



Presidential Commission  
*for the Study of Bioethical Issues*

## **TRANSCRIPT**

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Alzheimer's Association

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DR. WAGNER: This session also we have four presenters to hear from, this time focusing on the potential of neuroscience research in clinical applications. Thank the four of you for joining us. As before I'll introduce you one at a time as you make your remarks, and we will hold the Q and A until all four have presented.

So our first is Harry Johns. He is President and CEO of the Alzheimer's Association, an organization focused on Alzheimer's advocacy, research, and support. Mr. Johns was appointed by the Secretary of Health and Human Services in 2011 to serve as a member of the Advisory Council on Alzheimer's Research, Care, and Services. He also serves as CEO of the Alzheimer's Impact Movement and on the Executive Committee of Research America. Previously he was one of the four members of the executive team of the American Cancer Society. Welcome. Good to have you with us.

MR. JOHNS: Thank you. Happy to be here. Appreciate the opportunity. In our everyday work at the Alzheimer's Association we come in contact with the Alzheimer's community broadly. We fund more research in the world than anyone else in the nonprofit sector and certainly reach more people who are dealing with the disease every day than anyone else in the United States. So we touch this, they touch us each and every day. I really have been asked to talk about why this research is so important, and that's easy for me to do given the circumstances.

And just for the record I'll mention some things that I think probably all of you know, but Alzheimer's disease is progressive, degenerative, and fatal, one aspect that many people often don't realize. Everyone who has it will either die with it or of it at this point. The neurons die, the brain shrinks, functions are progressively lost, until, as you said, Madam Chairman, this morning more generally, we lose who we are. It's just devastating to individuals

and families and caregivers, and as you heard a little bit from Howard this morning, the numbers are just absolutely staggering. We estimate that more than 5 million people have the disease today, and that is, as we're now beginning to talk a little bit differently about these things, people who are symptomatic, as you already heard Howard touch on and I'll touch on a little bit myself.

There are 15 million unpaid caregivers to go with that, and in this particular disease that's critical because they are so impacted themselves. And those costs, \$214 billion in costs today, that will go up by the middle of the century to \$1.2 trillion in a single year. Those are not inflated costs. Those are in today's dollars. Right now CDC ranks it as the sixth leading cause of death, but a recent study from Rush in Chicago indicates, as we've believed for a long time, that more likely it is closer to the third leading cause of death. They estimate it at about 500,000 deaths a year from Alzheimer's, right behind cancer and heart disease. So as it relates to your inquiry today I think it's especially important to recognize once again that there is no way to stop it, no way to prevent it, and no way even to slow it down.

And regrettably these numbers are going to grow as the population ages. I'm a good representative of the boomer generation sitting here with you today. I won't identify anybody else around the room but I know I qualify. So those numbers are going to go from 5 million people who have it today to as many as 16 million, but probably somewhere between 13 and 16 million by the middle of the century, driving all those other numbers, and by then with the numbers of caregivers it will go to probably 50 to 60 million people directly affected by the disease, if we don't change its course. So the problem as we see it at the Alzheimer's Association isn't a question of whether or not the research should be done, not even really the question of how, though I'll certainly talk about those kind of things, most fundamentally, that is, but that it has to be done for all those people who are already dealing with it today and will be in the future.

In fact, just to reference the budgetary fiscal impact beyond the human impact that is I think so clear already, those kinds of budgetary issues have significant implications for other decisions of our federal and state governments that have huge societal consequences ethically as well. So the biggest problem today is that research investments in Alzheimer's pales compared to what we pay for the care and support, which are the costs that I just described to you, and that we are seriously underinvested in Alzheimer's compared to other major diseases. In fact, in Alzheimer's, for every \$26,000 we spend on care, we spend \$100 on research at the federal level. So the sustained and significant investments we've made in other diseases have made a huge difference. All of the major chronic diseases, cancer where I worked for many, many years, as you've heard, heart disease, HIV/AIDS, are down in terms of mortality; Alzheimer's is up 60 percent over the past few years.

And there's a clear correlation between the billions that we spend at the federal level on that research and the outcomes in those cases compared to the few hundred million that are spent annually on Alzheimer's. Francis Collins himself said in testifying to a senate panel on appropriations for HHS recently, and I'll quote here: "We are not at the moment limited by ideas. We are not limited by scientific opportunities. We are not limited by talent. We are unfortunately limited by resources to be able to move forward at the pace that it could take," answering a question from a senator on Alzheimer's research.

So, in fact, we also know, as I think you heard Howard say this morning, we can cut the impact in half if we can simply change the course of the disease for five years. To slow or stop progression or onset for just five years will have that effect. So the ambitious goal of the National Alzheimer's Plan is to have a prevention and effective treatment by 2025. So I will pose to you that the biggest ethical question at this point is that we have to fund the research at

adequate levels to achieve that goal for the tens of millions of people who are affected today and in the future. But let me be clear. There are other issues you've already heard about today that, as we hopefully do that significantly increased research, we've got to take care to do. All that research, of course, must be done with great care.

You talked a little bit this morning about diminished capacity. For many years in our area that was perhaps the biggest consideration. And we ourselves at the Alzheimer's Association recommend that people do have an ethically valid kind of an approach. Do not participate in studies decided only by a surrogate if they themselves cannot benefit from the treatment that they would receive and if it were only to benefit others. But I can tell you one thing is that the community surrounding Alzheimer's wants to participate.

We have a panel that is a group of individuals who are at early stage of diagnosis who advise us on how to work with people in their circumstances, and they are eager to participate in research, seeing it as a contribution, if not to themselves, despite what I just said, to their families and to others. Of course, the diminishment in capacity in and of itself is in play in that very conversation, but there is a clear sense in those groups of wanting to make those things happen.

Now, as you heard Howard mention this morning, there is a newer issue, which is that of research with those who are asymptomatic, pre-symptomatic, as the science has unfolded. In that particular case, of course, what I would describe as the risk-to-certainty ratio, that is, the risk of participating in the trial compared to the certainty of ultimately having the disease, is really driven more so by the denominator, by the certainty, because it is highly variable if you assume treatments are equal. So that is a need then for people to be very, very well informed as they consider their potential participation in such prevention trials, even though, again, people

are highly motivated. In fact, I would say to you folks that in this community it isn't a matter of just wanting to have this research advance and more swiftly, it's essentially demand from the community who has already been affected and who see the potential for the effect on themselves and society.

It is, if not in the streets, as you saw the HIV/AIDS movement at one point, it is at least not only as sincere but passionate about what needs to be done.

And so then I just want to touch very quickly with the limited seconds literally I have left on two other topics, which are the care to be taken in stigma and discrimination that you've already touched on, because those are very real. Under the new system, insurability should not be such an issue. Employability certainly still could be when we are talking about getting much, much earlier diagnosis in a person's life. And then finally, again also touched on already today but important to note, I believe, sharing of scientific data is a critically important factor at the research level. We are working ourselves on making that happen and believe it certainly should. Thank you.

DR. WAGNER: Terrific. Thank you very much. Next we hear from Sohini Chowdhury who is the Senior Vice-President for Research and Partnerships at the Michael J. Fox Foundation for Parkinson's Research. In her role there she oversees a team that focuses on first increasing engagement and developing partnerships with various stakeholders; secondly, developing and implementing strategies to improve recruitment for Parkinson's disease research trials; and third, managing the Parkinson's Progression Markers Initiative [PPMI], which is a \$60 million clinical biomarker study. Previously Ms. Chowdhury was the Senior Community Manager for the World Economic Forum's Technology Pioneers Program, and we are fortunate to have her join us today. Welcome.

MS. CHOWDHURY: Thank you. Good afternoon. Thank you so much for the opportunity to speak today. The ethical issues impacting neurological drug development in clinical research have been an important and growing conversation at the Michael J. Fox Foundation for Parkinson's Research since our inception in 2000. As with every critical challenge we encounter on our urgent mission to speed a cure for Parkinson's, our point of view is shaped by ongoing dialogue both formal and informal with thousands of patients and families.

First let me offer a brief background on our foundation and our model. Our exclusive mission of funding research, \$450 million to date, is somewhat unusual for a nonprofit disease research group. What's more, we go far beyond passive check writing to proactively partner with stakeholders at every stage of drug development, and we have built a team of scientists and neurologists and business strategists to prioritize the science closest or most critical to patient impact. We fund projects at institutions across the globe, but we also conceptualize, plan, and sponsor research of our own.

Across all of our research investments the highest ethical stakes have typically tracked to our highest risk and potentially highest reward work: Research conducted in patient and control volunteers to overcome the seemingly intractable fieldwide challenges that stand between us and a cure. Whether Parkinson's patients choose to enroll in traditional clinical trials, spit in a tube, or contribute data online or through emerging technologies like Smartphone apps and wearable devices, their participation in research is invaluable. New avenues of inquiry are opened when those living with the disease are given a seat at the table to help shape research goals and outcomes. By definition this means we must create channels for patients' voices to be heard in the establishment and evolution of ethical frameworks around research modalities. At

the Fox Foundation we are in the business of educating patients on these issues and building platforms to mobilize their involvement in the drug development process.

Our work has required us to develop a point of view on the bioethics of two situations in particular: First, encouraging patients to undergo genetic testing when no specific treatment is available; and second, calling for patients to release private and sometimes sensitive medical data at potential personal privacy risk. I'll talk about each of these in turn.

Genetic research in Parkinson's is currently experiencing a period of major growth and it's revitalizing every aspect of PD drug development. As is the case with many diseases with genetic risk factors, there is not yet a rational treatment regime specifically for PD patients who carry a Parkinson's implicated genetic mutation, nor is there any preventive course of action for those who discover that may be at increased risk for Parkinson's. By choosing to be genotyped, people with Parkinson's can help speed a cure that will ultimately improve treatments for all patients, not just those with relatively rare genetic forms of PD. Before I go here further I'll state something that's probably obvious but I do think it's worth restating. Genetics of different brain diseases can't be generalized. When it comes to Parkinson's disease, genetic status is not destiny. Most cases of Parkinson's are believed to be brought on by a combination of environmental exposures and genetic susceptibilities, with purely genetic cases estimated to account for no more than five to ten percent of all patients. Some people with genetic mutations linked to PD never go on to develop the disease.

In 2010 we launched PPMI, which is referenced, to validate Parkinson's biomarkers for earlier diagnosis and faster testing of disease-modifying drugs. Earlier this year PPMI expanded to include people at increased risk for Parkinson's disease due to known risk factors, one of which is a genetic mutation. The advent of direct-to-consumer genetic testing

modalities has sped up the debate over the relative merits and risks of critical masses of everyday citizens gaining possession of genetic health information, especially when results are provided without counseling or other resources to contextualize the information. Studies across disease indications have shown that individuals who choose to undergo testing and learn the results of their genetic status feel enlightened and satisfied. And especially in families with multiple cases of Parkinson's there can be a strong drive to objectively confirm or disconfirm the presence of a genetic risk factor. Still, no one correct answer exists.

We engage in regular discussions with our 25-member patient council, and we are privy to patients' and families' commentary at dozens of events across the country each year as well as in social media channels.

The individual decision to learn the genetic status varies widely based on countless personal circumstances, beliefs, and attitudes. Against this backdrop PPMI worked to determine the best course of action for the genetic cohort of the study. Some of the leaders were inclined to inform all participants, patients, and controls of the genetic studies. Others influenced perhaps by Huntington's disease and other neurological diseases felt that no Internal Review Board would actually allow patients to be told of their genetic status. Ultimately the committee made two decisions:

First, to share genetic status with Parkinson's patients screened, to contextualize the results to help them understand the rich potential contributions they might be in a position to make; and second, to give control volunteers, those who do not have Parkinson's, a choice to be informed, allowing them the option to participate in this study without the theoretical anxiety that could be provoked by learning of a genetic mutation that might never lead to the disease. In

all cases, whether one tests positive or negative for a genetic mutation, whether one is a Parkinson's patient or a control, genetic counseling is provided as part of the protocol.

When all is said and done, these decisions were based on core belief that patient feedback and information can be a catalyst to action, especially when couched with appropriate support. The story of Jessi Keavney bears this out. Jessi is a young mother who lives in Georgia. Her father has Parkinson's like his father before him, and she chose to be genetically tested and learned she had the LRRK2 mutation. This motivated her to actually enroll in PPMI. She wants to learn about the mutation and the disease, and she also understands that she's in a position to make an invaluable contribution to the search for a cure. As she wrote in a testimonial on our foundation's blog, her mutation has given her purpose.

Another ethical issue facing the global research community is the increasing call for patients to share personal data beyond the confines of the doctor's office, especially through online registries and new digital health tools. This really provides an unprecedented opportunity to expand the reach and the potential to gather research data from thousands of individuals. We are no longer talking about hundreds of people providing information but potentially thousands, tens of thousands, hundreds of thousands. And in a disease like Parkinson's, which is so variable across individuals, being able to get to those large numbers is invaluable for research.

That being said, we do recognize that the willingness of patients to undergo this has to be tied also with making sure it's done in an appropriate and ethical manner. And there's a lot of aspects that we have to think about as we consider this: Defining and sharing best practices for obtaining informed consent virtually, establishing a reasonable baseline for ensuring confidentiality and anonymity online, holding research sponsors accountable to protect the privacy of subjects engaging in virtual clinical trials via the Internet, and determining ethical

limitations conducting research via proxy. For example, understanding when it is or is not appropriate for a caregiver to complete an online survey for a patient who is willing but unable to participate on their own.

We actually have a few initiatives that are looking at this. One of them is Fox Trial Finder, which is an online, quote/unquote, like Match.com tool, that allows volunteers to input data to be matched to trials that are looking for individuals with their characteristics. And to demonstrate really I think the enthusiasm of the patient population to be involved in research, I can tell you that in the three years since Fox Trial Finder launched, we have over 32,000 people registered in the data base, and that is about 75 percent Parkinson's patients and 25 percent controls. I think it's important to recognize that when one talks about the disease community, one is not just talking about those affected directly by the disease, but also their family and their friends who wish to be part of the research endeavor.

I recognize that I'm running out of time, so I think I might just conclude by saying that while I cannot stand in for patients myself in stating these remarks, I hope I've been able to impart the great credit that our foundation gives them for their continuing enthusiasm, openness, and a sense of realism with which they come to research. Many understand that even if there is no direct benefit for them individually, their participation adds immense value to our scientific understanding. Moreso, they accept that there are risks to research engagement; there are trade-offs to hearing one's genetic status or for entering one's medical history into an online data base.

Our community by and large has chosen to recognize these potential risks and forge ahead. They know that the risk of stagnant research is far greater. As our founder, Michael J. Fox, has put it, "You are the answer you've been looking for." Thank you again for the opportunity to speak.

DR. WAGNER: An interesting example for us. Thank you very much. We'll hear next from Dr. Gregory Simon. He is an investigator at the Group Health Research Institute and Chair of the National Scientific Advisory Board of Depression and Bipolar Support Alliance. He's also a Research Professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington. Dr. Simon leads the Mental Health Research Network, a consortium of research centers associated with 11 large health systems across the United States, and he serves on the National Advisory Mental Health Council. We are pleased that you're here, Dr. Simon. Thank you.

DR. SIMON: Thank you very much. So the remarks I'll make today reflect my views alone but they certainly are colored by the various hats I wear, which are shown here and that you just described to us in that kind introduction.

I'd like to begin with my understanding of what I would say is the somewhat disappointing state of neuroscience research related to mental health conditions. At this point we attempt to define variations between individuals at various levels of organization ranging from genes, to cells, to neural circuits, to their psychological functions, to symptoms, to the categories we now call diagnoses. We are able to define each of those levels of organization fairly poorly and to measure them very inexactly, and our research is often limited to relatively unhelpful observation, like this particular genetic variation is moderately correlated with this particular type of symptom. What we hope will happen with the BRAIN Initiative is that this will be fundamentally transformed, that our ability to measure and more important to conceptualize individual differences at each of these different levels will become much sharper, that the picture will really come into focus, that we'll be able to crisply define variations at these different levels and line them up into clear causal chains. This would be a revolution. This will not, though, be

lock-step reductionism. We do not expect that we will say A always leads to B always leads to C, but having these causal chains in sequence will allow us to understand why it is, for instance, that some individual who shows a particular cellular abnormality does or does not develop some particular set of symptoms and whether the disconnect between those two levels of variation occurs at the level of neural circuits, at the level of their functioning, or farther upstream.

What we can be sure of, though, is that the picture will not neatly look like this. The categories that we now believe in, such as bipolar disorder or posttraumatic stress disorder or schizophrenia, will not line up into nice, clean lanes and these causal sequences will become clear in that way. We can be very certain we will see something that looks more like this, that those causal chains become intermingled, and that the categories that we now respect are shown to be nonsense. It's almost certain that the categories will be divided, categories will be combined, and that these causal chains will interdigitate with each other.

This new understanding I think will have some very important conceptual implications, and I list four of them here. One is it will become much clearer that all mental health conditions are developmental and that even conditions we believe do not have their onset into early adulthood probably have at least their precursors in utero, and some detectable differences may be present in early childhood long before we imagine that those conditions existed. That we will be able to identify specific vulnerabilities. Instead of general vulnerabilities, weak associations between genetic variations and liability to disease, we may really be able to identify person-level vulnerabilities that are quite powerful. That the categorical distinctions that we now recognize, distinctions between things which we think are different disorders and distinctions between what we think is disorder and what we think is normal existence, will certainly become blurred and we will see the opportunity for interventions to

become much more highly personalized, as we see in other areas of medicine where we're beginning to see highly targeted treatments to people with very specific subsets of what we used to think was a homogeneous condition. These developments I think will raise some important questions and was alluded to earlier this morning. The inexactness in our measurement and in our concepts spared us from addressing some difficult questions. Once we become much more exact, we might actually have to address some difficult questions. And some of the questions I think might be raised are raised by each of these developments. So we'll talk about those in turn.

If mental health conditions are truly developmental, we are going to have to think about how we balance downstream or what I would consider to be rehabilitative interventions, which are the interventions we have at our disposal now, for farther upstream or preemptive type interventions. For example, if we really wanted to reduce the population burden of bipolar disorder, would we favor early detention of upstream precursors of bipolar disorder which may well be present in preschool children, or would we direct our resources toward assertive community treatment, a well-proven intervention for people who are now homeless and severely disabled? I can tell you that in the National Advisory Mental Health Council at NIMH these kinds of discussions are very active right now: What is our obligation to those who are the most vulnerable and severely affected versus our obligation to the future in terms of the potential public health impact of upstream interventions? Second, if these specific vulnerabilities are really measurable, what kind of duty to protect does that create for us, especially for people who may be vulnerable to very specific insult? But we need to recognize our urge to protect often involves restriction of liberty or opportunity. For instance, if we really were able to detect people at very high risk for posttraumatic stress disorder after exposure to violence, should those individuals be barred from military service? If we really were, and relevant to the state of

Washington where I live now, if we really were able to pinpoint adolescents or even school-age children at risk for psychotic disorder, how would we differently regulate the use of marijuana for either medicinal or recreational purposes?

If categorical distinctions fade away, what will happen to many of our policies that are now based on categorical distinctions that actually are probably complete fictions? For instance, and just to use one example, the criteria for Social Security disability eligibility for depression require at least four symptoms to be present from the list created by the American Psychiatric Association out of practically thin air, and also requires marked restriction of activities or daily functioning. If we really understood what this animal depression is, or if we really understood the future animal which may bear some resemblance to what we now call depression, why would we choose a threshold of four symptoms? Why would we choose those particular symptoms? Or why would we even choose symptoms at all as the way of defining the presence, the severity, or the disability related to this condition? If we were able to define at multiple levels of organization what this animal is, what level of organization is relevant to this particular societal decision about eligibility for disability benefits?

And then finally, if interventions really did become highly personalized, how would we consider the benefits or the harms or burdens that are broadly distributed versus those which are very narrowly distributed? And just to illustrate, if we consider two different scenarios, if we were talking about preventing or preempting the development of schizophrenia, if we said, "If your child has a 5 percent risk of schizophrenia and for \$25,000 we could reduce that risk to the population background of one percent," or if we said, "Your child is going to get schizophrenia next month and for \$1 million we could keep that from happening," in a mathematical sense those two statements are equivalent. I think in an emotional and

psychological and maybe ethical sense they are not. The first one sounds like a question about a public health investment, and the second one sounds uncomfortably like extortion. And I think what we recognize, and we are starting to see this in other areas of medicine, is that these highly personalized and potentially dramatically effective treatments can sometimes in our current marketplace demand extortion-level price. The market recognizes that these decisions about benefits broadly distributed versus highly targeted are not necessarily fungible.

So hearkening back to what we heard this morning, we have to ask are any of these questions really new. And a lot of them are not. I think these are sort of your classic examples of autonomy beneficence tensions. They are about distributive justice or resource allocation. They are about collectivism very individualism when we begin to talk about things are widely distributed or narrowly targeted. There are, though, a few things about mental health conditions that I think are different. As was alluded to this morning, these conditions often affect people early in life, cause long-term disability, and are really among the leading causes of disablement that can often affect people even before their productive working years, the years they would marry and start families. The expression of mental health conditions is remarkably heterogeneous, both what we understand about how biology may be expressed across individuals or also how biology may be expressed within individuals across their lifespan. The heterogeneity is remarkable.

Mental health conditions still unfortunately carry much stigma and great burden of discrimination. I'll defer to Pat Corrigan who will talk about that in a few minutes. And also in the mental health area I think we see well-intentioned paternalism. As someone who is a former general internist, I can say that when I was an internist nobody thought they always knew what

was right for my patients, but once I treated people with mental health conditions, everyone seems to think they know what the right thing is. And I think there is a risk there.

I'll close with a story, actually, from a good friend of mine, Larry Fricks, who is a Georgian, who I used to work with at Depression Bipolar Support Alliance. Larry is one of the heroes in the effort to restore and respect the dignity of people who live with mental health conditions. Larry tells the story that when he was having his first severe manic episode and he was handcuffed in the back of a Georgia State Patrol car and was being taken to the hospital, the State Patrol officers kept taking the wrong exit and going around in circles over and over again, and Larry in the back kept trying to tell them which exit to take but they weren't listening. And to Larry the moral of the story is: "I may have been hallucinating, but I was not as lost as they were." The point being that if we would have serious discussions about what's right for people who live with mental health problems, there are some voices that we need to hear. Thanks.

DR. WAGNER: You opened up several issues that I want to come back to, particularly in this personalized predictive health area.

Pat Corrigan is next. Dr. Patrick Corrigan is Distinguished Professor of Psychology at the Illinois Institute of Technology, and he is the Principal Investigator of the Chicago Consortium for Stigma Research, the only national institute of mental health funded research center examining the stigma of mental illness. Dr. Corrigan has authored or edited 12 books and more than 300 papers and Editor of the American Journal of Psychiatric Rehabilitation. Previously Dr. Corrigan was Professor of Psychiatry and Executive Director of the Center for Psychiatric Rehab at the University of Chicago. We are pleased that you're here. Welcome.

DR. CORRIGAN: Thank you for having me. I want to pick up where Dr. Simon left off. For us an issue of medical ethics is a concern about stigma and the impact it has on the lives of people with mental illness. Since our center has been in business since 2001, research has exponentially grown. In 2001 about ten papers were published. Last year more than a thousand papers were published on mental illness, which puts us in an interesting position as a social scientist. It brings to mind the Dodo Bird effect. Some of you might know the Dodo Bird effect. It's from *Alice in Wonderland*.

In *Alice in Wonderland* the Dodo Bird hosted a race and at the end of the race concluded everybody has won and all must have prizes, which is the conundrum for behavioral scientists frequently shown in terms of psychotherapy. The original meta-analytic research in psychotherapy showed Freudian psychoanalysis did as well as cognitive behavior therapy, so practitioners are really stuck because we don't know what to do because everything seems to work. It's also a conundrum for social scientists because as social scientists we're really pretty much trying to show one thing works better than another. In this case everything seems to work. But it also is a problem for unintended consequences.

I think a wonderful example of unintended consequences and a metaphor for the work we do was shown by Jorge Bergoglio. When he became Pope Francis I he decided to name himself after Pope Francis because of his interest in social justice issues. In his inaugural mass he called for a reorienting of the Catholic Church back to the poor and the weak, which is surely a good idea, but he also said what we should do is focus on the least important. And what it does for an issue of social justice is it sort of suggests we should bestow upon the poor, or in our case upon people with mental illness, rather than empower them, and that more successful programs towards working with people with mental illness is a focus on empowerment. So a very mini

course on what is the stigma of disease. It falls in the same area as racism, sexism, ageism. It's a function of stereotypes, belief about the groups, prejudice, agreeing with the belief, and discrimination, which is what we care about the most, which is the behavioral impact of it. In terms of public stigma, one sobering set of research was actually done by Ben Druss, who is here at Emory. He looked at veterans' data, archival data from the Veteran's Administration, looking at primary care doctors dealing with veterans who showed symptoms needing referral for cardiac care, percutaneous transluminal coronary angioplasty. And the groups were organized into three: The first group of people who had no evident mental illness or substance abuse; the second group of people who from chart diagnosis or otherwise were known to have substance abuse problems; and the third group were those who had mental illness. And what he finds is everybody in the first group was referred to a cardiologist, 80 percent in the second group, and 40 percent in the third group, which makes this not only an issue of life and death but also the sobering idea that we are talking about primary care physicians here, not the naive public, as it were.

You see it in label avoidance. Label avoidance is a concern. The way the stigma of mental illness frequently is obtained is by seeing a mental health professional. I see you coming out of a psychiatrist's office; I know you're crazy. So one of the big ways to avoid the stigma is to avoid the label, and so research pretty consistently shows people with serious mental illness will avoid care seeking. This applies across diagnosis, so whether you have schizophrenia, depression, or a simple adjustment disorder, 45 percent of people won't seek out services. And of those who do seek out, 22 percent will drop out early. So there is a big incentive to avoid the stigma by avoiding treatment.

A similar issue is the whole evolution of the idea of resistance to adherence to compliance. Dr. Simon alluded to this, this sort of paternal thing of we know best and we should

assume that we should be making decisions for patients. This pretty much goes up as heinous crimes occur, in this case on the shooting in Connecticut.

What we're pretty clear on is that intervention should move from an idea of expecting people to adhere and to force them to comply, moving more to an idea of self-determination in terms of what kind of shared decision-making processes can we go into to help people make decisions that work for them. Our biggest focus, though, is not what is stigma but how to fix it, and so we wanted to look at some good examples of unintended consequences. Ways you would think would erase stigma don't really seem to work that way. One of them is the idea of mental illness is a brain disorder. 1990 to 2000 was the NIMH decade of the brain, and amongst other issues it was thought that by framing schizophrenia as a brain disorder we would blame people for their illness less, which is true. It leads to significant decrease in blaming for a disorder and also leads to an increase in the idea they are not going to get any better. Prognosis goes down. And the problem when you buy into the idea they are not going to get better, employers don't want to hire them, landlords don't want to rent to them, and primary care doctors provide a worse standard of care.

As I said, there's enough studies going around now that you can actually do meta-analyses. A colleague of mine did a meta-analysis on 16 population studies from all over the world. And what we were interested in is the degree to which the world has learned that mental illness is a brain disorder and its relationship to stigma. So what you find is -- schizophrenia is the red line, depression is the brown line -- across the world from 1990 to 2006 there is a clear increase in the degree to which the world understands schizophrenia is a genetic disorder, depression is a genetic disorder; similarly a clear increase in the degree to which the world realizes that schizophrenia and depression are brain disease. So maybe the good news is stigma

has gone down. And what you find is in this case stigma is the degree to which you would accept a person with mental illness as a coworker. One sobering issue is depression, because what I hear at conferences all the time is that the stigma of depression has been erased. That has actually not changed in 26 years. It's still pretty flat. And the other is the stigma of schizophrenia has gotten worse, that people are less likely to accept a coworker with schizophrenia. Similarly with a neighbor, no change in depression, much less likely to accept a coworker as a neighbor.

So what might be an effective way to deal with stigma? Lots of research has looked at the impact of education contrasting the myths and facts of mental illness versus contact, meeting people with mental illness and research that we've done. We've used my colleague, Bob Lundin, who has a schizoaffective disorder who shares the disorder and in his story challenges many of the stereotypes about mental illness.

So again, enough of these studies have been done to do a meta-analysis, and these are pretty important findings. We looked at 79 studies; 13 of them are randomized control trials. And we were interested in the overall impact of education in the blue and contact in the red.

We were interested in its impact on attitudes and on behavioral intentions. What you find, if you know meta-analysis, is each place there's an asterisk it led to positive impact, so education by itself does lead to a positive impact, but contact leads to an exponentially greater impact. Even more, in follow-up research any benefits of education are erased; benefits to contact seem to maintain better over time.

One other example of unintended consequences is social marketing. One of the benefits perhaps of education is you can do a marketing campaign. The Substance Abuse Mental Health Services Administration has done this in What a Difference a Friend Makes. It's a good marketing campaign. When you look at marketing campaigns, public service announcements,

you're looking at two things. One is penetration and the other is impact. Penetration is, if I came up with a dancing Coke can, putting it overly simple, penetration is the degree to which the population admits they've seen the dancing Coke can. And in a one-year period it went from about 30 percent to about 28 percent, which the people in Atlanta and the Coke can people would be overjoyed with because that's a pretty good hit rate.

But then you're interested in impact, and frequently the way they measure impact is the degree to which people go to websites. This is a website for What a Difference a Friend Makes. It has a hot button for a suicide prevention line. You can go right there and get help when you need it. The impact, what kind of impact did that have over time? From time one to time two is about a three-month period. He had about 2,000 hits up to about 8,000 hits, which is a pretty good odds ratio, but you need to look at the effect size. The effect size is on there. It's way down in the bottom because this was shown to 180 million people. It has very little effect size, and of those it did see 88 percent left after one minute.

So what it leads to in terms of what's considered state-of-the-art interventions for changing stigma is targeted, local, credible, continuous contact.

Stigma change should rest on the person with mental illness. We would have never thought about changing racial issues by having a bunch of white people do it. You need people with lived experience leading the charge. It needs to be targeted. It would be nice to change the population but it works better when you try to get employers and landlords and physicians to change their views.

It needs to be local. I live in Chicago. I can tell you anything that comes out of Chicago has no play in the rest of the state.

It needs to be credible. I work with the military. I am not military. If you're going to talk to military, Army talks to Army, Navy talks to Navy, and Marines are better than everybody else. It needs to be continuous. It needs to have contact. Finally, the grand plan if we were trying to erase the stigma of mental illness is the idea of people coming out, which had pretty big impact in the gay community. Similarly, if people come out proud -- Dr. Simon talks about Larry Fricks as a wonderful example of it. So coming out is probably the secret to erasing the stigma. Thank you.

DR. WAGNER: Well timed, and lots of information. All four of you, thank you so very much. Let me look around and see who wants to open up the questioning. Looks like Amy.

DR. GUTMANN: I'll just ask anyone to react to two observations that were really informative. One is it's a poorly known fact, as I understand it, that all mental diseases, conditions, are much less well funded in the medical area than other conditions and diseases, and how can that be changed without simply adding to what everybody sees as the burden of costs in the healthcare area. I ask that as somebody who really believes that there is an inequity here, that we really need to pay, not just pay more attention but pay more to address mental issues. And the footnote to that is, while we are charged in both senses of the term by the President, charged up by his BRAIN Initiative and charged by his BRAIN Initiative to investigate this, \$100 million is really in the broader or narrower scheme of things a very little amount compared to what goes into, for example, a research that I'm strongly supportive of, cancer research.

So how do we get -- everything you've said is in some ways conditional on cutting through these two issues of how much we are willing to support the very serious problems in human lives and the very important potential that you all represent. So do you have any advice

vis-a-vis that? It's very relevant to the implications of neuroscience research because there has to be enough of this research to get anywhere near the goals that you all want us to achieve and we want you to achieve.

MR. JOHNS: While I can't speak for all of the other circumstances, I would believe, at least based upon what I know about some of them, that much of this would hold true. One of the things that we have pursued is the very idea that there is such a substantial actual hard cost to go with what is the devastating human emotional cost. It is regrettable perhaps but real that those human costs do not always drive action in the way that the hard costs potentially do. So we have focused on what is the reality of the economic impact of all Alzheimer's disease and other dementia in the pursuit of what would be adequate funding for the research that could ultimately end the human effects. So that is imperfect, and I cannot tell you that we have succeeded to the point that we have adequacy in funding. I just told you in fact to the contrary. But it does seem that there is resonance with that sort of message when we talk to policy makers about that sort of thing.

DR. SIMON: The more time I've spent working with organizations of people who live with mental illness, the more I'm impressed with the message that they would like to get out is not, "We are pitiful people. Feel sorry for us," because that really is not a very effective message in terms of mobilizing society's resources, and to focus more on the lost opportunity, to focus more on the tremendous lost opportunity and the ability of a large number of people to live happy, successful, fulfilling lives. So I think ironically the message that we want to get out there about mental health conditions is not how bad and hopeless they are but how hopeful they are and how recovery really is possible. And that I think is what's going to mobilize resources.

DR. GUTMANN: Right. But, for example, there is a need for hospital beds for people who are diagnosed. And if you go to the emergency room and you break your arm, there will be a hospital bed for you.

If you have a mental condition where you need for short term a hospital bed, it's very hard to find one.

DR. SIMON: Ironically maybe how the BRAIN Initiative will solve that problem is my specialty of specialty of medicine does not have any procedure that involves a scope with fiber optics. But if we had a machine -- because machine-based treatments demand a much higher premium in our current culture and our reimbursement environment. So the moment that my specialty gets a machine I think we'll be in much better shape.

DR. GUTMANN: That's a very sad commentary on our health system.

MS. CHOWDHURY: What I would say is that I do think that we still operate in a system of silos. If you look at national government funding, we have NIA that mostly funds Alzheimer's, we have NINDS which funds mostly Parkinson's, we have NIMH, mental illness. And actually when it comes down to it, across all of these diseases there is so much still unknown when it comes to the brain. And what we are learning is that there are common pathways. There are common areas, whether it be inflammation, mitochondrial dysfunction, et cetera, that we are all exploring, yet we continue to do it in our individual silos thinking only of an immediate, small, narrow population and not necessarily taking in the fact that we've learned that Parkinson's disease has a specific type of depression. It's probably a PD depression, not the same as a regular depression, yet probably there's overlap that could be learned, yet we don't go there.

So I do think that one of the things that we need to think about if we are going to leverage, because these are huge issues, is cutting across the diseases as opposed to continuing to live in these silos.

DR. GUTMANN: That's just really important for us as a commission to address in the neuroscience area. We've already come out and said how important it is to integrate ethics. It's really important to integrate the knowledge of these diseases. That's an ethical imperative, I think, to move forward.

DR. KUCHERLAPATI: Thank you very much for your presentations. Several of you talked about patients participating in research studies, whether they're research or clinical trials, and so I wanted to ask you about that. There are some people who have come before this commission who have argued that if the patients are not going to benefit from that research, that maybe they should not participate. What I heard from several of you is that the patients are very anxious to participate in trials and that they are not necessarily looking for some immediate benefit that they may receive but they'd be willing to participate in these kinds of studies for societal benefits. Which of that view is correct?

DR. CORRIGAN: I just want to make sure when we talk about neuroscience that we dovetail with its quiet brother here, which is behavioral science, especially for mental health issues. Because while inpatient units might be useful, for people with serious mental illness, behavioral and social help is the biggest thing. And if you are going to develop a program for behavioral health interventions, like assertive community treatment as Dr. Simon talked about, you better make sure people who are going to use that intervention have an active role in it. So we have two federal grants now doing peer navigator programs to help people. One is African Americans who are homeless, and in another Latinos navigate the healthcare system. Because, as

you know, people with serious mental illness get sick and die about 15 years younger than everybody else. And that has a community-based participatory research team, which is very laborious, but we sit down for the last year with African-American homeless, trying to figure out what the secret is to getting them engaged in healthcare in Chicago. So at least in the behavioral health side you've got to make sure you're doing community-based participatory research.

MS. CHOWDHURY: I think the question of clinical trial participation is one that is driven by the disease and also by the individual and by the type of treatment that currently exists, if it exists at all.

I can't really speak for my colleagues in different diseases, but within the Parkinson's disease landscape what I would say is that for individuals who say that there is no real cure there or it won't affect them, what can they do, they probably have not spoken to a Parkinson's disease patient. I think most patients are realistic. They know that if they've had the disease for five years, there's not going to probably be a disease-modifying drug that will suddenly halt their disease in the next two years. They also recognize, though, that their disease may help contribute. I think that the fact that we are gaining greater knowledge on the genetics of diseases, again not necessarily a causal relationship but just an understanding that genetics plays a role, means that individuals are also aware that there could be implications for their families, and they want to give here and now to make sure that what they can do might benefit, not their child, but actually their grandchild.

I think, again, we sometimes give patients less credit for how sophisticated they are. Yes, they may go on the Internet and they may not understand everything, but they do have a sense of how the disease progresses, and I think to not include them in the conversation about whether they have a right to participate in research is doing them a disservice.

MR. JOHNS: I agree with much of that in the Alzheimer's world in terms of your question. There are really two things that I see most frequently, one which is the very assertive desire to participate on exactly the basis you've just heard from my colleague, because individuals want to make a difference, recognizing their own reality and the path that they personally face, and again, for their families, but beyond as well, that they know they have a contribution they can make. People really want to be engaged, whether it's speaking to groups or others, and the potential of being part of a trial, I think that is the predominant kind of thing. But no group, of course, is monolithic. I also hear people who say, for example on the progression of the potential to test in advance of symptoms, "Why would I want to know?" So there is a segment of the population that fits that description. We find in the research we do that more people tend to want to know on that basis, and I would tell you that I believe by far the strongest feeling is that, if they can participate, that is desirous.

DR. ALLEN: Thank you. I was very interested in the discussion about mental illness, and I had a couple of questions. One of them is that if the new recommended approach is to be out and proud, does that mean that we should continue for the moment to use the categories like schizoaffective or bipolar or depression that you believe, the experts believe are going to be mythical in just a few years of additional brain science, as a political short-term measure continue to use the vocabulary that we know doesn't really explain, reflect, the realities of the biology?

That's the first question. The second question is this: If it's true that mental illness is developmental and we are going to be discovering this and understanding this better and better, is there an ethical imperative not just to do research now to continue this quest for knowledge, but also is there an imperative to begin to prepare family pediatricians, educators,

and parents as to what it means for rearing and educating a young person if indeed we have to understand mental illness as developmental, even those that have a later onset?

DR. SIMON: I'd say about the first question in terms of the use of these labels, the current labels probably will not stand up to strong scientific scrutiny over time. There will be an interesting I think developmental process because these labels have positive and negative. The labels carry stigma, but they also for some people carry an identity, which is important in terms of belonging to a member of a group and having an explanation for their experience.

So I think it will be interesting to see how that develops over time. To use another example, the label of breast cancer is a terribly important label, but I think we are trying to understand that biology does not respect it, that there are some breast cancers that look more like colon cancers and some breast cancers that look more like lung cancer. So at the biological level the label may not have meaning, although it still may have important meaning in terms of explaining people's experience.

The question about development, I think we are likely to move into a world, for instance -- you know, one of the Recovery Act funded studies by NIMH that will turn out to be a tremendously good investment was a longitudinal study of school-age children in Philadelphia that discovered, using neuropsychological testing and imaging, the trajectory of children who would later develop schizophrenia. And what was clear was that there were developmental signals that seemed to be apparent in school age even before middle school.

And those certainly are not accurate enough now that we would want to tell people your risk level is this, but that will likely happen. And we will need to start thinking about those things much earlier, and that's going to raise some difficult questions.

DR. ALLEN: I understand that we are not yet routinely treating kids with schizophrenia at age three but we are giving kids psychopharmacological medications now at very early ages because we think they have early onset. Something we used to call bipolar now we call something else. We are already intervening, and I'm just worried about and wondering about how more organized and structured our responses ought to be in order to get better outcome for these kids.

DR. SIMON: Right. And to be sort of technical about it, I think that is actually a misapplication of our current technology, because what we're doing is we're attempting to treat an upstream problem with a treatment that really, if anything, has effects only for far downstream; that we're calling a fire truck when what we really want is a smoke alarm, and if we had a smoke alarm we'd never need to call the fire truck, and calling the fire truck sometimes can end up with damage to your house.

So what we're going to need, I think, is new interventions which are targeted appropriately and are not the very blunt instrument's that we have now. So I'd certainly share a concern about saying we should be prescribing antipsychotic drugs to large numbers of young children who don't show any definable abnormality.

DR. CORRIGAN: I just want to say this is also an example of unintended consequences, because who can be against a developmental focus on educating people early? What we need to be mindful of is the attitude about prognosis and focusing on symptoms that's been around. For example, do you know the prognosis in schizophrenia is the rule of thirds, that about one-third will get over it like a respiratory disease, about one-third will handle it like a diabetic disorder, and about one-third is what we think of as the tough diagnosis? And yet it's -- I learned in school to prepare the 18-year-old to live in the back wards the rest of her life as a

reality check, and in reality that's not the case. So we again need to be thinking about if we are going to identify people early, what the message is we're giving too.

DR. GRADY: Thank all of you for very useful comments. Let me ask a question about -- I mean, many of you have mentioned the importance of getting people involved in the discussions about what the research ought to be, doing community-based participatory research, et cetera. We talk a lot about community consultation in a lot of different ways, and I'd like to hear from each of you what you think the most important goal is of community consultation and whether or not you have a model or example of how it's worked.

DR. SIMON: One of the active programs of research we have going on now is focused on suicide prediction, which as you might imagine is a difficult area in terms of some of the challenges it's raised and some of the things we've done. In collaboration with the Depression and Bipolar Support Alliance we do surveys, we try to engage with the community of DBSA's constituents about their views about suicide risk and about appropriate interventions. Patrick and I were talking about this at lunch. It was an eye opener to me that two-thirds of people who had received involuntary treatment after a suicide attempt believed that involuntary treatment was often necessary. So those are important things to know, and we could get data on that.

We also very intentionally incorporate as members of our research team people with lived experience of having suicidal thoughts and suicide attempts, and they are involved in all the decisions that we make. So we are not expecting that those people will be the participants in our research, and we are not expecting that those outreach surveys we do will actually necessarily reach the exact individuals who might be the subjects of our research, but I think it's critically important to engage with people to understand their views and values.

MR. JOHNS: I'll just quickly say I don't know that we have a model, but we certainly have done a variety of things over time and continue to, whether it's in the scientific research realm, whether it's in the marketing research realm, whether it is in the communities actually assembling people for town hall meetings and more. So we do a lot of different kinds of things. I could not tell you, though, that we have an answer to what that question was.

MS. CHOWDHURY: I would second that. I would say that engagement in research is a marathon, not a sprint. The first thing is to deal with the fact that you've been diagnosed with the disease. When you decide that you are ready to participate in research, for some people that may be an immediate reaction, "Okay, I've got this. What can I do?" For others it actually may take years before they're ready to do it.

So what we have found out is that you actually have to use different mechanisms. We have things like clinical trial fairs, which are just like job fairs. We go to cities where there's a lot of research; we ask the institutions conducting the research to come. People hear a presentation about what does clinical research mean; what does consent mean; what's phase one, phase two, phase three; what are the goals. And then they get to go hear from and meet the institutions who are conducting research in their area.

We also have something called Fox Trial Finder Ambassadors, an online matching tool. The biggest I think impact that a patient can have when thinking about this is hearing from someone who underwent and participated in research. So FTF Ambassadors are those patients or community people who have been part of Parkinson's research and believe in it, and they go out and they talk about it and they dispel myths and misconceptions and things like that.

So I think the take-away is that there is no one model. I think there actually has to be a number of different mechanisms used.

MR. JOHNS: If I could just very quickly, it's an important point I think that we haven't really said. Even as much as we've talked about people's willingness and interest and demand and drive, if I had to give you the top level problem, it's underfunding of research. If I had to give you the second level problem, it would be participation in trials. So despite what we're saying, and I'm sure you know this but at least for the record I think it's important to note that we are confronted with what is the great difficulty, all this said, with having enough people participating to drive the science at a pace that would ultimately benefit all those affected.

DR. CORRIGAN: So partnership versus participation, because we're definitely looking at this from a different direction. For us partnership is a big issue. So if you're going to partner, first you better pay for it. So you have to pay people with lived experience to be on the board and do it. Second, you have to provide reasonable accommodations to them so they can do their work. With reasonable accommodations a lot of people are capable of doing this kind of work here.

Third, you have to avoid tokenism. You don't want to just put one person on. It's hard enough talking to you friendly folks as it is. Imagine if I had to deal with a bipolar disorder on top of it too. And fourth, you need to keep in mind where they are especially strong in any kind of research. They're strong going into research because they know what the issues are that we don't necessarily know, and they're hugely strong coming out because we take the stuff and put it on the shelf and they are the ones that are going to get it and go yell at politicians to get that stuff funded.

DR. WAGNER: Good points all. Nelson.

DR. MICHAEL: Let me ask you a question based on what Sohini said about what I would summarize as stove-piping of research initiatives in funding agencies. So I've worked my entire professional career in HIV/AIDS. There is an Office of AIDS Research in the National Institutes of Health. It's associated with the offices of the director. And even though the largest funding institute is the National Institute of Allergy and Infectious Diseases and NCI next, and then there's funding that's spread across I think its 19 ICs, OAR plays a very powerful role because it can cross-level those fundings and it can provide sort of a neutral ground at the OD level for discussions about funding that crosses multiple disciplines.

I was just looking on the OD Website. I notice that there is an Office of Social and Behavioral Sciences Research. I don't think that quite is the office that provides that normative function. But it's not my field so I'm posing the question to you. There was not always an Office of AIDS Research, obviously, at NIH, but because of the I think advocacy, some would call it activism in my field, this became something that was new. Is it now the time for this sort of change in the structure? And I don't want to specifically focus just on the National Institutes of Health but for other potential funders.

DR. SIMON: I think at the basic science level, at the preclinical level at NIH, there's actually really good coordination across neuroscience-based institutes for NIA, NINDS. There's a new neuroscience building and the labs overlap in their space, so I think there's some really positive developments. I think when you move into the sort of translational level and certainly when you move out into the clinical level, they are much more separated. And so the idea that even at the clinical level we are dealing with a lot of the same problems, that's probably not as well developed, and at the clinical level it is sort of true that, if you were to go to NIH and

say, "We're interested in studying depression in Parkinson's disease," NIMH would hope that NINDS would pay for that, and NINDS would hope that NIMH would pay for that.

DR. GUTMANN: Nobody would pay for it.

DR. WAGNER: And it wouldn't get done.

We are bumping up against the hour. John, I'm going to ask you to hold on yours. But we are going to ask you to reconvene as part of a larger panel with this morning's speakers after we return at about 2:30. Thank you all for a very, very informative session.