together, and to do what you just stated, to really make a difference. And you know -- and I am reminded again of just the tremendous research that is underway right now, and we are on the verge of amazing breakthroughs, and we need to say yes, and embrace what it -- all that can mean to so many individuals. So you represent not just yourself, but you are representing a whole bunch of other people. So thank you so much.

I wanted to ask Ms. Booth, too. You know, your family has faced a lot of challenges, getting your grandfather the best care possible, and particularly at the end, giving -- given the symptoms he was experiencing. How common is it for HD patients to receive services in long-term care facilities, and how challenging is it for HD families to locate a facility that can provide the appropriate care?

*Ms. Booth. Yes, so there are actually only 10 long-term care facilities that specialize in Huntington's disease in the United States. So that is a very few. And then, you know, people are driving hundreds of miles. So it creates, you know, a lot of frustration. So definitely, we need to work on expanding that, or also helping, you know, with the -- like, helping people be able to stay home and have care at home as long as possible.

*Mrs. Rodgers. Well, again, I appreciate you spending the day with us, and sharing your story, and advocating for so many others. I think this has been an important hearing for all of us, and I look forward to working together to continue to advance solutions that are going to improve so many lives.

Thank you, Madam Chair. With that I will yield back.

*Ms. Eshoo. The gentlewoman yields back.

Well, I think that parting is -- this sweet company, I think it is somewhat difficult, because we -- there is a lot of emotional tie between those of us that are seated here, and you that gave the testimony today.

I am proud to have brought this hearing forward. It was highly intentional, because it was, really, desperately needed. But you have been the stars. You have been the stars. Every member here, every member, has hung on every word that you have uttered.

To Ms. Abrevaya, what a wife you are. What a partner you are. What a mother you are. What a citizen you are. You have -- you are a source of pride to all of us, and it is really humbling to have you come into our committee room, and that you would repeat the words of your beautiful husband to the people of our country, and their representatives.

To you, Dr. Andrews, to all of the witnesses that were part of the second panel, thank you. You have been so

instructive to us. You have taken the very real stories of your day-to-day lives, really expressing to us what -- you know, the very burdens of humanity in your personal stories, taking care of your mother, taking care of your husband, and then speaking for all of the advocates and the patients across the country.

Members know that we speak for, what, some 750,000 people. You are speaking for millions in our country. And although this has been an extraordinarily long, drawn out, frustrating day, and I know that you are exhausted, but none of it has been a waste of time. None of it, not one minute. Even the waiting is worth it, and we are going to show you that it was worth it by taking up the legislation, working together to pass it. I think that there is a rock-solid commitment, here at the committee, to advance this legislation that Dr. Andrews and others, including the advocates, have said. You have been instructive to us. You have said, "This is what we need. It is the right ingredients. It is the right recipe to address what is what is ailing us.''

My hope is, more than anything else, is that hope comes out of this. And I have confidence that it will. I have been around here for some time. I can feel it. It is in the air. It is here. And I think that our best work is right at hand. So, as you travel home, know that you have made an

enormous, enormous, extraordinary difference. Know that, all right?

Bravo to you, Mr. Wallach. Thank you, thank you, thank you.

Okay, I would like to -- absolutely.

[Applause.]

*Ms. Eshoo. All right, to our wonderful ranking member, I have a request. It is a request for unanimous consent to enter into the record a -- really, a wonderful list of documents from national organizations, and -- I can read them all.

*Mr. Guthrie. No objection.

*Ms. Eshoo. Okay, no objection. Thank you very much, so ordered. All of these documents will be entered into the record.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. We thank all of those that submitted these documents. We value what is contained in them.

And, pursuant to committee rules, members have 10 days to submit additional questions for the record to our witnesses. And witnesses, we ask that you please respond as promptly to any questions that you receive.

And at this time, the subcommittee is adjourned.

God bless all of you. Thank you. Colleagues, you have been spectacular today. It is really an honor to serve with you. And all of our collective thanks, from committee members to the staff on both sides of the aisle. You have worked hard. You have put in many, many hours, and we appreciate it. Thank you, one and all.

The subcommittee is adjourned.

[Whereupon, at 8:49 p.m., the subcommittee was adjourned.]