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for the Study of Bioethical Issues

TRANSCRIPT

Roundtable Discussion

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DR. GUTMANN: Welcome back. So we asked each of you a deceptively simple question but it requires you to prioritize because we are just going to go down the line of people and ask you to pick one single issue that you believe is most in need of our attention as we write a report on the ethics of neuroscience research and the potential applications of that, of the results of that research. So if there was one thing and only one thing, and don't make it the global thing, but if there's just one thing that you think is ripe for our recommendation or our recognizing as a finding, because we do findings and recommendations in the report, what would that one thing be? It has helped us enormously in asking this question to get a sense of our presenters' priorities. So let's begin over here with Dr. Chowdhury.

MS. CHOWDHURY: I think that what I would suggest is more of a finding, and that is really that my take-away from today is that it is very difficult to try to find a commonality across the diseases in terms of the critical issues that are being faced. On a very high level you can, but I think the Devil is in the details, and as you go deeper into the particulars of the disease, into the state of the research and the state of the science, into the state of the genetics, into the state of whether individuals are able to consent, whether there is an aspect of the disease that may prohibit them as the disease develops, it becomes trickier and trickier. I think at least from the panel that I was on I thought that that really was highlighted. And so I think my finding would be that it is not going to be simple to kind of find a resolution to the issues that you were tasked with that cuts across all diseases, and instead it will have to go probably disease by disease.

DR. GUTMANN: So the implications of doing neuroscience research are that there really has to be focus on particular diseases. Is that -- or on particular issues.

MS. CHOWDHURY: Issues within the diseases.

DR. GUTMANN: Which may cut across diseases, like depression.

MS. CHOWDHURY: Exactly.

DR. GUTMANN: Okay. Got you. Dr. Nissenbaum.

DR. NISSENBAUM: I think speaking about the realm of data and access to data, data flow, maybe the one thing I would say is that we resist some of the tendency that we are experiencing because of the push for big data, and that tendency is just to want to aggregate, aggregate, cluster, and so on, and find a way to recognize the value of these contextual boundaries in particular to really maintain a very thick barrier between some of what's going on on the scientific side and, for example, the commercial actors who are going to want this data, government actors who are going to want this data, and even within the scientific context to separate out in a more delicate way the data as it operates within the clinical arena and also within the research arena. Because I think there are different norms, there's different histories. So just kind of maintaining of separation.

DR. GUTMANN: Thank you. Dr. Dresser.

PROFESSOR DRESSER: I'm not a doctor, but thanks.

DR. GUTMANN: I'll switch to first names. Rebecca.

PROFESSOR DRESSER: Professor Dresser, which sounds like Dr. Doolittle. I would say I very much agree with the first statement about look at the fine grain quality, and I would take it down to individuals. So there will be individuals who are capable of consenting to research and happy to participate and have a good experience. There will be those who initially consent, decide it's too much for them, and want to drop out. There will be those who, when you ask them, they are capable of consenting but they don't want to. And those preferences have to be respected. People who are incapable will have their surrogates. Some will be better than others, so you have to take that into account. Some incapable subjects will be fine in the studies

that they are participating in, but others will have distress and need to be withdrawn. So avoid sweeping statements, I would say. Thank you.

DR. GUTMANN: Thank you.

DR. CORRIGAN: Don't forget what makes neuroscience different from other health conditions, which is this impact on behavior. And so if you are going to look at behavior, you need to learn from what NIMH is doing in setting up its science agenda which is people with lived experience need to be at the table.

DR. GUTMANN: Okay.

DR. SIMON: Since Pat already said the most important thing, I'll have to go to number two. And that is we could really use some help I think with the more fine-grained and maybe even neuroscience- informed understanding of this concept of diminished capacity. And if what we are thinking about when we think about capacity is the capacity to understand and weigh risks and benefits, I'll get a little nerdy about it, but if we think of risks as a signal detection task, and what I mean by a signal detection task is, if I'm saying is this a high risk for me, I need to have some discriminate ability, can I tell a higher from a lower risk, but I also may have a general bias toward risk which may be a stable characteristic of me. And I think the cognitive aspect of capacity is that distinguishing capacity: Do I rank risks in the same order as other people who we would say have good cognitive capacity. But the general bias is important, and some people may have extreme biases toward averseness; some people may have extreme biases toward impulsivity; some people may have extreme biases toward hopefulness and some toward hopelessness.

I'm interested in this question, because when you deal in some of the areas I work in, for instance, suicide prevention, we might define the suicidal state as one which has an incredibly

intense hopelessness bias, so that if we were asking people to weigh benefits, they might make a really biased assessment but their cognitive ability might be completely intact in terms of their ability to talk about differential levels of risk and reward.

So what I'd encourage is some more serious thinking about this concept of diminished capacity and can we unpack it and even be informed by the different tasks, neuropsychological tasks that people are being asked to do.

DR. GUTMANN: Can I just quickly, would you agree, and Rebecca agree -- you're all, or a number of you are pushing us to disaggregate and look at individuals, but would you agree that there still needs to be ethical lines being drawn here between when somebody with X capacity should or should not be ethically enrolled in research?

DR. SIMON: Absolutely, but I don't --

DR. GUTMANN: We still need the principles to guide us in drawing the line.

DR. SIMON: Right. What I'm saying is I see at least two critical dimensions, and there may be more, and I think if we try to draw one line on something that has two dimensions, we'll never draw a line.

DR. GUTMANN: Got it. Giorgio.

DR. ASCOLI: Much of what we're learning about the human brain does come from research on animals, and I would plea with a strong statement of inclusion for no excuses on data sharing from animal research. On the elevator after the morning session somebody commented that it was disheartening that a third of the data is declared lost or anything like that. The resource represented this morning is considered a success story in neuroscience. There are other fields, and I was just talking to a colleague the last break that is in electrophysiology, and maybe one percent of the electrophysiological data is shared. So I think the situation is not even as

good as it might seem. I think that a strong stance on the fact that it is the ethical and right thing to do to share data, at least that is funded by public money, would go a long way.

DR. GUTMANN: Thank you. David. Let me just say on the animals we do have to, if we are talking about a lot of this research being animal research. We do have to support the highest ethical standards for animal research as well. But the highest ethical standards for animal research does not require the -- it doesn't overlap with the privacy and informed consent issues, but there are other issues of research on animals. Okay.

DR. WRIGHT: That's an interesting concept, proxy consent in animals.

DR. GUTMANN: There is, actually. Go ahead, David.

DR. WRIGHT: I think the number one take-away for me would be to explore novel models of conducting research in scenarios where subjects or patients have reduced capacity. EFIC is not the only model out there that has been described, and there are other potential models that we could explore, but it is right now one of the few tools that we have in the tool box. My concern would be to just be careful to avoid regulations without evidence of their practical impact or that they're really meeting the goal for which on paper they look like they're meeting.

DR. GUTMANN: We have a principle of regulatory parsimony which we have abided by with success to date and think have had very good response to that, which is not to say no regulation, but it is to say set a very high bar of certainty that the regulation is necessary and will be effective compared to its cost. And we are flooded with regulations in this area. Please.

MR. JOHNS: When you asked the first question of our panel, you asked about the underfunding, and I would say if you have a chance as a commission to make a recommendation across these issues to better fund them, I would pick it as the most important thing. Over and

over when we have seen issues adequately funded -- there are brilliant people working in all of these fields. Adequately funded, it's a little imperfect, but I believe they succeed if they are adequately funded.

DR. GUTMANN: Do you go by William or Bill?

DR. GRAF: I go by William. So thank you for this session on life span. I'm at the end of the table, and pediatrics gets not much, 3 percent of the healthcare dollars for pediatrics. It's always not much. All of these other issues are very important. We talked about advanced consent that has nothing to do with pediatrics, so it was a concept that doesn't apply.

I'm very interested in teenagers who are taking amphetamines and college students taking amphetamines, and I've written about that. But I think the biggest single issue is what's about to hit with prenatal diagnosis. I keep on emphasizing that. In this country guns and abortion are the two big issues. They are the most controversial. There's the culture wars. People talk about this all the time and it affects elections, but with the new era of eugenics and prenatal testing which is going to be cheaper and more sensitive, this is just going to explode. It's going to affect a lot and it's going to be a big topic once the general public starts to think about this.

DR. GUTMANN: So I open it up now for our commission members to ask questions. And we have several questions from the public, questions from the floor. Since we haven't taken any of the public questions, we have some, so, Jim, why don't you read one or two.

DR. WAGNER: There are a couple of them here. One from Nickalus Flemister from Tennessee State University, a student that's with us, and he's asking about data formatting. He's asking generally if the form of data, data formatting and compatibility confounds somehow the ability to share data. Presumably all the data you posted are digitized data, but is there a technological barrier that makes it burdensome for people to participate in data sharing?

DR. ASCOLI: Yes. It's a great question and it is, and there is a barrier due to the tremendous variety of the formats that the data come in. Pervasive practice of data sharing actually helps solving the issue, because as the data become available and is stored in public data bases, those public data bases ensure that all the data is converted in at least a common format. When this reaches critical mass, new investigators starting their own lab might choose their favorite format but they will also ensure that this can be converted into the public format.

And this in fact has happened in the imaging community where at the beginning MRI was essentially a Babel tower of noncommunicating systems, and many of the vendors as well as the labs as well as NIH came up with the so-called NIfTI standard, and now all the new players on the block are also following the NIfTI standard in addition to their own. So I would say that a good practice of data sharing is a solution to the issue of formatting the data as opposed to being impeded by it.

DR. WAGNER: And there is not yet public format, as you say, for these sorts of data, for example, the data your --

DR. ASCOLI: For the data that we are putting on, the morphology data, there is a de facto standard which is the format that in these reconstructions in the --

DR. WAGNER: Those images are conforming to a common public format.

DR. ASCOLI: That's right. So we post both the original source as well as the converted source. But for other fields such as time series and electrophysiology there are no standards yet.

DR. GUTMANN: Do you want to take another question?

DR. SIMON: As we move more into the clinical domain, I just want to echo that and say that the idea that harmonization and formatting is a problem is often a smoke screen to protect the investigator's proprietary interests, and it's not really a major barrier. And if anything, the

drive toward data harmonization using standard formats for sharing of data from clinical studies is an important boost to quality. It makes people do good documentation.

MR. JOHNS: If I could add just one last thing to that, because I personally believe this data sharing issue is just huge. If you take the Alzheimer's Disease Neuroimaging Initiative, which is a model for these kinds of approaches, all the partners, three sectors sharing across all those sectors and the information of this trial, agreed from the outset on that point that sharing would occur. There is now more science published from people who were not originally funded from that work than there is science published by those who were initially funded. So we've in fact more than doubled the return, if you will, on that effort. We are working with the Fox Foundation on an effort to share across ADNI and PPMI so we can learn across the two conditions on what are those two big longitudinal studies. There's just great opportunity in this sharing issue.

DR. GUTMANN: Take one more question --

DR. WAGNER: From the audience, yeah. This is actually on a different subject. Marjorie Timmer, here from Emory University Hospital, asks: When there is any doubt about a patient's decisional capacity, medical professionals tend to be biased, in her view, to believe that the patient is competent when he or she is agreeing and incompetent if he or she disagrees with the medical recommendation. That seems reasonable, seems like a plausible hypothesis. How can the patient's better interest and autonomy be protected against these kinds of biases?

DR. GUTMANN: I think, Gregory, you gave an answer earlier. It's really a good question, and I think you should reformulate your answer because I think it's very important.

DR. SIMON: But I think it's an astute observation that unfortunately in both research and clinical practice the working definition of competence is agrees with me. And so what we

need to do is we need to have a more informed neuropsychological understanding of what are the tasks, what are the tasks in terms of registering information, what are the tasks in terms of being - to order risks and benefits, how do I apply my general emotional tone or my general preference for risks and rewards to that information. Those things I think ideally we should be able to measure them more accurately and understand them better and come up with a definition that's a little more sophisticated than agrees with me or not.

DR. GUTMANN: But earlier you also made the point, in reference to something else but it was the same general question, that there ought to be some individual or ideally small group to whom researchers and clinicians are accountable for the standards and their application of the standards of consent.

DR. SIMON: Right. So when we, for instance, are approaching people who are reporting suicidal thoughts and trying to talk to them about participating in a prevention program, we need to have other people who have lived experience of thinking about suicide or making suicide attempts to talk to us about what's a reasonable and appropriate way to approach people and how do we communicate our intentions.

DR. GUTMANN: Nita.

DR. FARAHANY: One of the recurrent themes today is this kind of idea of what is diminished capacity, right? And so consistent with this question we've just had, Dr. Simon has given us a couple of ideas: The ability to register information, weigh risks and benefits. But I agree, I think it was Dr. Simon who said it would be useful to have a better definition of what diminished capacity means in particular contexts. Each of you are approaching this from a different context, and so what I was hoping is for anybody who might be willing to weigh in on it, what capacities specifically do you think are important for decision making from your

perspective fields, so that we can try to start to air much more specific concepts of what it means to have capacity for decision making and what it means from a context-specific perspective to do so.

DR. SIMON: In the area I work the issue that's really, really difficult to deal with is what I was sort of referring to when I said one's general predisposition, which we might consider one's enduring preferences or personality, but the extremes we might call hopelessness or at the extremes we might call, not to put too fine a point on it, paranoia. So when is it that we say this is a person who has a general mistrust of how other people might use information, and when do we say that shades over into something that we would say is not an enduring preference to be respected but becomes problematic. When is it, for instance, if you are dealing with folks who are thinking about suicide, would we say that a belief that things won't help me, somebody might say I'm not interested in doing that because I don't think that's going to help me, when is that a rational expression of someone's enduring preferences and when is it hopelessness that we say is part of the suicidal process? Those are really difficult.

DR. GUTMANN: Are you now thinking about clinical therapeutic research or are you thinking about research that doesn't stand directly to benefit the research subject, and does it matter? It seems to me that it does matter.

DR. SIMON: The weighing of benefits is usually only relevant to clinical potential benefits. The weighing of risks would be relevant to both, I think.

DR. GUTMANN: Helen.

DR. NISSENBAUM: This is a really provocative question because, again, in the information area most of us are making choices, say, reading privacy policies and not knowing what the heck they mean, and even people who are involved, I mean, general counsel at the New

York Times doesn't know what the information flows are. So when you are asking a person to make a decision like consent when you know that they do not have the capacity to understand what's being asked of them, so the question there is diminished capacity a state of the person in and of themselves, or is it the state of the person in relation to whatever the task is that you're giving them. So a person who is cognitively impaired might know that they are hungry and make a decision in relation to that particular goal, but if it's a more complex task, then we all have diminished capacity. So I'm wondering what the standard is in the first place and how you might want to go with that.

DR. FARAHANY: Sort of like the example somebody gave about being lost, right? I thought that was a great analogy, which is you might have a sense of orientation in space even if you don't have some of the other capacities.

DR. GUTMANN: Yeah, but this is a classic example of not letting the perfect be the enemy of the good. If the standard is perfection, you have to understand everything, weigh it, like your ideal rational actor, who is not my ideal person, but whatever. If the *reductio ad absurdum* is that means, since we can't attain that, we throw out informed consent, I would say that's the worst possible world to live in. So I would rather have a decent, good world in which we accept that people have imperfect capacities at their best. But some people actually who are hungry and manifest hunger don't know that they're hungry. I mean, there are people who are -- I mean, my mother-in-law, who is a wonderful woman and extraordinarily smart until the last weeks of her life when she had a stroke, she was hungry but she didn't know. I mean, she ate. She had the reflexes of wanting to eat. She had a survival instinct, there was no doubt about it, but there was no way we could have said she knew she was hungry. So that is diminished capacity.

I just don't want us as a body here to be skeptical of the idea that there is seriously diminished capacity. I don't think Nita was suggesting that, but I thought, Helen, you might be, that being skeptical of the idea of consent, that we owe it to people to get their consent when they have some capacity to give it. That's what I think is the minimal threshold for respect for persons. And if we throw that out, we throw out -- I mean, it's not the only -- it's necessary but not sufficient, but it is necessary.

DR. NISSENBAUM: I agree with you. I didn't want to do this reductio and say therefore let's just forget about this idea of diminished capacity, but I do think that maybe it has to be -- I don't know. Perhaps it should be considered as a moving target which says that in relation to different tasks, blah, blah, blah.

DR. GUTMANN: I pushed this because I want to refine the point. The point is you have to take into account what's at stake in the context and the range of capacities. We talked about that, the range of capacities. We still haven't answered the precise set of -- but I do want to get on to -- this is an attempt to get things out, but I have a list, so we can come back to that.

PROFESSOR DRESSER: I was just going to say don't reinvent the wheel. There's a big literature. People have been thinking about this in the past commissions and all these advisory groups. And it is task specific, so you have to focus on where there is a study, but there is a lot out there for you to draw on.

DR. GUTMANN: Nita, I just want to get some other questions, so we can come back. Christine.

DR. GRADY: My question built on this a little bit, but I want to take advantage of the fact that I have the microphone to say something I wanted to say this morning, and that is in relation to -- I think John presented the recommendations that have been made in the past on this

issue specifically as a failure, that nobody has come up with the right responses to the recommendations. And I want to recognize that I don't think it's totally a failure. There may not have been, there have not been really new regulations or new guidance from the federal government, but there has been a huge body of research on this particular issue, as Rebecca just said. You know, what is capacity? How do you measure it? There have been tools developed to try to help people do it. It's not finished and it's not perfect but there's a lot out there.

There also have been some regulatory changes. I mean, the EFIC I think is an interesting example of something that has happened and allows research in emergency settings that follows a different paradigm. So I think those things are good examples of things that have happened that may have fallen short of the specific recommendation to change the regulations.

And since you all heard how much we don't want to necessarily add any more regulations, my question building on that is: Is there anything in particular about the current either guidance in human subjects protection or practice thereof that you think needs to be changed in order to allow the kinds of research that you each promote to go forward more successfully? Whether that's more detail about capacity assessment, whether that's a new regulation on a model across states, definition of legally authorized representative, I mean, I'm making these things up, but is there anything you can think of in your own field, your own area, that would help in that regard? Anybody?

PROFESSOR DRESSER: I think it would help if there was some official recognition of dual consent, double consent. We heard that some IRBs won't allow that. I think that's a good ethical practice, and so that would be one.

DR. GRADY: Can I ask, just building on that, would you say that is one sort of new model of consent that we consider or the only new model of consent we should consider? See

what I mean? Are you saying let's look at dual consent or let's look at, I think you said earlier, a bunch of new models?

PROFESSOR DRESSER: That's one where I think there has been some material written to justify it. Some of these others I don't know that they've been investigated as well.

DR. WAGNER: Help me. Are we talking about sort of dual consent, the area you were talking about this morning?

MR. JOHNS: Certainly having caregivers participate is something we would encourage in those circumstances, with the consideration, of course, again, that the individual be a beneficiary of the research to not override that kind of benefit. Again, as I answered one of the other questions too, there are circumstances where once diagnosed we have lots of people who say they would like to participate in ways that theoretically they might not have previously. So that needs to all be taken in to account, but, yes, participation.

DR. GUTMANN: I would hesitate to call it dual consent. It raises a question, two questions. One is first what -- so in children, in pediatric research we have this standard where at a certain age the child himself or herself has to say yes, but that's necessary but not sufficient. And then you also need the parent or guardian consent. That's true dual consent, that you need both, they are both sufficient. I don't know if you're suggesting that if you get the consent of somebody with, you know, reduced capacity, then you also need the consent of somebody else as well. That would be dual consent. Otherwise it's not dual consent.

So we should -- I think what we can do here as a commission -- I want to go back to Nita's question as well because we don't have the time to go down and get your precise answer to this, and I don't think it would work if we did. I think we are going to be in the position of recommending that certain kinds of funded research go forward to make it possible for

neuroscience research to flourish in a fully ethical way. And we will need to specify some of the questions like what is capacity, what is the capacity to consent in different contexts. I think there needs to be more. What we're suggesting here, all of you, is that we need some really rigorous research that's context specific that isn't at this 30,000 foot level that in some cases is disease specific but it's certainly impairment specific and data driven. We need more research on that.

A very important data point that we were given is the two-thirds, one-third about people who have attempted suicide, whether they are in favor of being involuntarily committed. It's important to know that. It doesn't solve the question, because there is still a third who say they aren't in favor and two-thirds do, but it's a very important data point and we need more research like that to inform where and how you draw the line on consent to research in cases where without that research we will not be able to move forward in understanding how to diagnose and treat brain disorders. Okay. I have next on the list Dan.

DR. SULMASY: I have two questions, but in the interest of fairness and justice, you can put me down at the end of the line for the second question if it comes up for time.

The first just is sort of a comment on some of what just transpired in terms of discussions about the study of the process of assessing someone's capacity. And it seems to me that while there is a literature on this, the area that seems most understudied, and it may be part of what Dr. Simon has been suggesting and I think is a category that cuts across all of these disorders, is the category of judgment. We are very good at looking at sort of information: Can the person remember it, can they say what the consequences are, et cetera. But the sort of area that we need more work on, I think, is more what many people will clinically say is judgment and beyond the question of what do you do with an envelope that's got a stamp on it that's uncanceled, right, which is the sort of main test question we have. But pretty poor, right?

So people with frontal dementias have a problem with impulsiveness, and that's a problem in decision-making capacity. A person who is depressed can know the information, understand the consequences of buying a gun and shooting themselves, but what's problematic is their judgment about the value of their life, et cetera. And in the general research population at least, I've been involved in some studies with a colleague, Lynn Jansen, looking at something called unrealistic optimism among subjects who are enrolling in trials. This sort of thing is very prevalent in neurologic diseases, the Lake Wobegon effect, you know, their chances of benefitting from the study are better than the average person's. All of those things seem to be not -- that person could tell you, "Yes, I know that on average in a phase one trial less than five percent of people on average benefit from it, but I'm going to be one of them."

So is that, does that sound like a reasonable sort of statement to make, that if we are going to push forward on something in terms of looking at capacity that's not been studied very much, it might be the category of judgment in research subjects.

DR. GUTMANN: Yes.

DR. GRAF: Can I make some comments from the pediatric perspective again, just some different words instead of consent. Pediatrics got away from that word. They are calling it parental permission, and I don't know all of the arguments about why that went back and forth, but it's because parents don't own their children, they are the stewards of their children, they are the fiduciaries of their children, and they are speaking out in the best interests of their children, and they are the best people to speak in their best interests, which is what fiduciary means. So we have assent and then we have parental permission.

Our definition for teenagers for decision-making capacity came from two resources in the literature: "Decision-making capacity requires the abilities to receive and remember

information, to engage in mutual questioning and answering, to assess relevant information, and to use information to make and justify a decision." So it's a whole process and it does have judgment involved, definitely. But that's very difficult to measure. But I think if you are going to have dual consent, then you have to think also of the permission concept from next of kin, that type of thing. Maybe a different word.

DR. GUTMANN: I think those are the accurate terms. In pediatric research we ask for assent from children and permission from their parents or guardians, and the set of criteria for assessing the capacity is a reasonable set of criteria. They don't lead often to bright lines except in extreme cases, but they are good.

DR. CORRIGAN: I think in trying to drill down to your judgment capacity issue, Greg sort of alluded to this, there is a whole neuropsych literature that struggles with methods of how do you assess that, definitely what Rebecca would say would be very specific to the situation. But I think you may want to look at that literature for how do you assess judgment in some sort of psychometrically sound way.

DR. SIMON: We know that people who have what we would call depressive disorders, for instance, will tend to overvalue negative information about their futures. People who have what we would call anxiety disorders tend to overvalue threatening information or threatened loss. And to me the challenging question is to what degree do we consider that someone's enduring preference which needs to be respected, or do we say that's a problem.

DR. GUTMANN: John.

DR. ARRAS: Thank you. One quick anecdote in support of Dr. Simon's general point about the mismatch in depressed patients between cognitive and affective grasp. Paul Appelbaum, who has done more than anybody to chart the dimensions of capacity, once talked

about a study of depressed patients involving electroshock therapy, and he explained to one patient that there was something like a one in ten thousand chance of dying from the procedure. And this woman said, "Sign me up. I hope I'm the one."

So beyond the anecdote I want to switch to a very different sort of question. A lot of you have made the point that biology isn't destiny, that a genetic diagnosis isn't a sure-fire prediction that people will actually end up with some kind of disease. And we all recognize that these conditions that you are all talking about are really a complex combination of genetics and the brain and society. So my question is, given that there's a complex etiology for all these conditions involving both genetic, biological, and social causes, what is the relationship between the social science research on the genesis of these conditions and the medical research? Do you think that there's parity between those? You talk about being underfunded. What about social sciences? I can see a lot of people arguing that the reason why there are so many depressed people in this country is because of the way our society is set up. So is there a parity? Should there be? And do the researchers on the social science end talk to the researchers on the medical end? Is there real confluence?

DR. CORRIGAN: We may have both of us here because I'm a researcher in the social science end. We were talking earlier about NIMH, and I would say NIMH is over-oriented to the biological side. One evidence of that is the whole area of services in clinical research, which in the current agenda seems to be waning. The social scientists and the more primary scientists are talking to each other. I'd also say right now, especially in mental health especially from the scientific framework, that the basic biological science is dominant.

DR. SIMON: I would say that I think the new neuroscience, if done right, should be a boon to social science researchers, because instead of having, as I talked about, this gamish of

things where we say a lot of things are related to a lot of things in a very nonspecific way, leaves us without much help. But what we are really interested in, I think, are in those causal chains that run from genes to cells to circuits. We are interested in the disconnects. What we are really interested in is somebody who has a high genetic risk say for PTSD and is exposed to some violent trauma but does not develop PTSD. What is it in that person's environment that helped them so that that did not happen.

The new neuroscience we hope will allow us to measure those intermediate steps, and measuring those intermediate steps I think if anything will bring into focus and increase the value of our understanding of other kinds of differences between people and their environments, because we can actually see them. And instead of having people over here talking about these things and people over here talking about these things and arguing which are more important -- you know, I'm sort of a math nerd so I come to when you have two different types of people who each think what they do is most important, you should search for an interaction effect in the model, because what that means is you're going to find interaction, and in interactions people have to come together.

DR. GUTMANN: As a total math nerd, I totally not only agree with what you said but I think it's important that as a commission we consider saying something to make sure that the origins of the BRAIN Initiative, which are very focused on mapping the neurons of the brain, mapping those circuits, doesn't narrow our understanding and the funding of what will propel neuroscience research, especially as it is going to have the capacity to answer some of these issues of disease and human functioning forward. It's going to be really important that there be the breadth that, Greg, we were just talking about, because otherwise it's going to rapidly hit dead ends. So that's very helpful. Barbara.

DR. ATKINSON: Dr. Corrigan said that people with lived experiences should be part of the whole process, and I wondered specifically what areas you would recommend or we should recommend that you use people with lived experience, I mean, which particular areas of the whole neuroscience research.

DR. CORRIGAN: Well, in the NIMH agenda there are people with lived experience in study sections, there are people with lived experience in councils, so in terms of figuring out questions, priorities, RFAs.

DR. ATKINSON: So you were thinking about it more in terms of the research agenda, not whether they should consider what informed consent in their disease would be or other things. I guess that's what I'm getting at. Is there a broader use of people with the lived experience?

DR. CORRIGAN: So again, more practically the research we do is run by a consumer research partner, so our informed consent process is worked out with them. Again, a very good practical example is doing research with homeless people. Of course, the potential coercion of the services that go along with participating in intervention.

MS. CHOWDHURY: I would actually add that, at least from a Parkinson's viewpoint, we would say that there is value in having patients be part of the IRB review process. I think that often when we -- I've claimed the role of a funder when we speak to researchers and ask why they are not doing X, Y, or Z. In this particular case, lumbar punctures for Parkinson's disease, in terms of the state of the science CSF right now is the most likely candidate for biomarkers or understanding what's going on in the brain. The answer is, "Well, they won't do that. Patients won't agree. We can't do that. We can't ask that." Well, we were the funder and the sponsor of

PPMI, and we made it mandatory to have, if you were five years in the study, seven LPs. And we had no problem recruiting and we've had no problem securing LPs.

So I do think that patients have a voice to play in deciding what is appropriate for a protocol, what's realistic. I also think that some of the practicalities of studies, things like travel reimbursement, timing as clinic visits, if you have a patient perspective, you actually will get better engagement because they will tell you that they need parking or they need this or they need that; whereas, if it's just researchers, that most likely will not come up.

DR. GUTMANN: Christine, you had an unasked question.

DR. GRADY: I might have already asked it. I guess the only one thing that's still troubling me a little bit is this -- I've heard both that there are too many silos, too much distinction, too much mental health here and neurological disease here, and then I heard we have to be really careful to make sure that we think about making recommendations taking into account the specific context, the specific disease, and the differences between diseases. So I guess that feels a little bit like a tension to me. I'm not sure if anyone wants to say anything more. How do you do both of those things at the same time?

MS. CHOWDHURY: Maybe I'll start since I brought it up first. I see what you're saying but I'm not sure I agree that there's such a tension. I think when it comes to research, cutting across diseases is very different than when you look at the ethics of individuals engaged in research. For Parkinson's disease genetics plays a hugely different role than it does in Huntington's, for example, yet our field is informed by Huntington's. We have researchers who say you absolutely cannot tell people their genetic status; it's not appropriate. Why? It's not their destiny. There's a very different role that genetics plays, yet when you ask them, many of them are also Huntington's researchers or movement disorder specialists.

So I do think that across research when we start to look at biological pathways and we're looking at imaging modalities and the sharing of technologies to see whether many diseases can benefit from it, there I see there needs to be a breakdown of the silos. But I do think when it comes to the ethics and the role the patients may play in research and how we engage them in research, the nature of the diseases are different and they have to be taken into account.

MR. JOHNS: I would concur with all that. And there was another discussion earlier that I thought I would comment on that's related, I believe, in the sense that the ability to cut across the federal government activities, for example, is a little bit different in the sense that we are actually then trying to cut across the different entities on one topic, compared to what is the collaboration we can also benefit from across diseases at the same time. Those two are different but both important to maximizing outcomes. Neither of them easy, but they are both very beneficial if they can be improved.

DR. NISSENBAUM: I was one who said keep the context separate. I just wanted to clarify. By that I meant these larger social contexts. So you might have the commercial context where marketplace norms prevail, and I think those silos should be maintained. But I would agree with the idea that within a technical healthcare environment, that the interaction is very important.

DR. GUTMANN: So I want to ask a totally different question to get any of your take on it, because the thrust of what we heard today was very much trying to find a way in which we can increasingly treat those people who either actually or prospectively have an impairment, whether it be Parkinson's or dementia or any number of other diseases, conditions that will affect human flourishing, very much get them to be part of and participating and treat them with the respect and the participation they deserve. So that's sort of the thrust.

So here's my question: To what extent is it threatening to that view of the way to treat individuals with these conditions, the findings, the way that the findings are sometimes, often actually, used as neuroscience research and brain imaging showing that people have, very vividly showing that they have serious impairments of the brain, parts of their brain that are not firing that in normal people do fire to show that there's danger or to have frontal lobe capacity and so on, the kinds of things that some members of the commission like Nita have done a lot of research on that are being brought into trials that show you should treat these people as insane and not therefore competent to be found guilty or innocent and so on.

So there's a whole other aspect of neuroscience research that is to some people's minds showing that there are people who are not functioning as normal human beings, and other people say that they shouldn't be held responsible, and if you can't be held morally responsible for things that you do, how can you be seen as competent to consent to research. So you see what my question is. Is that threatening in some ways? Is that something that we as a bioethics commission should worry about the use of neuroscience research?

This is not science fiction that I'm talking about. It's here and now. There are neuroscience researchers who are showing pictures of individuals, very specific, very context specific, very purposeful images of people's brains and trying to establish that those people are not competent to be held basically morally responsible. If there is any ethical implication of neuroscience research that has gotten the most journalistic attention, it is that. And if you are going to go that route, it is pretty darn hard to go the route that a number of you have been urging us to go, which is to have a much more nuanced, context-specific, so on, understanding of the competence of individuals who are suffering different forms of brain diseases or disorders.

You all look some version of stunned by this question. It is a version of can we have our cake and eat it or is there something wrong with this picture? And there are fantasies going on that are actually not so conducive to the views that you want to move forward in neuroscience research.

DR. SIMON: The easy way out would be to say I think we -- I have to say there's capable and there's culpable. I'm interested in the capable part, and to be honest with you, not terribly interested in the culpable part. The culpable part comes down to dichotomies, and all dichotomies in the end can't stand up to any sane scrutiny. But we require those dichotomies anyway because they're -- well, maybe there are three verdicts. Maybe there's guilty, not guilty, and guilty but mentally ill, but there's still only three categories.

I think what this brings up is maybe the same kinds of data, the same kinds of information might be used to inform those different decisions. But I would certainly hope that if we are interested in understanding and improving capability, that we would be able to somewhat insulate ourselves and say the culpability questions are totally different questions. I don't think they're measured on the same axis at all.

DR. GUTMANN: With all due respect -- whenever one says that, with all due respect, you know I'm going to disagree with you. With all due respect I think it is -- it would be nice for this discussion if we could do that, but as Nita was shaking her head, so I have to say if the legal standard were so neatly cordoned off from any question about capacity to consent, then it would work, but the legal standard isn't cordoned off from that. It's understanding the consequences of what you do. And if you can't understand the consequences of your actions, then you can't consent to research, because you don't understand the consequences of that.

Now, it's not the same people who are in the courtroom, but the push of some neuroscience researchers to claim that they can show through these images that somebody is not capable of understanding the consequences of his or her action, I have to submit to you, and this is where going across boundaries really matters, does threaten many of the claims you want to make for the capacity of individuals to consent to research.

DR. SIMON: All I can say about that line of work is I don't do that, and for good reason would choose not to, because I think the idea that it is somehow deterministic, you know, that any of these things we measure or even conceivably in the future could measure. I was talking earlier about the idea of, you know, the model that includes all the interaction terms that ultimately explains these things is going to be a pretty complicated model with a lot of inputs that don't show up, at least right now, on an FMRI.

DR. GUTMANN: Well, determinism per se is not wrong. Sometimes things are deterministic. But I think it is the case, and I've read a lot of this literature, that the claims, the hype that's being made for what you can tell right now from these brain images is wrong and it's threatening the more subtle and nuanced and important claims that you were making of the interaction between what is physically determinate in the brain and the environment.

DR. SIMON: It's an amusing historical artifact that in I think it was the DSM-III of the American Psychiatric Association, or maybe it was the III-R, the preface had a very clear statement: "Nothing in this book should ever be used for purposes of legal determinations or deciding if people are disabled." And, of course, that's where all the sales went, if you look at who is buying copies of the manual. To my mind it is a misuse of a scheme of understanding that really was not developed for that purpose. We probably have to accept that any scheme will be misused to those purposes, though.

DR. GUTMANN: Raju.

MR. JOHNS: Just one last thing on that, some of this may have to do with the very nature of the discussion earlier about what's cross-cutting and what's different. I'm not the scientist, but in Alzheimer's one of the things that is absolutely known fact is that you can have the accumulation of the plaques and tangles which are signature to the disease and have no symptoms. So in this particular situation it may well be, and again, I think it's a situational measurement here, in this case you will likely see to the best of my knowledge the behaviors through the symptomology as much as you would be able to identify it on what would be a PET scan, for example, with the appropriate lighting of those plaques. So again, it may well vary across the spectrum.

DR. GUTMANN: But the important thing about that research, which I've looked into, I don't do it, obviously, but I've really read a lot about it, is you can have the symptoms, the physical symptoms in the brain, and not manifest the behavior. You can also have the physical symptoms and manifest the behavior in some cases and not in others. And that suggests that even when you manifest the behavior, we don't know the extent to which it's totally determinate by the physical symptoms. And that we see over and over again in the combination of medical and social science research. Things like altruistic behavior are very context dependent. They are not simply, as much as we might like to believe it, just a consequence of character training. They are very context dependent.

DR. WAGNER: Steve may have a comment on that.

DR. HAUSER: Can I just weigh in on this? Is much of the question the strength of evidence and whether we are dealing with an observation that has in rigorous ways been shown to be adequately specific and sensitive based upon the thresholds that we think are reasonable?

DR. WRIGHT: And even at that its population science and you can't necessarily apply that to the individual. It's right in front of you.

DR. HAUSER: Absolutely. So to move to a single individual, one needs to have a highly sensitive and specific observation.

DR. GUTMANN: Yeah. And I would just say that that's part of the ethics of neuroscience given what has been put on the table at stake here, that we make sure that that's integrated into the claims that are made publicly for it. Raju, you have been patient.

DR. KUCHERLAPATI: Amy, I just wanted to comment about whether or not, the question that you raised about images, whether they can be used in the courtroom to consider an individual competent or not competent. I cannot answer that particular question, but the whole drive in the last 30 or 40 years, certainly in psychiatric and neurological research, is to get away from the notion that psychiatric illness is not just an environmental problem, but it has a biological basis like any other disorder. So if I have a lung cancer, it is possible to be able to take an image and that would be incontrovertible evidence that I have a lung cancer. And we may not have such an imaging methodology today to be able to determine whether somebody has a particular psychiatric illness, but that's the goal.

So I think I would imagine that whether it's imaging or some other kind of biomarker that could be used to be able to assess whether a particular individual has a particular type of illness would be fantastic, and we might actually get there. So I don't know the legal ramifications and implications of that, and it may not be there today, but we certainly hope that it will be there.

DR. GUTMANN: We might get there and we might hope that we would get there, but might and hope doesn't -- the fact that we have the image for lung cancer, there are other diseases

that we don't have just the image for, and it may be the case that we won't for a long time have the image in the brain that maps directly onto the disease.

DR. KUCHERLAPATI: I don't know about that.

DR. GUTMANN: But we don't have it now.

DR. KUCHERLAPATI: We don't have it, but I think my level of -- I'm not talking about when we will get there. I guess what I'm saying is that's the goal of being able to do these types of research, to be able to more accurately diagnose patients with particular types of illnesses. And if we know what the diagnosis is, that we'd able to provide whatever the appropriate treatment for them will be. So it may not be there today but it will happen.

DR. WAGNER: By studying the morphology and function. That's the whole purpose for the Brain Project, right, was to see how closely we can tie all of these things.

DR. GUTMANN: But nobody has disagreed. But don't confuse that with accepting what any researcher says you can read into an image. And we are now in an era where many, many, not just one or two, but many researchers are reading into images things that no good science will allow them to read into. And I think that's a serious problem.

DR. WRIGHT: It was called phrenology at the beginning of the century.

DR. GUTMANN: It's a serious problem we have to deal with.

DR. SIMON: When you think about where will this take us in terms of diagnosis and classification, one of the problems we have, I think at least in my field, is that these categories we use, these diagnoses, blend two totally different conceptual tasks. One task is what I call the walls of a condition, which is what separates it from its neighbors. And the other is what I call the floor, which is what separates it from people who don't have any problem at all.

The walls, I expect we should be able to do much better with that. We should be able to say this thing we call schizophrenia is not one thing; it's six different things, there's this, there's that. The floor is fundamentally not a neuroscience question. The floor is a social and cultural question, and neuroscience will never define the floor. We can't expect neuroscience to ever say -- if we no longer talk about depression but if we talk about a particular way, for instance, of processing emotionally relevant information, this sort of biased information processing characteristic, what we might be able to do is define that in a neuroscientific way and to identify much more clearly. But what we wouldn't be able to do is, since that trait, that characteristic will certainly be continuously distributed, neuroscience will never say where you draw a line on that continuously distributed trait and say what do you call diseased or what do you call ill. That will ultimately be a social cultural question.

DR. KUCHERLAPATI: It's not too different from other types of medical conditions such as hypertension, for example, which is a continuum. But we know who to call hypertensive and who not to call hypertensive.

DR. SIMON: Well, maybe, but I was a general internist in a previous life, and I know that number changes too. The LDL threshold, the diastolic threshold, the systolic threshold have all changed in my career. So they're practical decisions in that case based primarily on our therapeutics. If we had therapeutics which worked better and had fewer adverse effects, our disease threshold drops. Nothing changed about the fundamental nature of the condition. What changed was a practical question about our interventions.

DR. NISSENBAUM: I just wanted to weigh in a little bit because I'm really taken with this idea of using it in a court of law. The standard there might be beyond a reasonable doubt. It's not going to be one hundred percent. We have all these probabilistic estimates, so you might

look at the brain picture and say the chances are such and such; of course, it's not hundred percent but it's very high. What we're seeing in the use of probabilistic information, maybe in a court of law the area is very formally controlled and judges are very experienced, but there are ways -- I forget who introduced this idea of the lengths people will go to for marginal gain. I forget who introduced that idea. But in the commercial arena in advertising, this question of discrimination comes -- insurance. People's lives are being affected by only, you know, marginal gain, by probabilistic information we have based on some indicator. And I think that neuroscience -- you know, I don't know if you've heard of that neuroadvertising, the use of --

DR. SULMASY: Neuromarketing.

DR. NISSENBAUM: Neuromarketing. So although in some very rigorous environments we're not going to go in that direction, I think for those who are not, who don't have to meet those standards of beyond reasonable doubt, whatever standard that is, there is the danger of misusing the discoveries we make on an individual basis and also on an aggregate basis about the way our brains work and how we can manipulate through various impetuses, or what's the plural of that, impeti.

DR. GUTMANN: Nita.

DR. FARAHANY: I've remained quiet a little bit as we've thought through this issue of culpability in the courtroom because this is an area that I focus primarily on in my research. I think I agree with Dr. Simon entirely, which is it's wrong to really import wholesale medical diagnostic criteria which is designed for diagnosis to try to answer normative questions about culpability. And yet it does happen quite a bit. There was a recent Supreme Court case that was looking at the definition of mental retardation for purposes of execution, and quite a bit of debate about this mismatch but failure of the legal system to come up with its own normative standards

to be able to answer important questions. Thousands of cases over the past ten years have used neuroscience to try to answer various normative questions in law, from neuroimaging to different types of neurological testing, and we are at this point where this question about diminished capacity or capacity needs to be defined in every context. And so the question that I presented to all of you earlier, which is which particular capacities matter for decision making in the context of your own research, I think matters a lot, because there's a lot of overlap in law for the types of capacities you need to be blameworthy, to have competency, to be able to assist in your own defense, to have psychotropic medications, lots of different questions, but I think it varies by context. And so to your point earlier of we have to really talk about capacity in context, I think that's right, and I think that's an ethical and medical question. It's a question where we can say what are the capacities that an individual has but what is it that we care about, what kinds of capacities do we care about for a person to have in order to find them blameworthy, in order to find them able to participate in the clinical trial, et cetera. I just wanted to kind of echo and agree that it can't answer and yet it does potentially bear on questions in law, because if we want to know if a person is competent to stand trial and we say here are the capacities you need and you'd be able to understand the proceedings against you, to be able to understand the consequences of a punishment, to be able to understand what's happening, those things are things that medicine, science can help us answer; they just can't answer what questions we want to answer to begin with.

DR. GUTMANN: Do you want to -- you had a list earlier that you gave us for pediatric consent, and it was a darn good one.

DR. GRAF: Which again is summarized in the literature.

DR. GUTMANN: I think it would be good for you to -- do you have it? Say it again, because I think it would be good to see if people have different criteria for adult consent. This is for pediatric research.

DR. GRAF: We had a word limit. We were trying to get this into a nutshell. After reading two books, this is what I came up with.

DR. GUTMANN: I don't believe when we do these things orally that we can have the same precision as when we write things down in our reports, but we can at least get out some of the major criteria that exist in the important contexts we are dealing with, so go ahead.

DR. GRAF: "Whereas the principle of individual autonomy is recognized as the basis of medical decision making in adults, autonomy cannot be an analogous principle in children and those adolescents who lack full decision-making capacities. Decision-making capacities require the abilities to receive and remember information, to engage in mutual questioning and answering, to assess relevant information, and to use information to make and justify a decision."

DR. GUTMANN: Any additions to that?

DR. ARRAS: (Inaudible)

DR. GUTMANN: I think it's important, if we are going to be in the spirit of this, this is in the context of asking children for assent where there is a dual requirement that children assent and that parents or guardians give permission, and the criteria for parents or guardians is going to be more rigorous than for the children.

DR. ARRAS: I'm sorry. I thought you were asking if we could carry this over to the adult sphere.

DR. GUTMANN: I'm asking what more, because you need more rigorous criteria for adults.

DR. ARRAS: So maybe one would be you'd want the decision to reflect a subtle pattern of values of the person.

DR. SULMASY: I was going to say there's a sort of sense of that authenticity, sometimes talked about as stability, whether this is something that's been there persistently. There's another problem that comes up clinically all the time in delirium where clinically lots of people say, "Oh, they're not seeing pink elephants right now, so therefore I can get them to give consent," where they will see pink elephants again in another hour. They may have said no before and now they're saying yes. So there's stability both short term and long term. And I think significant is the ability to express one's decision. I think people who, for instance, have, to the extent you can get a pure expressive aphasia, will not be able to tell you that they understand and can manipulate the information, et cetera. So to some extent, while I might believe that the lights are on and the person is getting it, I can't necessarily make a judgment that person has decision making capacity. I think what we got was a sort of useful sort of general summary of, as you said, books, but the total area I think is much more complex.

DR. WRIGHT: I think also, at least in the context of the research that I do, you need to have a higher bar for saying yes than you do for no, so they need to definitely have some capacity to be able to say yes to the research, but even minimal capacity they can say no. So it's a different set of rules.

DR. NISSENBAUM: I wanted to say something about this area that's a little peripheral, which is that when you are presenting either patients or research subjects with these choices to which they either or must not consent, and we've been really focusing on the subject's consent and what are the conditions to make it meaningful and so forth. The one part of the story that we haven't really focused on, and as a privacy researcher it immediately attracts my focus, is what

are researchers and clinicians allowed to ask of research subjects and patients. And the reason I think that I have more trouble with consent than maybe others in this room is that you perhaps are making assumptions that whether or not the patient or the research subject wants to consent or not, the clinician or the researcher will not be posing immoral or unacceptable choices. They are all going to be within a range of acceptable professional behavior; whereas, in the world that I inhabit, the choices that are presented to people could be violently tricky and violently against their interests and so forth.

DR. GUTMANN: Just give an example, since you are carrying some example in your head.

DR. NISSENBAUM: I'll give you a very trivial example. When you go to a store and they say can you give me your Zip Code, what you don't know is with the Zip Code they can unearth this huge amount of information. So you are giving your consent to give your Zip Code, but in fact through that there's all this other stuff that comes along. It's like a trick thing. They are baiting you with a certain thing but you are not aware that all this other stuff can follow from it. And so that's part of the story that I want to hear that I would urge. The researcher has to be able and the clinician -- I trust the researcher and the clinician to be doing basically pro-social things and things that are beneficial to individuals within a certain acceptable range. And I think that if I'm reading this report, I want to hear that this commission is paying attention to that.

DR. GUTMANN: So just for the sake of our commission making clear what we are on record and will continue, we are absolutely committed to the idea that consent is not enough. It is never enough just to get consent. You have to know -- there are certain parameters of what you can do with consent that are fine, and there are others that are off ethical limits. We have to be more specific about it and give specific contexts, but consent, because individuals can't

possibly in some cases anticipate the possible effects of their consent and it is not reasonable to ask anybody in a medical context, let alone in the context you're talking about, to actually absorb all the possible bad things that could be done with consent, that's why professional ethics has real bite that goes way beyond consent alone. So that's important. John.

DR. ARRAS: Just, Helen, really quickly, ideally that's what the function of the institutional review board or IRB is. The IRB is there to assess whether certain offers are legitimate and whether others are too risky.

DR. GUTMANN: That's the process, John, but the standards have to be imported into IRBs.

DR. ARRAS: Right, but the standard is the standard of excessive risk.

DR. GUTMANN: We struggled with this in a case where...this applies, and it's worth our dwelling on for a moment because it applies in really good research. We struggled with this in the case of pediatric research for Anthrax vaccine. Where it's nontherapeutic research, it's for a public good, a very important public good, which is protecting children in the case of an Anthrax attack. And we came down with a conclusion that was widely praised but did not satisfy either extreme view of this research is so important you have to go ahead with it, period, or this research imposes risks on children who are not going to directly benefit so you can't do it. And we came down with the view that what would be ethically consistent with existing standards, which are very open ended and didn't specify in this case, but consistent with the high level principles, is going ahead but only with an age de-escalation where you get the risk minimized with the youngest adults and so on. I think that is the classic case of context-specific standards. And we would like to recommend something similar but we're not going to come up with the specific standards in each one of the diseases and so on. But we can recommend that

there be funded research that joins the scientific community and the ethics community with people who are participants that makes very specific standards that will work to move the science ahead that are ethically acceptable.

And with that I think we've sort of reached our time limit and probably really gotten so much and had the capacity to pick your brains. And we welcome any more that you would like to tell us, but I hope you will accept our collective thanks for your help in our project. We are adjourned for the day and we will reconvene at 9:00 tomorrow morning.