



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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DR. WAGNER: Let me ask our guests to come forward, Professor Dresser and Drs. Graf, Wright, and Feldman, if you could come forward to the table here while we get underway.

Commissioners, I'm imagining that in order that we can hear fully from all of our guests this morning, we may have a short lunch this afternoon, and that will be just fine.

In his charge to the Bioethics Commission President Obama noted that it is important to consider ethical issues in neuroscience, and I quote, "... as they relate to different life stages from infancy through old age." Thank you Raju. Our panel will do just that, examining neuroscience research and related ethical issues across the life stages. We'll hear first from Dr. William D. Graf. Dr. Graf is President of Pediatrics and Neurology at Yale University School of Medicine. He is Committee Chairperson of the Ethics Committee of the Child Neurology Society and is active in the Ethics, Law and Humanities Committee of the American Academy of Neurology. Welcome, Dr. Graf. Good to have you here. Please, the floor is yours.

DR. GRAF: Thank you. I'd like to thank the commission for the opportunity to participate. My comments today do not necessarily represent the Child Neurology Society or the Ethics, Law and Humanities Committee of the American Academy of Neurology but most perspectives will be shared by practicing developmental pediatricians, child psychiatrists, and child neurologists.

I'll briefly discuss pediatric bioethics, prenatal diagnosis, gene transfer therapy, and pediatric neuroenhancement, but to begin, it's important to keep in mind certain bioethics values, pediatric bioethics values, without presuming absolute norms or universal standards.

Neurodevelopment is the essence of pediatrics. Neuroscience research producing genetic, pharmacological, magnetic, electrical, surgical, and computer technologies may gradually influence the process of human neurodevelopment. We recognize infants, children, and

adolescents to be works in progress, but the realization of good outcomes in adulthood can be predicted and also ameliorated in childhood. The foundation of health and achievement in later adulthood is highly inheritable but genetic assets depreciate under adverse neurological and social circumstances. Moral values, which are traditionally fostered by parents, family, and teachers appear to be established in early childhood. Neuroscience research has demonstrated other areas of brain development well into late adolescence when social maturation is characterized by the need for greater bonding with peers, heightened emotions, and less impulse control compared to older adults. Recognition of these neurodevelopmental processes governs the proscription of certain activities during adolescence and legal restrictions that differ from adulthood.

Neurodevelopment is the process of developing autonomy, a path to the widest possible autonomy and self-reliance later in life. Ethically, legally, and socially it is presumed that most parents generally love their children and are willing to make great sacrifices of their own interests to act in the best interests of their children. Rarely the respect for parental authority must be balanced by an obligation to prevent undue harm. Although it is accepted that there's no singular path to human flourishing, preserving a child's right to an open future is integral to a child's wellbeing and the best opportunity for the pursuit of happiness in later adulthood.

We recognize neurodevelopmental spectrum judged over a continuum both chronological- and ability-related. Chronologically we observe variable maturation in children and changing needs and evolving developmental expectations from infancy through school age into adulthood. Most neurodevelopmental abilities fall within a broad range of typical, albeit highly individual, and what we call developing authenticity. Neurological impairment on the one hand and true

prodigy on the other are viewed as outliers. Ability can be measured by performance and accomplishment and influenced by nature and nurture.

Neurodevelopmental disabilities may be categorized as well under broad spectra such as the autism spectrum disorder where the advantage is public recognition of atypical neurodevelopment. The spectrumization process, however, reduces both specificity and severity leading to markedly rising prevalence where the disadvantage is public misperception about causation and the role of environmental factors such as immunizations. It is imperative that neuroscience research continue to elucidate the many underlying causes of various neurodevelopmental disorders lest we permit misdiagnosis and mismanagement as an alternative. Translation of neuroscience research to the treatment of neurodevelopmental disorders will require specific knowledge of biological mechanisms in each and every child.

Neuroscience research across life stages begins in the prenatal period. One active neuroscience research area is collecting the transcriptome data to study the molecular organization of the developing brain. Another neuroscience research area uses next generation sequencing techniques in the analysis of maternal plasma cell preDNA in high sensitivity, high specificity screening of genetic and genomic disorders, a topic that has previously been presented to this commission.

Negative eugenics and positive eugenics involve the pursuit of human perfection, and both have extensive world histories over the last 150 years, but by an order of magnitude major advantages in both prenatal imaging and genetic screening technologies are gradually leading to the perception that technology will allow the option of choosing a healthy baby. What we see as inconclusive prenatal neuroimaging of minor neuroanatomic differences is very common. It causes parental anxiety and clinical dilemmas. Expanded prenatal genetic testing includes

benefits, limitations, and consequences. Genetic testing may diagnose severe disorders but tests also expose genetic variants of unknown significance, carrier status, susceptibility genes, conditions of late onset, and nonmedical traits. Except for selective abortion, the identification of genetic errors will not lead to immediate medical therapy for most patients.

Questions regarding the best interests of the future child need to be addressed. Is the genetic information directly beneficial to the child? Will genetic knowledge deepen beliefs in genetic determinism? Will genetic knowledge affect child upbringing? How will this technology affect the child's autonomy and the child's right not to know? Is life with disability bound to be considered second rate? Uncertainty scenarios underscore the critical need for comprehensive pretest consultation and informed consent, judicious reporting of test results, and access to genetic counseling to enable patients and parents to make well-informed decisions.

Gene transfer technologies are a growing area of neuroscience research that hopes to provide a cure for some single-gene neurological disorders such as adrenoleukodystrophy. Somatic cell gene therapies use various in-vivo and ex-vivo methods to transfer healthy genes into cells through safe and effective vectors. Before such technologies can be implemented to reliably cure genetic disease on a large scale many practical challenges remain. The bioethics of single, rare gene disorders involve conflicts between the harm of natural death versus the harm of potential iatrogenic injury, especially during the pioneering phases of clinical research. Knowledge gained from pediatric research must be obtained in a way that recognizes the vulnerability of children and respects their best interests.

A biological bioethical paradox arises in gene transfer research because earlier implementation generally allows a higher probability of gene transfer effectiveness. Even better transgene uptake should occur in early fetal development during increased cell mitosis, making

the most suitable research candidates those who fully lack autonomy. Basic arguments in favor of presymptomatic somatic cell gene transfer include the potential to treat or prevent fatal diseases, providing the only hope for many families. Religious, scientific, and medical groups all agree in principle that somatic gene therapy is appropriate for humans. The essential principles of human gene therapy studies emphasize acknowledgment of human risk and experimentation and the potential for adverse effects, the need for patient selection and protection, and the process of consent review regulation and the monitoring of financial conflicts of interest.

Much larger questions remain on the possibility of germ line gene therapy and the moral rights of future people. The concept of informed consent stems from the core ethical values of individual autonomy. Third-party decision making processes will always pose a threat to a child's rights to autonomy. Phase one studies are exclusively nontherapeutic experimentation in nature and may be ethically unacceptable because of the dangers of therapeutic misperception by desperate parents. Some gene transfer trials may now combine phase one and phase two trials traditionally used in assessing pharmaceuticals for both toxicity and efficacy, allowing some genuine therapeutic optimism for study participants.

Children and adolescents are growing up in an ever faster-paced world. The evolution of computerized technologies has resulted in faster processing speed, nanotechnologies, robotics, GPS, and the desire to multitask. Applications of these technologies disrupt some typical human activities and gradually influence the traditional neurodevelopmental process. For numerous and various reasons we are observing increases in the prevalence of attention deficit disorder diagnoses and the use of ADHD medications, especially in the United States. For pediatric neuroenhancement, for example, the use of amphetamines in healthy children and adolescents,

reasonable people may disagree about whether certain practices may be harmful or potentially helpful; however, the practice of pediatric neuroenhancement challenges the role of medicine in society. Pediatric bioethics calls for cautious reflection about how our conduct and actions can be justified in real-life medical decision making. Physicians have an ethical obligation to resist overdiagnosis and overmedicalization and prevent the misuse of medication in children and adolescents.

So in summary, neuroscience research gradually changes our understanding of the developing brain and proposes methods to treat genetic diseases or modify neurodevelopment in the future. We need ongoing ethical, legal, social, and neurodevelopmental reassessments of all pediatric neuroscience research. Thank you.

DR. WAGNER: Thank you, Dr. Graf, and we'll have comments and questions after all of our presenters have presented. Next is Dr. David Wright from right here, as a matter of fact, Emory University. He is Associate Professor of Emergency Medicine, Director of Emergency Neurosciences in the Department of Emergency Medicine here at Emory in the School of Medicine. He's the principal investigator of the Emory hub for the Neurological Emergencies Treatment Trials Network and is co-principal investigator of the Emory hub for the new National Institutes of Health Stroke Network. He has done a great deal of research in the area of neuroprotectants. And I thank you, David, for joining us this morning.

DR. WRIGHT: Thank you. First I'd like to say that I'd like to sign up for the cognitive enhancement study that was mentioned earlier because I really need it.

What I'd like to do is just give you a perspective from a principal investigator and emergency neuroscience researcher. I think given the last hour's talk, that this will be fairly

poignant and bring some of the issues that we have and challenges really to the table. What I do actually in emergency neurosciences is really where ethics hits the road, and it shows that regulatory ethics don't always inform practical ethics. So that's the pretext from where I'm going.

It wouldn't be an ethical talk unless I gave conflicts of interest. I'm inventor on a sideline assessment concussion device, and I'm going to talk a little bit about a clinical trial where the product is licensed by PhRMA and I'm listed as an inventor on that.

So welcome to my world. Emergency research is very challenging. There are a lot of things that are going on, a lot of moving parts. Things that impact what we do: the urgency of the condition, the environmental factors, safety of the patient and the personnel who are responding, conflict in priorities, a multitude of providers and handlers, and often a lack of treatments and interventions. This is where time has never been so important. It matters. It's actually your enemy and it really sets the stage for what we do.

It is a moral imperative, however, that we find solutions and new treatments for patients who are, as you can see, completely incapacitated and cannot provide any type of consent. And the magnitude of the problem is actually quite immense. Let's just look at some of the numbers. We have over 130 million visits to emergency departments in this country every year. That's a third of the U.S. population. Not all of these are emergencies but it's very important to recognize four out of ten of the top causes of death are related to neurologic issues in some form or fashion. If you look at cardiac arrest, for example, it's going to end in a neurologic issue ultimately, and we need to find new studies and new devices and new treatments such as this one that can improve the outcome of these patients before they become brain dead or impaired.

So just in context, this is really where we operate. It is difficult to take care of these patients, but you want to put a research protocol in the middle of that? Welcome to it. It's very hard to do and it is very challenging. These are just some of the issues that are related to that. These involve life and death situations. It's time critical. These patients are impaired, as I noted. These are unanticipated events, and so most people don't plan for anything like this. Their relatives and legally authorized representatives are nowhere to be found, and if they are, it's fraught with trouble. So how can you really ethically do research in this arena? We do, and we keep these core principles in mind, which I'm sure you're all very familiar with, and we must do that because we have a sordid history in this country of doing ethical research. And federal agencies are not immune to this, as you can see. We are very close to Tuskegee, so this brings that to home.

The elephant really in the room here, as has been mentioned many times previously, is the inability for us to protect autonomy and respect for persons in these scenarios. These patients are completely incapacitated for the most part. And when you get into doing research for the greater public good, it's a slippery slope, so we have to be very careful about this and keep the ethical principles of research in context.

So some people would say that we shouldn't do research under these conditions. I hope I have just shown you that we really need to, and I beg to differ. Animals can inform us in proof of concept but they cannot answer the questions that we need to answer in humans, and we must proceed to human research. Traumatic brain injury is an example of this. This is what I do specifically. It's been brought to light. It's a huge problem. The conflicts in Iraq and Afghanistan, and the media has caught onto it with our sports, but it's been causing significant problems for many years. In fact, the CDC, Thurman called it the silent epidemic prior to media

catching on. It causes 52,000 deaths a year in this country and lots of morbidity. What is 52,000 deaths? I sort of gloss over when I think about epidemiology, but this puts it in perspective. It's 175 747s crashing every year. What would the FDA do if that was happening? We would shut the program down until we figured out what was wrong.

Well, this is traumatic brain injury in this country. \$76 billion spent every year on it, and unfortunately our graveyards are full of our patients and also our clinical trials. A lot of promising agents have been brought forward but every single one of them has failed, so you can see why the animal models alone will not work, because it doesn't necessarily translate. Where we are in traumatic brain injury is we have no treatment. So, yes, I do feel like Sisyphus here from Greek mythology pushing the rock up the mountain, only to watch it fall again every single time, but we are undaunted and continuing.

There's a lot of great research going on. This is Don Stein who noticed about 30 years ago -- that's how long it takes -- that his female animals were doing better than his male animals. Long story short found out that progesterone seemed to be very neuroprotective. In fact, there's now over 300 publications showing that it is neuroprotective in some form or fashion. So we launched the clinical trial ProTECH 3 in 2009. The reason I tell you all this is to tell you an example of really how research ethics is very difficult. This is a hyperacute study. We had to get the drug in within four hours. These patients by definition are impaired. So we applied for and operated under exception from foreign consent from the FDA. This is a critical tool for us in emergency research. We could not do what we do without it. It's very important for us; however, it is fraught with challenges.

One of the things that we have to do is community consultation all across the United States, and it is very resource intensive and very difficult to actually do. And there's actually,

even though large volumes of guidance, it's not always practical. We had a hundred thousand patients, or participants rather, in our community consultation and public disclosure events, but interestingly none of the patients enrolled in the study or their family had ever heard of ProTECH. So the question is, talking about research on ethics, is this process really effective. I don't know the answer to that yet.

We also had a typical consent pathway for a proxy consent. I will tell you under emergency conditions proxy consent is also an incredible problem. We enrolled one patient who the gentleman that was with him swore he was his brother, and, in fact, he was, but only his Harley brother, so we found out the next day after consent was invalid and had to proceed forward. We also have family members who show up completely intoxicated and themselves impaired and cannot provide consent, and/or they are in the accident themselves and they cannot participate in that process.

So why do we do all this? We do it because we care. I'm sticking with sort of the life span theme here. Yes, we want to improve longevity but also productivity in our elderly life. So it's really important that we conduct this research.

I'm not going to present this here. These are just sort of the take-home summary from some of the things that I feel that are important in this type of research. First, it's critical that we do it, but there are numerous challenges that need to be addressed as we move forward in emergency neurosciences research. And that's my presentation.

DR. WAGNER: David, thank you very much. Next is Howard Feldman. Dr. Feldman is Professor of Neurology and Executive Associate Dean of Research at the Faculty of Medicine at the University of British Columbia in Vancouver. He is the Clinical Director of the University of British Columbia Hospital Clinic for Alzheimer's Disease and Related Disorders. Dr.

Feldman is a fellow of the Canadian Academy of Health Sciences and the American Academy of Neurology. Previously he served as the Inaugural Fisher Family and Alzheimer's Society of British Columbia Endowed Professor for Research in Alzheimer's Disease, and Therapeutic Area Head for Neuroscience Global Clinical Research at Bristol Myers Squibb. Dr. Feldman, welcome.

DR. FELDMAN: We are going to move from the emergency room to consideration of issues of dementia. One might think that these are diametrically opposed, but in fact the themes run constantly between them, as you'll see.

I too would draw to your attention the disclosure. The perspective that I will share with you is shaped by both the clinical interface in academia and having had a three-year period in industry where I tried to develop new treatments for Alzheimer's disease.

So the scope of this problem is enormous. It has now become the focus of the G8. I had the opportunity to participate in a summit in December where Prime Minister Cameron focused the bright light on dementia and particularly these kinds of data that today there are two and a half to five and a half estimated million Americans with dementia, 35.6 million worldwide. Sixty percent of this problem will come in the developing world to make our life even more challenging. It's expected that their numbers will double by 2030 and that the cost of care will move from \$200 billion and \$600 billion worldwide today to upwards of a trillion. If the costs of dementia were a country, and unfortunately it's been whited out, it would be something like the 21st largest economy in the world. So we begin to scope things that don't escape the public attention and are going to call for ever-increasing attention.

So the outlook that I would share with you, since the word "integration" has been very important, integrates a view of how we've begun to understand this disease, and I would say that

you could interchangeably move Alzheimer's, Parkinson's, Huntington's. All the neurodegenerative diseases seem to have very similar themes, which is the pathology of these diseases begin before symptoms begin. This is good news because it gives us a running start at the opportunity to potentially treat disease, but as you might imagine, it creates a whole series of ethical conundrums of intervening in individuals who may be identified to be asymptomatic at risk or presymptomatic, and as I'll show you in a slide or so, the prodrome may last for several decades. So that's a good news and a bad news story. We have a running start. It's a long period of time.

We've talked and I've read in your report around the recognition that consent and capacity change over time, and this is no exception. We could imagine someone starting in a program of research with full capacity and then it changes en route and the program of therapy may be ongoing, and how are we going to deal with this. Some of the identification of presymptomatic gets to genetic disclosure, genetic identification, and dealing with all of the issues that we've started to talk about this morning: research, care, commercialization, and privacy. I'm not going to touch on end of life, but, of course, with a problem of this order and at this stage of life, it's of paramount importance.

Within the research arena we've taken the view through some very compelling data that prevention is the thing. So if we could meaningfully alter the onset of this disease, that is to say, if we could delay this by one year, we would cut the prevalence by 10 percent. If we could delay it by five years, we would cut the prevalence by 50 percent. Now, I should add that takes into account a timeline of four decades, but nevertheless, it is absolutely compelling from a public health perspective.

This is the window of opportunity that you see in front of you. The yellow block represents life span wherein individuals are acquiring various types of representation for the pathology of the disease but are still cognitively normal. And it is also possible to make this a bit more complex that people may die with the pathology of the disease but never express the symptoms. So it's not only inside the yellow block that we have this period perhaps of one or two decades, but we also have individuals with the pathology who don't eventually express symptoms, and that's troubling when one begins to look at preclinical intervention.

So what are the considerations? Scientific validity. If we want to make an intervention in the preclinical space, how much scientific validity do we need? At the moment we have no treatments that effectively work on the disease. They need to be developed. Can they meaningfully be developed within the preclinical asymptomatic space or ought they to be developed in individuals with full-blown disease? And what if the treatments will only work before the disease is full-blown and established? So it's a conundrum that we have to deal with.

We also don't have surrogate outcome measures. We can't treat and get an early read-out of whether the treatment is effective. Individuals in primary prevention studies will have no symptoms. There will be no measurable benefit. It may be decades before we know definitively whether this has helped, and our surrogate measures are not very accurate in terms of predicting whether there will be long-term clinical benefit.

Having said this, you say, well, we are not ready for preclinical intervention trials, and yet presently we have NIH and other funded trials working on preclinical disease. So it's very important to recognize that in the sequence of things we're doing things at a time when we lack full understanding of the implications. And it will be years for clinically meaningful effects, as mentioned. There will be risks of longer term treatment, and I don't think we know what those

are at the get-go, so as we begin to treat people, we have to think about a time course that will span decades.

We have to mitigate therapeutic misconception. I am fearful when I'm in clinic that if I tell someone that they have the pathology of a disease when they're asymptomatic, they are only going to hear they have the pathology of the disease. They go home with the notion that they've got the disease. They forget the part about they may or may not get the disease. And it's a very serious concern that I have about disclosure in a preclinical state.

Diagnostic disclosure, I think that we need -- it's already been mentioned this morning -- community viewpoint. I think this is an area where we really need a deeper understanding of what the ethical standards are to work in this space. We need to hear from the public. We need to evaluate how we are going to measure the benefit and risk, how we are going to handle incidental findings, and how we will understand the predictive risks which at the moment are incomplete.

We wrote a paper earlier this year outlining a framework where we could imagine that we begin to create a hierarchy, we look at biomarkers, and we begin to look and balance the risk against the benefit. We think that this is the kind of framework that needs to be developed, but we also have this caution that we ought not to run before we have the framework in place. So we leave this as a position paper that we put out last year.

So within the complexity of considerations we can easily appreciate the public good that will be attached to the prevention of Alzheimer's disease. We see the threat to our wellbeing. The economists are posing very dire societal problems that will come without effective treatment. We have the risk of long-term preventive treatment without really understanding all the dimensions, without clear scientific validity, without the ability to read out symptomatic

benefit, without clearly defined surrogate measures. And we have diagnostic disclosure, the way that will be understood, the risks of harm, the risks of benefits that will come from that. Thank you.

DR. WAGNER: Thank you, Dr. Feldman. Much good thought for us to follow up on there. Finally in this panel we are going to hear from Professor Rebecca Dresser. She is the Daniel Noyes Kirby Professor of Law and Professor of Ethics in Medicine at Wash U, St. Louis. She is Vice-Chair of the Hastings Center Fellows Council and an at-law columnist for the Hastings Center Report. In addition to authoring and editing numerous books, Professor Dresser has written numerous journal articles as well as commission papers for the National Academy of Sciences and National Bioethics Advisory Commission. In 2011 she was appointed to a four-year term on the National Institutes of Health Recombinant DNA Advisory Committee, and also was a member of our predecessor commission, the President's Council on Bioethics. Welcome.

PROFESSOR DRESSER: Thank you. It's great to be here and to be a speaker instead of one of you with all your responsibilities.

So I'm going to focus on the research ethics in all these areas, and as John mentioned, this is a very tough area. There is a lack of consensus, very complicated policy situation. Two Presidential commissions as well as numerous other groups have reported and recommended limited impact. Many of the old issues are still unresolved, and the current research regulations don't address the topics that I will discuss.

You also have to get into the weeds. There are many details. It's easy to lose track of the big picture, especially if you are trying to address dementia, psychiatric conditions, brain injury. Psychiatric conditions and brain injury populations tend to include younger people, sometimes more kind of adversarial situations than in dementia. Often there is fluctuating capacity or, well,

they are in and out. And then dementia where you have a decline, although there can be variation within the same person, someone with dementia, and certainly among the population there is great variation.

But let me try to give you at least a rough idea of the big picture by framing the major topics and issues. So first: Capacity to decide. We don't want to stereotype people based on a diagnosis. You have dementia; you must be incapacitated. You have depression, whatever. You don't want to disrespect the autonomy of people who are still able to make their own choices. On the other hand, you don't want to fail to protect vulnerable people who can't understand the decisions before them. That would be taking advantage of them for the greater good.

A proper capacity standard, lots written on this, most agree is the ability to understand and reasonably remember facts about the study, about the risks, procedures expected, potential benefits, and to express a choice, appreciate how the information applies to you. There's a lot of empirical research on capacity for you all to look at. Remember that this has to be something pragmatic. It has to be something that researchers can apply in practice. So you can't get too highfalutin with this stuff. People are individuals in all these groups. In order to assess capacity you have to have a conversation with each one. You've got to evaluate, you know, "Okay, here's what the study is about, so tell me why you're here." And if they say, "Well, they told me I was coming to the dentist," then you know there's a problem there. People use quizzes. At our Alzheimer's center there's kind of a basic quiz with five questions about why are you here, what are we doing today, to get a ballpark idea of what people are aware of. Capacity is not all or nothing, so there are many people who can participate in a limited way. In dementia research it's very common to use dual or double consent. So you ask the person is it okay if your spouse, son,

daughter, even neighbor friend, sits in and we talk about this together. Probably most of us thinking about research, we'd benefit from this, but this is something that's really quite common in dementia research and I think could be used more widely.

What if a person is incapable of deciding? Who is the appropriate decision maker? You heard a reference to the legally authorized representative. That's what the common rule says. Leaves it to state law. So a number of states do have laws but probably most do not, so there is custom, a close relative. Again, some people use friend. There is no explicit law on this but it is done. A research proxy could be designated in advance. I'll come back to that. One question is should surrogates receive training on their role. People are coming into this and they don't know what they are expected to do. Should they be present during research and procedures? Is that part of their role?

Now, advanced choice. So the positive dementia, you can show respect for a person's autonomy or authenticity, as Dan said, prior values. Negative, think about this, when you're making a decision about participating in future research: What are the facts about the study? The study may not even exist now, so you can have very limited information about risk, benefits, alternatives, and so forth. Importantly you will have limited information about how you would experience the research as somebody who is different from who you are now. So what would it be like to go through a brain scan if I have dementia? So how well can people understand that.

I think you also have to understand that people, by the time they are going through the research based on advanced consent, won't remember why they gave consent earlier, at least normally they wouldn't. So I think in my view relying purely on advanced consent in this area would set the ethical bar too low. I think you still need a surrogate decision maker on hand when

the research is being conducted, and the other protections that I'll get into in a minute, potential limits on risk and the role of assent and dissent.

On the other hand, I think if you wanted to say, well, we require advanced consent, that would be setting the bar too high. Very few people are going to make these things. As mentioned, most people don't make them for treatment, and that's something that people are much more aware of. This is always going to be a very limited population who would ever make these things. So if you require them, you are not going to have many subjects.

It's interesting empirical data I've been looking at. Surrogates tend to apply best interests over the person's past preferences. There is some nice quotes. One person, a surrogate, said: "The situation is that there was a person there that kind of went away and can't judge for themselves anymore, so you could either judge from their past self before they had Alzheimer's or you could judge from their present selves. And mostly I kind of center around their present self. So I think that whatever is making that person happy right now is what I should be centering my decisions on." Another one talked about her mother who said: "Before she might have agreed to research but now she would not. This is my mother with mild dementia, not the mother that didn't have it. If she wasn't already compromised she might think, 'Oh, you know, I'd like to help.' But she just doesn't have that tolerance anymore."

Assent and dissent, this is the idea I think you talked about with children before, that these are not people who are unconscious. They have experiences, so they have burdens and benefits of participating in research. The idea of acquiring assent is based on their limited understanding you should get their agreement to participate. And at minimum, if they object physically or verbally, you should respect that. Now, maybe you can go back in an hour or two and see if

they're in a better mood, but in general overriding an objection would be a serious ethical concern.

And then finally there are discussions about should we limit risks as we do in pediatrics. I won't go into that because I think you know about that. You do have to remember, again, that risks and burdens that seem to us no big deal could be terrifying for somebody who doesn't understand why this is being done to them, doesn't remember what you just told them about what you're going to be doing, so you have to think about that.

And I really agree with this idea of community engagement. If you are talking about integration of ethics, including representatives of people in the planning of studies I think can really help to produce ethical research. Thank you.

DR. WAGNER: Thank you, Professor Dresser. We are going to open the floor, but I would like to ask you: Among the readings that we had was a piece by Scott Kim at the University of Michigan who was trying to weave together these thoughts of authenticity and capacity and the ability to assent to be a subject, and he writes that there's also an interpretation issue, in that, the example he gives, it's quite possible authentically to get someone to admit that they are very willing to be a participant in spite of the fact that they don't have the capacity to understand what that means. Could you talk just a little bit about how it is we interpret, how it is that we can have some confidence in interpreting that someone is in fact appropriate, that the consent they're giving is appropriate to go forward?

PROFESSOR DRESSER: I'm sorry. I probably have read that in the past and forgotten. I didn't see the article. I do think in general in research we worry a lot about the authenticity of consent. We have a lot of research showing that many people who are in research

don't understand particularly the lack of direct benefit for many of them or the low chance of that. So, you know, you worry about that even more here.

I'm not sure if he was also alluding to the fact that many people in these populations are so dependent on others and --

DR. WAGNER: I think he was simply asking the question is the willingness of someone to participate sufficient.

PROFESSOR DRESSER: So I was going to get to that. They are very susceptible to suggestion, pressure from people they count on to help with their care, from their doctors, so I think that it could be a special concern here that people would be saying yes because they want to be good to the people they count on.

One thing that people have proposed is that the capacity assessment should be done by someone who is independent of the study, who doesn't have a stake in whether they enroll enough people. And I'm not sure how much that would help with that but that's one idea.

DR. GUTMANN: This was a great foursome of presentation that will help us tremendously. And, Howard, your outline on that one slide was a terrific outline of the ethical and practical issues of moving forward, so I think that will help us a lot. I'm going to direct my question to David. I'd be happy for David to respond and then anybody else to respond, because I think it just highlights the challenge, the elephant in the room, if you will, that you literally put in the room in that picture. You said many times, and I understand entirely why you said it, but many times you used a version of the sentence "It's imperative to conduct this research." And the first, second, and third thing that we have to ask as a bioethics commission is, is it ethically valid to conduct this research, because there are multiple times that we've been called upon, just our commission and previous commissions, where the researchers and the scientists had a

medical reason to say it's imperative to conduct this research where it was ethically not valid to conduct it. So in order to find out whether penicillin is a prophylactic for sexually transmitted diseases, it is medically imperative to conduct research on human beings but it was not and is not ethically valid.

Rather than make this as a challenge, because I'm on all of your sides as far as wanting the science to move forward if it's ethically valid, here's my suggestion that I want to play off. It's a question. Rebecca said, and you've said as well, we don't have enough advanced directives to do it, so you have to get consent at the moment. In the case of emergency medicine, that makes it very difficult. If it is the case, as it is, that it's so important to conduct this research, why don't we as a society put more effort into getting advanced consent, and/or make it clear that if you are getting the huge resources of society in medicine, that we are going to do research at the moment of saving your life that is of minimal risk? In other words, can we get communities, our community, to put more of an effort of our community into getting the advanced consent when it's more valid than it is at the moment you're in an emergency room to doing at least some range of the least risky research on people? That's my question. Because I think it's extremely difficult to get, you know, sort of valid consent at a point of people under the highest stress, not knowing whether their relatives are actually their brothers or not. So it's a long preface to a very important question for us to deal with.

DR. WRIGHT: Thank you, because that was actually probably the most important point from the talk, which is that it is imperative that we do this research. From my perspective it is unethical not to perform the research, because we don't know if what we're doing now is correct or not, and we could be killing you without knowing it unless we actually do the work and do the research to find out whether what we currently have, the CPR we're currently doing,

the resuscitation we're doing is correct. So I think it's very important that we do it from an ethical standpoint. We have to do that to find out whether what we're doing is working. To answer one of your other questions --

DR. GUTMANN: But you understand that we can't accept that statement? You cannot know whether it is imperative to do research unless you know whether it is ethically valid to do it.

DR. WAGNER: Again, the penicillin example.

DR. WRIGHT: Yes, completely understand.

DR. GUTMANN: The people you are doing the research on are not the people who are going to benefit from it, so there's got to be some set of ethical standards before you can say it is imperative, all these things considered, for us to do the research.

DR. WRIGHT: I understand that, but it is equally unethical to continue doing what we do without knowing whether it's the right thing to do. I mean, how else would you do any medical -- I mean, all of our medications and everything we do at some point has to be tried.

DR. GUTMANN: Right. So then we have to find an ethically valid way of doing it but we have to figure out what the ethically valid way is.

DR. WRIGHT: Correct. Yes. I don't think we differ on that. The other issue is, if you start looking at advanced consent, you can look at organ transplant, you can look at other things, it's very difficult to do. As mentioned before, very few people are going to be able or will bring it to the attention, because especially in our arena where you're young, you don't think it's going to happen to you, paying attention to doing these advanced sort of types of consent is really impractical. And the other part is that each study is going to have its own risks and its own

benefits, and I don't know how you would really judge whether you would want to participate in a particular study or not unless you could weigh those risk and benefits. So I'll leave it there.

DR. ARRAS: I too want to thank all of you for a really terrific panel. I want to go back to the question of decisional capacity. And to get a sense of the lay of the land in terms of regulation and practice, during my little report from our subcommittee I mentioned the great difficulty that august bodies in this country have had in coming to grips with this issue. Past Presidential Commissions, IOM, NIH, they've all felt it really important to develop better understanding, better policies on decisional capacity. No action has been taken on any of their recommendations. Okay? So here's my question: Does it matter that they failed? Are we muddling through okay without a revised clear set of guidelines? Do we need that? And if it's still important to make an effort to develop guidelines where previous efforts have failed, can you say something about which areas need the most work, where are the biggest gaps in our ethical practice and regulation regarding decisional capacity?

DR. GUTMANN: Rebecca.

PROFESSOR DRESSER: A couple of comments. My perception just politically is that there is more receptivity to some added regulation among the dementia research community than there is among the psychiatric research community. From what I know, for example, with the Clinton Commission recommendations it was the psychiatric community that really opposed them. So I don't know how that helps you, but whatever.

You know, we are muddling through but there could be two costs. One is that people who could be participating in research are not because researchers, the lawyers in their hospitals, whoever, are concerned that they don't have enough protection to enroll people who have questionable capacity, so there could be less research going on. And then the flip side is there

could be a lot of research going on among people who have given consent but they've actually been incapable of giving consent.

DR. WAGNER: Yes. Go ahead, Howard.

DR. FELDMAN: I would just say that in some ways there's a call for a public dialogue that needs to be enhanced over where it stands today. And I think you're right. So the question of should there be something on your driver's license or should it be at that level of discourse where everyone is thinking through where they stand on this issue in advance, it's hard to be very specific. There are a zillion things that you might have to cover, but I think brain disorders are the thing that society fears the very most. It's more than anything else, and we shouldn't lose sight of that, which doesn't make it inappropriate to have a special -- you know, we have organ transplantation, and it would not be inappropriate. Of course, I have a bias as a neuroscientist around that, but I think it's worth considering.

I think in part in answer to this question as well, I think we're touching on parts of the public discourse. So in the examples that I've given you today I think we're missing community impact as an externally validating group that should be telling us how far away we are. It's not going to be perfect.

The other thing that came up is -- personally I've had a struggle with our ethics review board. We have always taken the view when we enroll a patient with dementia in a trial that we have a dyad. It's not simply the person participating; there is someone else in the relationship. Our ethics board would not allow us to co-consent people. They said it removes the autonomy of the individual when you co-consent; therefore, it has to be one or the other. And in a way it dissociated us from where our comfort was in relationship to our real understanding that at the

end of the day the dyad will go home together and live together and experience this thing together.

DR. WAGNER: All good points, and I think this community engagement conversation is an important take-away.

We've got Barbara, Nelson, Nita, Dan, and Chris. To get that done in 15 minutes is three each. So Barbara.

DR. ATKINSON: I'll try to be fast. One of the threads going through has been the one that Jim raised about if you have somebody who is incapacitated, say, with Alzheimer's right in the beginning, and the question of harm comes into it. What I'm wondering is in neuroscience could there be something like in pediatrics with the minor-over-minimal risk kind of judgment of what the harm would be as a piece of the consideration in the whole consent process.

DR. WAGNER: That may as well be a comment for the commission as well as for the group. Rebecca.

PROFESSOR DRESSER: That's been proposed, and there's a thorough discussion of that in the Clinton Commission report and recommendations.

DR. WAGNER: Nelson.

DR. MICHAEL: So this is directed more at Rebecca. You asked the question during your remarks about whether or not training for surrogate decision makers was something that was reasonable, and, Howard, in your comments just a few moments ago you mentioned some of the friction between ethical review committees and the dyad of having a surrogate plus the actual subject themselves. I would endorse the idea. I think it would be comforting for the community to understand that you had some degree of uniform training of surrogates because that is protective of the relationship and it's protective of the science.

But I also wonder whether or not it would be useful to have, especially in your dyad paradigm as you go forward, to have ethical review committees, IRBs, whatever you'd like to call them, depending on what country you come from, during continuing review to establish once again, to reestablish the adequacy of ethical strength of the surrogate truly being a surrogate. Not only do the patients change themselves in their ability to provide informed consent, but the surrogates may change, relationships change, and whether or not -- if we are going to be looking at clinical outcomes that may take 20 years to develop, those relationships are going to change as well. And that obviously provides an ethical burden back on research oversight, but I think it might provide a degree of comfort to the community going forward if these relationships were continuously reassessed. Just wanted to get your ideas on that.

DR. FELDMAN: I think it is compelling that the consent process clearly, if we're going to work in the space that I showed you over two decades, lots is going to change, and I would agree that the process of consent cannot stop at a cross-sectional point and you declare, "Okay, we've got it. Now we're good for the next ten years." So I do endorse that.

PROFESSOR DRESSER: I think those are good points. I think it probably would have to be the research team every so often does the assessment and reports. I don't think the IRB itself could do that.

DR. WAGNER: Thank you. Nita.

DR. FARAHANY: I want to turn back to some of what Dr. Graf was speaking about, the pediatric diagnostics help breed fetal DNA testing. And I think there's kind of two distinct issues you raised, among many, but two distinct ones that caught my attention, one being the right not to know and the implications for the potential life that we're talking about; the second being the problems of what we don't know and getting information back to parents during that

process, so how little normal baseline we have to understand when you see some sort of abnormality on a scan, how meaningful that really is and the kind of anxiety that that induces. But I wonder how different that is in this context than in any other neurological context. Right now we don't have normal, for example, fMRI across a population in really any context to know what the normal baseline is, and so a lot of what we're getting is false positives that are inducing anxiety in individuals, and we don't know the development, for example, of seeing early plaques, how long that results in Alzheimer's, or seeing little spots on the brain, what does that mean, or mini strokes in migraines, or things like that. So if you could speak to whether or not this is a unique concern from your perspective in the pediatric population because of the pregnancy process, because of the kind of information and the assimilation of information, or if this is just a kind of pervasive problem across giving kind of preclinical information that we don't have a lot of knowledge about in the neurological context.

DR. GRAF: These are really good questions. So imaging is one thing and earlier diagnosis genetically is going to be something different. So the ultrasound was the big tool we had forever, and that was somewhat sensitive. The fetal MRI scan is really only good after 20 weeks, and the fetus is approaching viability at that point. It's more sensitive and it's picking up much later very minor anatomic details. And I've done multiple consults on women and peers about an expectation for how a fetus on an imaging study picked up very, very minor anatomic details, and we've followed those babies and they've done just fine. I've had many parents become very angry about the bad information they received which made them consider a third trimester termination. Obviously it's a sensitivity issue.

So imaging is slightly different. What we anticipate with self-read DNA, again the emphasis there is between diagnostic, invasive, and screening noninvasive. So this week in the

hospital we had a baby who I consulted on with Down's syndrome whose mother had self-read DNA testing, so I --

DR. FARAHANY: Which had come back with low risk?

DR. GRAF: Well, my understanding is that's 99 percent sensitive, but this family was in shock. So again, there are limitations both in terms of sensitivity, and people really need to understand the difference between screening and true diagnosis, and then you get into, with all the data you are going to get and it's going to get to be much, much more, picking up on all of these unknowns, not to mention incidental findings.

DR. GUTMANN: We should just say we really wrestled with this when we were charged with doing the pediatric and giving advice on the pediatric, Anthrax. And we really did wrestle with it and got conflicting advice from the pediatric community, which was to be expected. I mean, it was to the credit of the community that it was willing to air its differences. And it really does raise some of the most difficult issues of consent to research.

DR. WAGNER: Dan?

DR. SULMASY: First, Amy, maybe a way to reconcile your discussion previously with Dr. Wright may be to say that we have an ethical imperative to do ethical research, right? That might by the way to say it succinctly.

Second, though, I wanted to direct my questions to Dr. Feldman. I think you really do us a service by having us think about primary prevention research, which is something we don't typically think about in this setting. It obviously holds great promise, but there are also great conflicts and possibilities for exploitation based, for instance, as you suggested, on the fears that people have and the obvious profit motive there is for a very large market of people who would want to get access to primary prevention so they don't get demented.

We know if we're going to give a drug, if you're an oncologist and you're giving a drug to somebody, you've got to prove that it's safe and effective at certain standards before you use it, but it seems to me that we've not thought that way typically, at least in most of the western world, about prevention, right? That we rush to do things quite quickly. So I wonder about what standards you think from an ethical point of view we ought to have for primary prevention relative to treatments, therapies for those who are sick in terms of evidence before we diffuse it. Should it be lower because there's the possibilities of forestalling huge benefit for millions of people? Should it be exactly the same? Or should it actually be higher because the population in which we're intervening is not sick at all?

DR. FELDMAN: So when I thought about this in the first instance, my response is primary prevention should be very safe because you are dealing with individuals that are asymptomatic that may or may not get the disease, and it would almost be unconscionable to lose your life as an individual being treated with a therapeutic that's not well understood to try and prevent a disease that you may or may not ever get, right? So it has seemed safer to work in the realm of public health at things that can be applied at a population level that are safe and well proven, in the first instance. But having said that, if the latter concerned, you've got enormous populations at risk, and how are we going to balance that? So to be very specific, they are using an amyloid antibody in a primary prevention setting. It's never been shown to work in the disease. It's now being used in asymptomatic at-risk persons who have the biomarker that's positive. What are they going to do when people start dying in that trial? How are they going to make the decisions of the risk and benefit and where will it come down? And that's where we got to that paradigm of how do we accept risk and benefit. So my response would be I have my own personal feelings about it, but I think we have to have a larger view of this, and that's the

part that I struggle with. And I would like to see a little more struggle in the community at large for some of the reasons that you mentioned.

DR. WAGNER: We could go on and on. Christine Grady has been kind to consent to pursue her question offline under duress. So I owe her one. But let's try to take as close to just a ten-minute break as we can. That would bring us back here at 11:20. Thank you all very, very much.

DR. GUTMANN: Thank you very much.

(Break)