



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Amy Gutmann, Ph.D.
Commission Chair

James Wagner, Ph.D.
Commission Vice-Chair

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DR. GUTMANN: We are blessed to have a great group of people presenting with expertise that is wide ranging in neuroscience, research, the ethics of neuroscience research and the ethics of the potential applications of the results of this research. And this is a unique opportunity for us as a Commission to hear from you. So give us one recommendation that you would like to see us, what we do in our report, whether it be what you want to make sure we attend to, something you think is really important for us to observe in the report.

Let me put this in the context of what we have been working on as a Commission. We are committed to giving the best proactive advice we can to enable the neuroscience to progress in a way that is maximally beneficial to individuals and society in a way that integrates ethics early on so that the regulatory burden is minimized and the potential of neuroscience to do good is maximized. That's our goal. And we're going to hold you responsible this afternoon, not for what we write in the report, but responsible for this afternoon for giving us the best advice you can give us in addition to what you've already said to us.

So pick one piece of advice you would like to give us or one observation you would like us to take into account. We will go around, and then I will open it up to my fellow Commission members to ask any questions and anybody in the audience who would like to write down a question or a comment, please feel free to do so. Carlos, shall we begin with you?

DR. PEÑA: Sure, there is always a risk of sitting at the end of the table when going around.

(Laughter.)

DR. GUTMANN: You had a 50/50 shot.

DR. PEÑA: I know.

DR. GUTMANN: I don't know if you feel like you won or you lost, but I have a feeling I know which.

DR. PEÑA: One thing I heard, and I think has come up with the different perspectives that you have invited here today is that where there are opportunities to bring different stakeholders together, we try and find where those forms or venues exist already. And so within government, there is a forum that I mentioned at the close, the Interagency Working Group on Neuroscience. I could see as the White House Neuroscience Initiative has a number of activities, the way to interrelate these activities would be a nice way to bring around specific topics like bioethics.

Where there are other opportunities because I also observed that during the panels you have different perspectives, if we can bring those stakeholders together in sort of unique forms as well is also an area that we could pursue.

DR. GUTMANN: Great and you can pass the baton now.

DR. REPPAS: So before I heard all the great commentary today, I think I came into this assuming that there is nothing particularly unique about neurotechnology. And having heard all the things that people have had to say today, I think I stick with that conclusion. And so I would ask the Commission to really think about whether the protections that exist for patients, for consumers that are already out there, and I think may not work perfectly but work pretty well, whether we really need to tweak these in a domain specific way. And I really think a lot of the concerns that neuroscience and neurotechnology bring up are not really unique, and that there are a lot of protections out there already. So to the extent that the Commission recommends new guidelines, I think just bear in mind that there is also a cost to these, and so particularly with the perspective of industry, the people out there who I think, and Helen put this very well, it is one thing to basically press away inside the Academy with interesting experiments with small numbers of people, with papers and publications and grants, the rubber really hits the road when industry has got to move this out to a point where it can impact patient care. That is incredibly difficult. And just bear in mind that that job is already tough, and try not to make it tougher unless there are really good reasons.

DR. GUTMANN: Clear defensive move that you will not budge from. All is well with the world as long as we don't recommend any additional regulation.

DR. HOFFMAN: Yes, I'm a pediatric oncologist by training, and a lot of the issues that have been talked about certainly have crossed my path. I worked at the Cancer Institute, tried to get children to agree to phase one studies. Sometimes they agreed, their parents didn't. It was very interesting in those occasions.

One of the things that is new to me, I spent a lot of time in the drug area, and the food and drug area, and we haven't talked a lot about the dietary supplements and their role in terms of management, but the one thing that sort of causes people to try new things and to go "off the grid" as they say in terms of mainstream practices is really the fact that we've had not such great success in many areas. Alzheimer's is one area, a prominent area, schizophrenia, people are still saying what we do with this?

And so the one thing I heard from speakers here was the fact that we can now look at targets, a lot of polymorphic targets. This is not the standard drug model of a lock and key model where we have a drug and receptor site. We may not know what those receptor sites are. There could be multiple receptor sites. And so what I would like to call for is to have perhaps the learnings from the databases and from the imaging and from all of that area somehow translate to the pharmaceutical industries to pull from the perhaps complex products. I deal with complex products, which is not a model for the U.S. right now in terms of drug treatment, but to see how we can get a broader thinking pattern in terms of trying to give up on sometimes knowing mechanism of action.

There were two products approved to the U.S. market we were involved with. We don't know how they work. They have multiple active, some really unknown actives.

And so I think the sort of out of the box thinking, there has to sort of blend what we are learning in the neuroscience area to perhaps therapies such as drugs because there has been major limitations in the drug area for quite a few of these brain indications.

DR. GUTMANN: Thank you. Peter?

ADMIRAL DELANY: I'm going to suggest that we're talking about complex behaviors, not just a single issue. And I would like to recommend the thought of thinking about information and data differently. I mean obviously I'm a data guy, and I like numbers but too often I think we are focused on the gold standard model. And there's an awful lot of information out there. So maybe that is part of leading to safety, but we need to be thinking about other practice-based evidence that would help inform our research designs and inform our decision making about going forward and help inform such things as education plans to help physicians and practitioners think through what they're going to do when they have a young person come into their office and say, "Hey, I'd like this because it will help me get through my test."

So, I think we're as a society pretty ready to focus this. This is a single, we look at it too narrowly, and we need to treat it as a complex issue but also treat it as there is other data and other information that could inform the process other than clinical trials. And as a child of the NIH myself, I'm probably uttering a heresy, but I do think there are other kinds of information that are important that are missed.

DR. GUTMANN: Reiner?

DR. REINER: I'm going to follow up on that and recommend that especially in the context of neuroscience when we think about the kind of medicine that physicians really are trying to offer today. Too often, it goes exactly to that magic pill and yet wellness and the wellness of the person, the whole wellness of the person, is often very closely tied to how well their brains are. Whether they are offering them pills or whether they are offering them other ways to do this, I think that we need to help physicians be able to assess that and actually even work in that wellness space rather than just in the illness space.

DR. GUTMANN: Deven?

MS. MCGRAW: So, to some degree I'm where John was in the sense that certainly what I've seen in the direct to consumer world with respect to privacy, there isn't anything about direct to consumer neurotechnology that raises any different issues necessarily or more urgent issues than in the DTC [direct to consumer] space with mobile health apps writ large.

Having said that, it certainly would be helpful, to the extent the Commission is concerned about the privacy issues related to the data that is generated from the consumer's use of these tools and what happens to it, is to think about whether it is possible to endorse what has already frankly been called for, which is a privacy framework that is much more consistent across the board. So that we don't have, and whether that is through regulation or through guidance, a combination of voluntary enforceable codes or not the extension of HIPAA, which we've talked about, but something that makes sense and targets what the risks are to consumers

in using these tools, which is there is not a lot of transparency. There is often not a lot of control over third party use. And then the potentially harmful uses of data for redlining or discriminating against people in certain contexts.

DR. GUTMANN: Many of you may know this but we don't hold all of you responsible for reading all of our reports, but we have endorsed as a Commission, and all of our reports have been unanimous, so we have unanimously endorsed the principle of regulatory parsimony, which means we will not call for extra regulations unless there is obvious need. And we would either call for a prior cost benefit analysis or cite studies that suggest that the benefits would be greater than. So we've actually been true to ourselves.

And, secondly, I think it is just important to go on record that we also are not, and we've said this in our first neuroscience report, we don't think that neuroscience raises unique ethical issues. That said, we still think even when an area doesn't raise unique ethical issues, we should address the issues that it raises and shares with some others. And you've just underscored one of them for us.

Jerry?

DR. MENIKOFF: Picking up on your theme about improving the system and making it function better, I would like to go back to the issue that was raised earlier, a blend of regulatory and ethical aspects in terms of in this particular area. I think it is a bit unusual in that we have a melding of federal provisions and state provisions. And it is interesting in terms of the ethical aspects of why we do research. It is a sort of a free rider, public benefit, public good sort of thing that everybody benefits from it. To what extent should we be having a system that is more federal that doesn't look so much perhaps to state law. I think they are fascinating issues, and they sort of fix squarely with a lot of the big topics you are thinking about, particularly in this particular situation.

DR. GUTMANN: Thank you. That is an issue we tackled within another area, but we haven't actually looked at it specifically in the neuroethics area in the neuroscience area I should say.

Paul?

DR. APPELBAUM: So, sticking with the consent area but moving off a bit from decisional capacity, particularly when we are dealing with clinical populations that are likely to be the target of this kind of neuroscience based research, they are likely to be groups for whom traditional approaches to informed consent work least well. Giving people 20 page, single-spaced consent forms, having research assistants read the 20 page forms to them, both of which are sort of standard practices, don't work well for anybody, but they are going to work even less well for these groups. So this might be an area in which particularly to encourage experimentation on the part of investigators and IRBs to come up with and to support creative ways of conveying information and getting consent from participants.

DR. GUTMANN: Interesting. I would be very interested, Steve, at some point because you work in this area whether that has been your experience, but we will come back.

Adrian?

DR. RAINE: One broad and one very narrow point. The broad point is that I have a perception currently of a kickback against neuroscience, very broadly, books called *Brainwashed: Mindless Neuroscience*. And, of course, we do need a very critical approach to neuroscience and its application in society. On the other hand, we don't want to throw out the baby with the bathwater. So it is just a broad general concern.

But the more narrow concern is picking up something Amy mentioned about nothing unique about neuroscience except in my area of work, being anti-social criminal violent behavior. Perhaps there is something unique there.

As a researcher, having spent four years working with and for prisoners, I wish that did not occur because I do think it has held back advances in our understanding of the social and biological basis of crime and violence. And I think that over the decades, we have all been diminished by the overprotection of a vulnerable population, inevitably a population that does certainly need protection.

DR. GUTMANN: Yeah, an important point for us to consider. Helen?

DR. MAYBERG: I wanted to also reemphasize the theme from our group, but I think to broaden it based on what you just said. I think bad science hurts everybody doing science and maybe not just bad science but just incomplete science. And I think that if science always leads, and particularly back to the BRAIN Initiative, there is a lot of almost grandiose hopes for what might be accomplished in the new BRAIN Initiative, the new DARPA Initiative. And, again, it is going to have to be iterative, step-wise. No one is going to get to make the "Hail Mary" pass just because they throw a lot of money at it. And that it is not about money, it is about step-wise progress. And the science will move at the speed that it does.

But I think that also applies that when things—and that is particularly true when things are invasive. That does make it special in that you have more opportunity to really hurt someone or to set the science back. But I think that the assumption that less invasive means the bar is lower or the science is really bad because the community, the culture, sees it all the same. You are studying the brain, and it is all garbage, as was implied in some of these more contemporary writing. And that is really kind of unfair to thousands of scientists trying to ethically and scientifically in a very robust and measured way try to figure out something really complicated.

So, I think that just because something is safe, yes, it may be more accessible, but the public that uses it needs to realize that if there really is an evidence that it works, well, let the buyer beware. But it actually has more of an effect on just your pocketbook or what you do to yourself. I think it invades and biases the culture in ways that actually is a backlash for other kinds of science that may be directed toward other very patient-oriented things. So, I think that

everybody is in this together, and we need to find ways that we mutually inform even though safety may be at different levels.

DR. GUTMANN: Thank you. Nick?

DR. BOSTROM: I think one might characterize bioethics as the effort to try to prevent that which should not be done and to enable that which should be done. Traditionally, I think the discipline has been much stronger on the former, preventing that which should not be done. But particularly within the enhancement arena, I think there is a big opportunity to start playing the second role, to try to enable that which should be done by looking for opportunities for things that would be very valuable. And then seeing what is it that hinders advancement in those areas, particularly the ways in which the regulatory framework for introducing new diseases and medical treatment has been based in the traditional role of medicine, which is to try to diagnose, prevent, cure and ameliorate diseases, to which that framework might be unsuitable for an enhancement medicine that also tries to find ways to amplify and enhance normal functioning. If one can identify the ways in which this old framework no longer fits and accommodates these new possibilities, then one might open up ideas for informing that that could help create more progress towards like enhancers that actually work. So that would be perhaps a more sort of intellectually ambitious take on the mandate that this panel has, but I think one that somebody at some point will need to undertake.

DR. GUTMANN: Yeah, and I, again on behalf of the Commission, it is a point well taken. It is a general point, but it applies in high relief in neuroscience that we want to enable that which should be done every bit as much as preventing that which should not be done because lives are at stake in either, on both ends those goals equally put lives at risk. If you don't enable what should be done, you may not be saving lives or enhancing life. And if you don't prevent what shouldn't be done, so it is, I think that is an important point. And we shouldn't just focus on what shouldn't be done.

Steven?

DR. SMALL: Thanks. I would like to just make a comment or two about the "no unique ethical issues" related to neuroscience. And I will do that in the context of two issues that are important to me that I brought up. One is in terms of use of data, which was brought up many times. Whether a massive data set that is the genome or a brain network or a social network or a purchasing network from Amazon, whether those have the same issues, and I think they probably do. I think in that sense there are no unique ethical issues related to neuroscience. I think it is personally invasive to have your information about your genome or your networks or your social networks or your buying behaviors, I think the issues are pretty similar. And that has been pointed out.

The other issue is the question of modifying brain circuits. And I'm not sure that I agree that there are no unique ethical issues related to neuroscience, although it is not obvious. And in this case I will make a comment about modality, which came up many times. Modality matters and modality does not matter.

Now, it is certainly true that taking a Kaplan class will make you get higher scores on your SAT. That is a modality of brain intervention. That is reversible. If I go and have some other behaviors for a while, I will change the brain back. I can change the brain around. Every activity I do will change my brain. I can change it for better or for worse with normal experience-dependent activity. I can probably do that with tDCS [transcranial direct current stimulation] or TMS [transcranial magnetic stimulation] or other things that I mentioned.

The question that I would like to bring up is whether or not these invasive methods, where you are taking out a piece of the brain, whether that in fact has separate ethical issues related to it. And because, the reason I say that, is because in some cases like that there is no experience-dependent plasticity that is going to make up for the lost tissue. That tissue is gone. It can be permanent. Now, experience-dependent plasticity is very powerful. And we can do a lot of things to regain the functions of small areas that are lost. There is no question. But in some cases we probably can't. And I think we have to be very careful about that.

The last issue about modality matters that I would like to bring up is I don't know if Steve Hauser was saying this or not, but I will say it a different way without attributing it to him, which is the discussion about cognitive enhancement. I believe that it relates intimately to the question of sports motor enhancement. I think that there are analogies there that we have not discussed. And I don't want to come to a conclusion, but the whole time we were talking during that session about it, I was thinking about motor enhancement, and so I think modality is an important issue.

DR. GUTMANN: Well, you know in Annie Hall, the Woody Allen scene where Woody was talking about what Marshall McLuhan said and he came out. We can ask Steve Hauser here whether that is what he meant as well.

(Laughter.)

DR. HAUSER: Like that scene, I agree with Dr. Small. He is saying exactly what I thought.

(Laughter.)

DR. GUTMANN: You channeled Marshall McLuhan very well. Paul, I don't know if you want, if you would trade with Carlos now that everything has been said but not everyone has said it, so Paul?

DR. FORD: So I think a great array of topics and in fact it raised more issues. But one thing that I hope you pay special attention to are the issues from neonates through adolescence. And that perhaps with a developing brain, the neuroplasticity, a positive obligation is perhaps to make sure we have good norms in the data, that aren't stigmatizing so that the normal variations in the brains, of these developing brains, are recognized but not in a way that is damaging. The importance of social development needs to be carefully traded off. And in particular I have in mind we have raised the question of when is it justified in doing a deep brain stimulation for somebody with Tourette's who is an adolescent who the argument is what kind of

benefit it is to be able to fit in for this brain that is now developing? Is that big enough to put the maximum risk?

And going to the point about taking a part of the brain, I work regularly with the epilepsy surgery folks, and there is this constant debate about taking part of the brain early so that it allows this neuroplasticity that there still may be as opposed to waiting until later to maybe the seizures will get worse.

But these are unique issues to the neonates, children, adolescents that I think we should pay special attention and not be fearful of. "Physically invasive" I think is the wrong metric. The metric is harmful, right, because there is some non-physically invasive things that are much more harmful than some of the physically, and have higher risks than deep brain stimulation, some of these chemicals that can more permanently destroy. So I think we want to be even-handed and particularly we need more attention to the children as they develop.

DR. GUTMANN: Open it up for anyone, presenters or Commission members, to add questions and comments? Yes, Nita?

MS. FARAHANY: An issue that has come up a lot today is risk/benefit analysis. And while several people have said they don't think there is anything unique about neuroscience, I think there are some unique issues that have been raised with respect to risk/benefit analysis, and how we think about it and how we think about it in different contexts. And whether or not we need a different model, so for example in cognitive enhancements, if our traditional models for the FDA [U.S. Food and Drug Administration], are thinking about risk/benefit are adequate when the kind of benefit that we're talking about is less easily quantifiable at a general level since it is going to be very personalized and individualized for how people measure it and how you enable people to have access to something that the FDA might not, for example, think would meet their risk/benefit analysis.

So, I'm hoping, given that you have different perspectives and different aspects that you are coming from, if you've thought about this issue of risk/benefit. I know Helen had a quote at the end of her presentation, which suggested a very different kind of risk/benefit in the patient population that she is looking at.

So, is there a different model that you might propose for how you think about your particular area for risk/benefit analysis?

DR. GUTMANN: Start, yes.

DR. SMALL: I didn't see any hands up, sorry. I'm not sure there are major differences in neuroscience compared to other fields with risk/benefit, but I'm not sure.

I recently had occasion to take care of a patient who had an epileptic focus in Broca's area of the brain, and I'm the language guy in the department. And the question that they asked the patient was, "Would you like to have your seizures cured, which we think we can do with an 80 percent chance, knowing that you will not be able to talk or would you like to

continue having seizures with the intermittent ability to talk?” And this patient ended up electing, and the epilepsy surgeon agreed, to take out the so-called speech area of the left frontal lobe. I thought I would bring that up as a point by which a discussion could ensue.

The same is true with children. Our pediatric epileptologists strongly believe that development of children with recurrent seizures is markedly impaired compared to the development of children who don't have recurrent seizures. And so they advocate removal of, for instance, the temporal lobe, a big piece of the side of the brain, very, very, very early. And so there is two neurological stories that may be could lead to some discussion.

DR. GUTMANN: Yeah, and those neurological stories, I would be happy to have any discussion right here, but there also ones we can as a Commission look further into because those are the kinds I said for the Commission that we believe we should look at neuroscience even if it doesn't raise unique issues. I wasn't precluding that there are some very, you know, if not, they may be unique or close to unique issues, and they certainly highlight, the two examples you gave certainly highlight why it is important to come to terms with the ethics of this area early on.

DR. SMALL: But they may not illustrate at all that neuroscience is different. If I told a child I was going to take a part of his lung, and he had no exercise capacity after that, I don't know it is different but it is something we could discuss.

DR. GUTMANN: Well, exactly, we don't know. And whether it is different or not, it is still an open ethical issue that we should grapple with. So you are absolutely, as I said, to coin a phrase “spot on” in calling it to our attention.

Freddie Ann?

DR. HOFFMAN: Yes, you had asked about the flexibility of the FDA in terms of thinking processes. The agency really has in the past shown that it can be flexible. One of the areas I was involved with is breast implants, and how to quantitate the benefit from breast implants, which was a real thought process in terms of the agency. So that is one point I wanted to make, that the personal preference of people and their mates was very important and it may not be what the device does per se.

The other thing was the new normal. In speaking about enhancement, and I'm new to this sort of discussion but of course it tags into dietary supplements and things I work with, is what is normal? The agency has done a lot of thinking in terms of limits for say blood pressure and cholesterol. It used to be there were lower limits. Now, there's no lower limits on either of those. As low as you can be standing and have a blood pressure, you are okay. So, things have changed. But I think this is really a conversation that has to be thought about, that people are actually, truly perceiving personal benefit, which is how the agency approves drugs. I won't speak for devices, but then the question is how can we capture that information in terms of a regulatory agency? I'm not speaking for the agency. I don't work there anymore, but I think that that is a conversation that has to go on.

DR. GUTMANN: Paul?

DR. FORD: So, just to follow up a little further with Dr. Small. I think there is probably a categorical difference between some of these side effects that are going to change our speech or our apathy, the example I gave, or trading off a little bit of cognitive function for better motor function...

DR. GUTMANN: Yes.

DR. FORD: ...that aren't as obvious. I know what it is to be out of breath, but I don't know what it is to have memory considerably lost or to be apathetic about the things that I love most. And so I think this is one place where I struggle of how do I help people who are facing this decision, how do I get them to fully appreciate what their life would be like without this in order to. So that is one of the places where sometimes a more paternal or maternal view of clinicians or researchers might be appropriate if people aren't fully appreciating how this could change their life.

DR. GUTMANN: Peter and Peter?

ADMIRAL DELANY: I want to go back to the cost benefit. I think what is becoming much more prevalent in these discussions now is tipping point. And I don't think there is anything unique about cost/benefit per se. What I'm hearing today is there are some unique tipping point issues. And if I was going, so what would tip a person to say, "yeah, I will take out a part of my brain" or what would tip physicians to say, "you know, I will go ahead and prescribe an enhancing drug"?

So, I think if I could suggest the area that might have some real traction is trying to get some metrics developed for what kind, understanding what pushes the tipping point, not only just for but also push back. So if you want to get one of the guilds to change their behavior, what is the tipping point for them to go, "okay, we are not going to do this anymore"?

So that might be your, that is not unique to any of the cost/benefit studies, but what the metrics will be for this kind of science are somewhat different. And they're going to be different pressure points, whether you go at the community level, which you were talking, the individual patient level, or kind of the mezzo level where you get into the guild discussion.

DR. GUTMANN: The other Peter?

DR. REINER: Well, we seem to be clones because I have a very similar comment, which is thank you, Nita, for suggesting this cost/benefit that the benefit is so hard to quantify. And I think that maybe that is some work that we in the field really need to do is to put our heads to the task and get better about defining what the benefits really are because we talk about it in these hand waving terms, and I think we can do better and we should.

DR. GUTMANN: Helen?

DR. MAYBERG: I think you know the slippery slope of trying to figure an outcome metric is kind of what we are all dancing around. And when you look at the transition in psychiatric trials and drugs, you know, it is always about how to eliminate a placebo response because that is considered bigger than the actual effect of the drug. And the lack of appreciation of the fact that people do have an expectation that something they take will improve something that has a problem. And that is actually good to work with unless you have a very small effect size, and then it is hard to measure, and you need much more people which makes your trial difficult. So we are back to what is good enough? How do we measure it? How do we proceduralize it in a way that has meaning? Because many times a number isn't reached and an outcome measure has been chosen that actually is related but slightly off, not quite orthogonal to actually what matters for patients.

And I think that we are using, as we move into invasive or neurotechnology as opposed to neuropharmacology to affect the brain, we need a different set of rules. And, quite frankly, we use the same outcome metrics that we always did even though by definition we are probably doing something that shouldn't be measured the same way. And we haven't taken the time to actually figure out that difference, and it is killing us.

DR. GUTMANN: Could you give an example of that?

DR. MAYBERG: Sure. So in Parkinson's disease, it is a disorder that is tremor, rigidity, slowed movement, problem with gait, problem with emotion regulation, problem with autonomic dysregulation, problems with cognition, all of those things, a biology that is well known. DBS [deep brain stimulation] for Parkinson's was first developed to impact tremor, then to impact tremor rigidity, moved from stimulating the thalamus to stimulating the subthalamic nucleus. Exquisite basic data that has been highly celebrated and known, the model for all of this. Never make any presumption when you stimulate in the subthalamic nucleus that you are even going to affect primary processes of gait. People still fall even though their tremor and their stiffness is better. And so when the studies were designed, they didn't use the entire metric of all Parkinson's measurements, they isolated the part that they thought that they were affecting. If they had actually used the entire United Parkinson's Scale and said, "well, I affect five of the 20 items," if it is a big enough effect, it still won't be diluted, it never would have been approved. It is very clear that many aspects of Parkinson's are not affected.

In depression now, we expect all the symptoms to go away. It's mood, motor, cognitive, circadian rhythm. We are very exquisitely maybe turning off the mood part, maybe we shouldn't expect all the rest of it to change right away, so why do we use metrics that require that? We should, again, if the science doesn't move and take advantage of what we know from different other applications, then we will be doomed to keep repeating the mistakes and then kind of wondering why it keeps not working.

And so I think we have to step back, regroup and kind of think and not kind of jump ahead and say, "Oh, well, I have a better place in the brain and mine will work." No, it is probably not a better, there are lots of places in the brain, and what do you want to affect and what is the primary thing you want to affect and have an appropriate measurement and not just what does the patient think they want. Because I will tell you with depression you get the psychic

pain to go away, and then a little while later people want a job. And they're dissatisfied because they can't get a job or they can't, and so, again, it is a moving window even for what people want. And that's I think something, I'm not saying I know what the answer is, so please don't ask me.

(Laughter.)

DR. MAYBERG: But it is a moving window and it has to be a part of the conversation as we kind of go back to a drawing board between academia, industry and every new device or something that we will do including the shareholders, the patients.

DR. GUTMANN: Steve?

DR. HAUSER: So, Helen, that was my exact question. And like with Nita, I was going to begin with your last slide, and I think DBS is a great example of a neurotechnology that we know works for some indications, that is potentially transformative in other terrible highly prevalent problems, and yet we are seeing a roadblock in translation. And just focusing on that roadblock, I wondered if you had answers or you had specific questions. Is it flexibility and outcome measures? Is it having a system where secondary signals can then be rapidly followed up with trials that can deliver acceptable data? How do we speed translation here?

DR. MAYBERG: So with a caveat that I have no idea but do not want that sound bite to be the only that I say. I think that only with some perspective of time, having done some research, can you actually look back at what you did to see where the fault lines were and where you kind of fell into a pothole. You are constantly focused on what you do and following the rules that you set for yourself plus keeping an eye open to what everybody else is doing, and it is not always in step.

What I think is happening is that in any kind of device-oriented work, and again when you, I looked up the foc.us us thing, and there are instructions on the Internet: "If you put it here, it is not good, but if you put here, it is better. And if you put it this way, it is not good." So obviously location matters, even when you are sticking something on your cortical surface. It is very clear in TMS in depression that location matters, and everyone is trying to inform.

So (a), there is where you put it and what data is necessary and sufficient. Is it like cooking tomato sauce where just taste it, and you can kind of figure it out? Or is it like baking where you actually better measure? Different approaches may need different levels of precision. So precision of targeting, which means how do you do the work to kind of know? Well, that is where the BRAIN Initiative and all of the neuroscience is going to have to inform and may need to be iterative.

Then you have got the issue of which patients to pick. That is a real problem in psychiatry. You are not going to solve it now, but in movement disorder, they learned over time by doing lots of people with Parkinsonism, that unless you responded to Sinemet, DBS in the subthalamic nucleus would never make you better than your best on Sinemet, so that a Sinemet responsive person was ideal. So they had a biomarker. They didn't know it when they started,

and it wasn't a restriction. It took a lot of data, and no one threw out doing studies in Parkinson's and said it didn't work when they did that because they went at people who developed side effects first.

Then I think the big super unknown is this outcome measure and what to do. And, as I was discussing earlier with some people, this changing timeline of what you do to a patient as you stimulate their brain, we all presume that you just take something away. No, any of these interventions may be doing one thing like blocking something bad, but it actually may be facilitating something else, plasticity. And that may not be what you think it is. It may be important to do the first, but the second may actually introduce things that interfere with your outcome measure.

So, I think it is, I think that, you know, again, it is easy for me to say, "Oh, well, just go back to the drawing board." But I think it actually is true. You have to collect all the data, have everybody talk together and rethink, was the way we approached it at the beginning, not that it is right or wrong, I mean we are also competitive that it is kind of like one is right. If I'm not right, I must be wrong. No, I think everybody is right for different reasons, and everybody has to pool what they have learned because they have looked at it a different way. And I think we just have to take a few steps back and survey what we've got scientifically, and then can make informed decisions about what to do. And then we may still be wrong, but at least we won't make the same mistakes again.

DR. GUTMANN: Carlos?

DR. PEÑA: Yes, I timed it to be the last of the questions.

DR. GUTMANN: Yes.

DR. PEÑA: So a couple of comments. One is that I think it is, I mean it is great to hear these comments from a diversity of stakeholders for the agency, so that is one thing I just wanted to note.

The second thing is the risk/benefit ration that we undertake at FDA, I'm still thinking through where there is a real difference for neurotechnologies, but it is a step that we have to take for every product that we review. So we don't have the luxury to not perform that risk/benefit ratio.

And one product that comes to mind is deep brain stimulation for dystonia. That has been a humanitarian device exemption approved for children, ages 7 and up, when there is 90 percent head growth. And there is a risk/benefit ratio there in that it is even a harder assessment because it is probable benefit. It is not a true full-blown benefit, it is probable benefit.

So, I think this risk/benefit ratio is important. It is something that we regularly go through for all the products, and it is very good to hear the discussion on how important this is to neurotechnologies, where there is a difference or not between other types of technologies.

DR. GUTMANN: Open for other questions and comments? Nelson?

COL MICHAEL: It's a follow up to Helen's comments. Do you think your thought about, retrospective and looking back, almost like doing a cross-sectional analysis of a number of studies that may have had unintended outcomes that were still potentially clinically useful, is that more important for people at the practice level so that they could potentially implement these approaches using off label use indications or is it more important for funders to then reload and do new clinical trials with now questions better defined? So that you could actually ask some of those questions that you couldn't have interpreted or couldn't have expected years in the past, but now looking forward prospectively could ask a very focused question where a randomized control trial might be useful?

DR. MAYBERG: I think it is both. There is nothing to stop anyone from buying an available device. I am not advocating off label use clinically of a device, but there is certainly enough papers written and instructions of even the iterations of how to do things better that one could read. And neurosurgeons are smart and can read and can implement. And if you, and you can certainly get access to these. They are expensive, but you can do it.

If that is happening, you don't hear a lot about it. Even with the HDE [humanitarian device exemption] for OCD [obsessive compulsive disorder], people aren't sure exactly what to do. And if you know how to implant it, what the rules should be to make it work. And it is not happening I think as much as people might have anticipated it might.

I think this is more about, and again, back to the BRAIN Initiative, there is a call and a plan for a really high bar for technology innovation that is going to encourage new kinds of devices, more invasive things in the brain, very clever ideas. And just because you have a great device doesn't mean these problems go away. So, I think that I would hope that those kinds of studies, which are on the grid to get started, are going to have to kind of go through this exercise. They are going to have to go through it to deal with the FDA to get approval. And so I think that it is incumbent upon everybody instead of just in the silos of an independent company, and again they have their goals and their shareholders, but at the science level, at the federal level, how can we share information to enable things in the same way pharma did to go backwards and share data so that people could have a better appreciation of what happened outside of the prospective trials.

DR. GUTMANN: So how much sharing is there? There is a documentary that actually got a lot of, got a pretty big audience for a documentary about basic, the interaction of theoretical physics and experimental physics, called *Particle Fever*. If you haven't seen it, I have no financial or other relationship, you should see it because it is a story, a true story, about the cooperation and collaboration of physicists all around the world to test the existence of the Higgs particle.

And there is a scene in this documentary, since it is a documentary, it happened in Aspen, where one of the theoretical physicists is giving a kind of Aspen-like talk and somebody in the audience says, "I'm an economist, and I want to ask you the question what is the payoff of this discovery going to be if the Higgs particle exists?" And the scientist replied, "The payoff is

nothing, and it will explain everything.” And he goes on to say, “When radio waves were discovered, they weren’t called radio waves because people didn’t know what their use would be.”

And we could multiply that and many of the scientists on the Commission, as well as those of us who appreciate regulatory parsimony. And the reason for it is we want to explain more, but the question I have is in this case, in the case of *Particle Fever*, from the beginning physicists were working together in a collaborative way from multi, from different perspectives because to make this happen, they had to because there is a huge collider that has to be created.

Is there collaboration now apart from the BRAIN Initiative? We are going to be asked are we going to recommend something like an ELSI [ethical, legal, and social implications] for neuroscience? How much collaboration is there right now among different, it is a huge community?

DR. MAYBERG: Well, I think it depends, again you can’t overgeneralize. I mean in my community, we’ve kind of with the help of actually President Wagner, I mean we now have a center to enable bidirectional translation between engineers and psychiatrists and neurologists and neurosurgeons, partly kind of motivated by the fact that there was a lot of redundancy in our own institution, and that we could leverage everyone’s expertise so we didn’t keep making mistakes.

But I think in the bigger picture, there are always, I mean everybody knows that no one does anything alone with this. You have to have the basic scientists, who actually if they are going to scale up what they do with measuring thousands or millions of neurons, they have got to actually know that a mouse and a worm doesn’t naturally scale up. Maybe it does, maybe it doesn’t, but that the reverse translation also has, so I like to think of it as a bidirectional translational approach now. And it has been a forward translation, not always a bidirectional. And I think everybody who works in this knows that. I don’t think you legislate it, but everyone is realizing you can’t get there without doing it now.

DR. GUTMANN: Yeah, and of course the collaboration with ethics is important too given the subject matter of neuroscience.

Yes, Paul?

DR. FORD: So, I think particularly when you think about the deep brain stimulation group, I think you have some excellent opportunities for collaboration. Helen and I have known each other for a number of years. We have been associated with centers that have been in competing trials or trials funded by other mechanisms. And you look at that group, and the ethics and the neurosurgeons and the neurologists all work fairly well together when we come across these issues.

So, I think there are paradigms for the ELSI to work nicely in this community because this is a demonstration that whether it be Paul Appelbaum or Paul Holtzheimer or others

that are working at different centers, when it comes to the ethics, we have come together a number of different time and ways. So, I think it is a possible group for collaboration.

DR. GUTMANN: Paul?

DR. APPELBAUM: There are also models that can further facilitate that, so NHGRI [National Human Genome Research Institute] for example, The Genome Institute and a number of its genomic sequencing grant initiatives has required, along with the science component, an ELSI component. There may have been some people who would have done it anyway, but when it comes as part of the requirements of a RFA [request for proposal], then it certainly happens. And by compelling, if you will, those parties to work together, it has also built longer term relationships that will allow in the future more work of this sort to take place on a voluntary basis.

DR. GUTMANN: Yes, John?

DR. REPPAS: I think it is worth differentiating between this type of cooperation at the discovery or the preclinical level and at the subsequent level. So, I think what we are talking about here, and to your example, I think academic collaboration in terms of let's say qualifying a target, which is what we're talking about here, whether it is a place to put a DBS electrode or whether it is a molecule to target. I think there is a pretty clear cut case, although it is very hard to implement in real life to everyone getting along.

I think once you have that target qualified, right, and once we all can agree I'm going to put my DBS electrode there to go after medically resistant depression, if that's the place to go, then you have this problem of who pays for those studies to actually go out and there show that works? Okay, and right now the existing model, as you all know, is it is the private sector that comes in, right. It is the people who front the risk capital. There is some federal involvement in this. The NIH [National Institutes of Health] does some of this, but for the most part, if you are going to go out there and basically go after a new indication, it is either a big public company or it is a venture capitalist, right?

And to your point, Dr. Michael, about reloading, you don't get a chance to reload. Once you've blown through 40 million bucks and you've missed your end points, it is game over, right. The plug gets pulled, right.

And it is terrible not because you may have just missed your end points, and you may have created a substantial amount of clinical and public health value around the technology, you just didn't set out to do what you said you were going to do. The problem is what happens with that information? Well, right now it basically disappears. And I'm going to challenge my friend Carlos here and say that the one person who knows what happens is FDA, right. And the most useful repository for all of this information, which is...

DR. GUTMANN: So Carlos, you are for the purpose of this discussion...

DR. REPPAS: He's the man.

DR. GUTMANN: ...FDA, you are the man.

(Laughter.)

DR. REPPAS: But the sad thing is here when I go out there and figure out a new space, the people that I can talk to, which are the best people to talk to, are actually investors because there are some investors out there who know why everything failed, and they know where the bodies are buried. But it is a sad statement on the way things work, that they are the people that you can turn to, some neurosurgeons let's say, but for the most part it is the investors who really understand this. And yet FDA is sitting on a whole lot of useful information that tells us how to iterate around technologies that may have just missed their end points.

So, I would say if we are going to throw out suggestions, and this is a big suggestion because it is never going to happen...

(Laughter.)

DR. REPPAS: ...but let's try and unlock some of this clinical trial value that the regulators have.

DR. GUTMANN: Yes, Peter?

ADMIRAL DELANY: We have now actually moved from corporate entity as a person to an agency as a person, and I'm very scared. Actually, I want to follow up on this one because this is something that used to, is something of great concern, and there's two pieces to this. One is: you get your next grant not from using your previous data. I mean I don't know if it has changed in other things, but for the most part when I was an NIH project officer, you went out and continued to collect new data; and there is this kind of goal that you make it available. I have not seen it really happen much. So maybe it is happening, and I'm just not paying attention, but I've tried to get data from some of my colleagues, and that doesn't happen.

So, I think what you are saying it is not just FDA or that new corporate entity, but I think there really isn't a mechanism that is making much of the data that people are collecting so they can pull these things together. It happens sometimes on some of these big projects like the BRAIN Project or the Genome, but there are tons of little studies that are going on those really pulling different kinds of datasets together.

The other thing, and this is the corollary too, is there is this big problem with how a lot of our researchers continue forward in their career. They don't get credit for some of the things we're kind of throwing out. So you are also talking about changing the corporate culture of academe as well as in some sense private sector.

So that is a discussion. And to me that is a tipping point. If you can get to the point where, I started pushing social workers in my background to start coming to NIH. First of all, they kind of published often in the "Journal of Obscure Findings"...

(Laughter.)

ADMIRAL DELANY: ...with 10 people, but they didn't get credit for (a) interdisciplinary work, but they also didn't get credit or time to start writing after big grants. They got credit for different things that were kind of siloed. And we are doing less siloing, but there is still a lot of mechanisms to go that if you really want to make this the norm, they are not there yet.

DR. GUTMANN: Deven?

MS. MCGRAW: I just wanted to follow on on that point. So, there is an Institute of Medicine committee that is currently looking at developing responsible strategies for the sharing of already collected clinical trial data. And it is not the only effort. I sit on that committee, so that is how I know it. It's in the study phase now, so there is not much that I can disclose other than to say that in public meetings, all of these issues have been raised, including academic credit for finding new ways to use pre-collected data, which you are all aware of. So, I just wanted to put that on the table.

DR. GUTMANN: Nick?

DR. BOSTROM: Another one of these suggestions that will never be implemented, but if we ask about say cocaine, heroin, crack cocaine, why are they banned, so it is because, well, they are addictive and long term use is extremely dangerous to your health basically. So that is a good reason, but there is like one group of people for whom those concerns would not apply, which would be the terminally ill. So, it doesn't matter if it is addictive if you are going to be dead within a few months anyway, and the long term doesn't exist.

So, you could propose that rather than having people go out with a whimper, sort of withering away from horrible cancer and at best having some pain alleviation, why not let them go out with a bang?

DR. GUTMANN: There is morphine.

DR. BOSTROM: It makes kind of sense. Yeah, but at most that kind of sedates you and takes the pain away. Why not have something more uplifting to look forward to?

DR. GUTMANN: We have gone far away from neuroscience as far as I can tell right here but go ahead.

DR. SMALL: I'm going to change topics back to data sharing. I just wanted to mention that there are independent organizations trying to work on data sharing as well. So, the Organization for Human Brain Mapping, for example, of which I'm a member, has put together a committee. And the committee has on it a lot of editors, and the editors of the highest impact journals that publish imaging findings got together at the last Human Brain Mapping meeting and talked about requiring that everyone who submits certain kinds of imaging articles to these

journals would be required to submit their data in certain formats to data repositories. That has been tried, and it has been successful in some domains already. There are some such repositories but never a huge concerted effort across lots of journals.

DR. GUTMANN: That is one reason why we don't as a Commission, I mean these examples are a reason why the very same people who would nod in approval of no more regulation, will also recommend some new requirements of data sharing, for example. And that's, you know, consistent, perfectly consistent with regulatory parsimony. We are not saying that there should be no requirements if you can determine by looking, by backward looking studies that those requirements are essential to actually make the public investment in science maximally pay off for the public. And there has been a big move in more data sharing of late in ways that raise no privacy, some of them raise no privacy concerns, and are really important.

Similarly, with collaborations, if you have a science, which is in its early stages and has some ethical risks attached to it, to require that a major grant has an ethical component and some investigator who has expertise in this area, that is something that is well, you know, at least jumps the initial credibility bar and worth looking at. So those are all things that you've thrown out that we really will take very, very seriously.

DR. SMALL: I just want to point out...

DR. GUTMANN: And I see Steven is eager to...

DR. SMALL: I'm sorry.

DR. GUTMANN: Go ahead.

DR. SMALL: I just want to point out that although this is mostly, a lot of these data are basic scientific findings, I just want to point out that to do all the targeting that everyone is doing for intervention, relies pretty heavily on these sorts of data. And so it has some value to the clinical world as well.

DR. GUTMANN: Absolutely. I am aware of the value of time for everybody, and I don't want to have, over stay your welcome. You have been fabulous. And we encourage everybody to continue to communicate with us. Any follow ups, we would be eager to hear. But I realize that the time has come for us to thank you once again, and we do thank you very much. It has been very edifying.

(Applause.)

DR. GUTMANN: And let me just say that I want to thank my fellow Commission members and our vice chair, Jim Wagner, who is not only an exemplary vice chair of this Commission but, as Helen said, practices some of what the Commission preaches in the collaborations he has encouraged at Emory University.

Please anyone who has comments, submit them on our website bioethics.gov.
And I want to ask Jim Wagner to make the concluding comments.

DR. WAGNER: I really also thank you all for the wide-ranging comments that you've made and your contributions helps open our minds to some things, but also helped me, and I think several of my colleagues, to converge on some things, which is so important for this next step in our activities.

Thanks to the commissioners. Amy, always, as always, thank you for your leadership.

DR. WAGNER: Safe travels to all.

DR. GUTMANN: Thank you all.

(Whereupon, at 4:25, the meeting was adjourned.)

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