



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Current Issues in Genetics

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DR. WAGNER:

Okay, since our other Commissioners have the privilege of having your bios in their briefings, I'll go ahead and introduce you to the rest of the room.

We welcome today, Ellen Clayton, who is the Craig-Weaver Professor of Pediatrics and Professor of Law at Vanderbilt.

She has advised the National Institutes of Health and other Federal and international bodies on topics ranging from children's health to the ethical conduct of research.

She received the William G. Bartholomew Award for Ethical Excellence from the American Academy of Pediatrics Section of Bioethics, and maybe the thing to do, a few of us have already spun up, Ellen, rather than introduce all three of you, I'll let Ellen go ahead and make her presentation.

DR. CLAYTON:

Well, let me begin first by thanking you for inviting me to make a presentation to you. I want to make three quick comments, in response to Hank, and then I'm going to proceed to the purpose of my talk.

With regard to his final comments about data, I would suggest that there are three major problems.

One is that I think his statement of the field about deidentification is not correct and in any event, is misplaced. He made some factual statements about what's done with dbGaP.

But I think more importantly, some of his statements actually undermine, almost entirely, the field of epidemiology. Happy to discuss that afterwards, but I just want to put that out there.

But what I want to do today, is to do one thing, and that is to suggest that the way we have been talking about whole genome sequencing is actually based on a set of assumptions about how things that are going to work out, that are incorrect, and that, if we challenge those assumptions, then I would suggest that there are things that follow from that. Well, if my thing is going to advance, we'll see.

Okay, here are some predictions. One is that genome wide tests will become part of clinical care in the future. This will not be done with consent.

Francis Collins, in his book last year, suggested that we would be doing this on newborns. I think he is exactly right. So, I think what we're going to do is have whole genome sequencing on people from birth.

I think limiting access to this information will be difficult, if not, impossible, and I think this is attributable only in part, to the direct to consumer tests.

I think that patients will have access to this information, and if they don't have access to it in their medical records, they will get it through direct to consumer tests. This information will be out there.

Then my final point is that — which is that interpretation is not going to be limited to medical settings or to clinicians who are well versed in genetics.

I am a general pediatrician and one of the things that I have learned is that parents get knowledge about their children, not only from me, but from all over the place, from their grandmother, from the internet, from just about everywhere. This is going to be that way for genetics, as well.

There will be information all over the internet that is going to purport to help people understand this information.

So, I think the situation that we have here is that the DNA will be sequenced. It will be available and there will be all kinds of interpretations out there.

Some of the challenges, we've already heard that errors are inevitable. One thing we haven't talked so much about is pleiotropy. The fact is, we only have 20,000 genes. We're pretty complicated. That means that every single gene does lots of different things, and so, when you find a variant that does one thing, it's almost surely going to do something else, as well.

At least in the near future, our understanding of genomics is going to be incomplete, and more importantly, the genome is only part of what actually matters, and our understanding of gene environment interactions will also be incomplete and by environment, I include the metagenome, our cultural environment, just about everything else.

So, we will have incomplete information. The result and uncertainty means that people will demand follow up. It will often not be evidence based. It will often be ethically inappropriate, and it most assuredly is not ethically — economically sustainable.

We already have evidence that this is going to happen. This is a graph from Bloss et al., that appeared in New England Journal earlier this month. This is a study in which workers in the San Diego area were offered Navigenics testing. These were all high tech, healthcare workers.

The way this was played out in the media was that people weren't freaked out and it didn't change their behavior.

But this slide actually is quite interesting, because what it shows here is what people intend to do, in light of their test results, and the boxes here, the green things are things for which we have a clearly proven intervention, i.e., colonoscopy, if you're at increased risk for breast cancer — colon cancer.

Things in yellow are things about which there is possible benefit. All the stuff that is pink is stuff for which the alleged intervention has no proven benefit, and I just want you to point out — note here, that the two arrows point to things that people — interventions that people say they want, for which there is no proven efficacy, colonoscopy for Crohn's disease and cardiac stress tests for atrial fibrillation.

This is going to happen. People are going to want things for which there is no evidence base.

So, it seems to me that the real information is this, because the information will be available, and that is going to be to develop a policy consensus about when not to act on genomic information, not when not to access it, when not to act on it.

We can talk about when not to access it, but I think we cannot assume that those limits on access are going to hold up, and where the action is going to be is on what we do with the information.

More weight will need to be given to practice guidelines and comparative effectiveness analyses, in which we consider, among other things, costs, not only the actual cost of administering the tests, but also, the harms that may follow from the follow-up, particularly for invasive interventions. These will be backed up for clinicians, by payer policies and economic incentives.

As a general pediatrician, and as most of the physicians here in the room know, increasingly, we are getting paid for performance, and that means not only paid for outcome, but paid for process. In other words, doing what we are suppose to do and not doing what we are not suppose to do. This is what is coming down the road.

I'm going to suggest that this means that patients' desires for medical interventions are likely not going to be determinative in many cases.

This often elicits unhappy responses from my listeners, but it really challenges the clinician/patient relationship. This is something we run into on a day-to-day basis, already.

Parents who come in and want amoxicillin when their child has a virus, parents who want a head CT, when their child just has a tension based headache, a stone-cold neurologic exam, etcetera.

But what this really is going to do, and I'm going to suggest this to you, also, this is really going to challenge the domain about what physicians ought to control and what they ought not to control.

So, for example, it makes a lot of sense to say that only surgeons can do surgery. It makes a little bit less sense to say that someone who wants advice for how to interpret information should be limited only to their clinician and that maybe, they ought to be able to go out and get information on the web.

I think this issue about what the appropriate domain of the monopoly of the clinician is, is open for question here. It's been open for a while, but this does it, I think, with new — I think with new acuity.

These are not new issues, but the magnitude of what we're talking about here is potentially overwhelming, and I think that the only way that we can do this is to get ahead of it, to figure out how we are going to recast the healthcare system and the clinician/patient relationship, in light of this tsunami of information that's getting ready to come down on us.

So, I think the challenge before us is this. First of all, we have to get the science right, and the science — and we need to look not only at what the genetic variation means, but also, what everything else that affects human health means, and that really means that we have to look at the impact of culture, the impact of socio-economic status, all of those other things that actually affect our patterns of genetic variation.

And so, I would urge you, when you think — you know, when you're thinking about what genomics means, to entertain the possibility that at the end of the day, even if we know everything about genomics, there is going to be a whole lot we don't know, and we've got to figure that out.

The next thing we have to figure out is the issues about policies. I have accessed and raised a question about there, because frankly, I think that's a non-starter, but we at least have to talk about it, and we really have to talk about policies about use.

This is going to call into question, the issues of clinical actionability, and it is in — and honestly, it's going to need to take into account and acknowledge the fact that the healthcare system has many incentives and also, that people are going to get information from many sources, not just us, who have, indeed, degrees behind our name, and there are a lot of other interests involved, and then frankly, when you look at clinicians and patients, what you're going to find is that they are not always going to be pulling in the same direction, that patients, in fact, may have desires and I think we can say, will often have desires, that don't have a scientific evidence base.

Clinicians will have a lot of other interests. They have always have divided loyalties and they will do so, here, and so, the challenge is going to be to figure out how we are going to put into place, systems regarding the use of this information that are going to be ethically and politically tolerable.

I think that's really the challenge, but I — but to go back to my beginning point, I think we have to assume that sequencing is going to happen, that the sequence data is going to be available, and that there is going to be information all over the place, that purports to tell us what it means. Thank you very much.

DR. WAGNER:

Ellen, thank you. Very clear and crisp message. I look forward to getting back to the Q&A on that.

Susan Wolf is with us, and she is the McKnight Presidential Professor of Law, Medicine and Public Policy, and I'm not certain, the pronunciation, is this Faegre?

MS. WOLF:

Faegre.

DR. WAGNER:

Faegre & Benson Professor of Law at the University of Minnesota.

Professor Wolf is a member of the IOM and a fellow of the American Association for the Advancement of Science and the Hastings Center.

Her recent work focuses on managing incidental findings and individual research results in genetic and genomic research, oversight of nanobiology and nanomedicine research, and legal and ethical issues raised by neuroscience.

Welcome, Susan. It's a pleasure to have you here.

MS. WOLF:

Thank you. I'm delighted to be here, especially to talk about one of the most pressing issues that crosses genetics and neuroscience today, and that's the issue that Dr. Collins and others have referred to, which is what are we going to do with the massive amount of information we're already generating in both realms, and specifically, incidental findings, that the research was not designed to find, but that almost inevitably emerged anyway, as well as individual research results.

So, quickly, what I'm going to do, and there is more in my slides than I'm going to talk about, because I know, they continue as a resource for your reference, is I'm going to talk first about what do we mean by incidental findings, individual research results and the contrast to aggregate research results.

Some work on the incidental findings, problems, some work then on the individual research results problem, and how both of these are converging in the study of what do we do with the massive amounts of information increasingly archived in biorepositories, biobanks, large data sets.

Let me give you my punch lines first, so, you know where I'm going.

Research routinely generates incidental findings and individual research results of potential clinical or reproductive importance. We are late to the party.

This has been going on for a long time, but only fairly recently, has been well recognized.

Debate over what researchers should do about all of this information, I'm going to argue, represents a fundamental challenge to the conventional line we've traditionally drawn in law and in bioethics, between research and clinical care, and that this is a very big deal, this challenge.

An emerging consensus suggests that researchers, indeed, do shoulder some duties to return, to offer back to research participants, some incidental findings and individual research results, but we don't know which ones, yet.

We don't have consensus about which ones, and I'm going to talk about some of the consensus efforts already in the literature.

Finally, the cutting edge of this problem remains biorepositories, large scale data sets and secondary research utilizing them.

So, what am I talking about? I ran a project, and Dr. Collins was kind enough to refer to it, it was funded by NHGRI. So, what you see here is the consensus definition we devised. Ellen was part of that, a finding concerning an individual research participant, that has potential health or reproductive importance and is discovered in the course of research, but is beyond the aims of the study. That's the incidental part. It's not what you were looking for, but there it is.

Contrast individual research results. We're still talking about individual, that's key. We haven't gotten to aggregate, but here, we're talking about the stuff you were looking for, the data that you developed in pursuit of the explicit aims of the study, the focal variables.

Finally, aggregate research results. This is what we typically regard research as producing. This is what we publish. What did we find out, as to the full population or sub-population under study?

Work on this problem has been heavily funded by NHGRI at NIH. We did the first major national grant project on incidental findings. We've got another one now, on this biobank problem.

But I'd also like to acknowledge, important collaboration with Judy Illes, who you're going to hear from in the next panel, on an early panel, about this problem in the domain of neuroimaging, and also, recent collaboration sponsored by NHLBI at NIH, looking again, back at genomics.

Okay, this is an important problem. I feel supported by some of the earlier presenters, including Dr. Collins. I want to note the Eric Green, head of NHGRI, in the paper that he published a week ago in Nature, that Dr. Collins referenced, called this an acute challenge. It is an acute challenge.

The paper published two weeks ago in Science, that Dr. Collins also referred to, talked about the incidental findings problems and return of results, as arguably, the most pressing issue in genetics today.

There is a new funding announcement from NIH. Part of what makes this important is that we're still out there doing the social science side of this, but the attitudinal data that we have to date strongly suggests that research participants and the public want this information. They want it. If a researcher has important clinical or potentially — although the data on this are softer, reproductive information, people want it.

Some of them were unaware that researchers had this information, and there is a bit of a revolution, maybe hyperbolic, but a certain upset out

there, at the notion that this information may be data that researchers sit on and don't return.

Research practice, indeed, has been not to return this information, for a lot of reasons, running from funding, to this dichotomy that I'm going to talk about, the idea that researchers think, "We're on the research side. We're not in the business of clinical care. We're not teched up for clinical care. I don't have a lot of genetic counselors on my budget, and the like."

But internationally, in particular, Barbara Knoppers was referenced earlier. She's been one of the people writing about this. Other countries are ahead of this — of us, on this, and some, beginning to recognize an actual right, I'm going past researcher duty, to participant right, to get this data back.

Let me illustrate the problem and give it a little bit of real world content.

Our early project on this looked at genetic family studies, genomic micro-array research, neuroimaging and CT colonography, often called virtual colonoscopy, which involves CT of most of the torso, from the base of the lungs to the pubis.

And so, you can see on my slide, all sorts of potential incidental findings, ranging from the one which has the oldest literature, mis-attributed paternity, in genetic family studies, all the way down to in genomic micro-array research and all sorts of genomic research we're finding chromosomal abnormalities.

Whenever you think you're looking at this genetic variant, but your technology returns more, welcome to the world of incidental findings. There will be more out there for some of your research participants.

Here is some early data, actually, on genetic family studies, with mis-attributed paternity. That's not early data. It's not well validated, but the estimates are that in 10 percent, depends on the research population, of the research participants, you may well find mis-attributed paternity.

Here is a quote from Isaac Kohane, Zac Kohane at Harvard. He is one of the people who have been most active in incidental findings, talking about genomics and saying what, actually, a previous witness suggested, nearly everyone is going to have some kind of incidental finding. It may be recessive, variant, associated with an important potentially lethal disorder. But look at the numbers for imaging. They are much higher.

In research, fMRI and MRI have — of the brain, potentially, up to 84 percent of scans, a ton of study on CT colonography, up to 89 percent, in a recent New England Journal of Medicine article of research

participants. Pretty much all of us have something going on in our torsos, and CT colonography may well image it. Key questions.

So, what are researcher duties, to look for these, to hunt for these? What should researchers do when they find them? Should they obtain a clinical consult?

Often, the researcher doesn't have the expertise to interpret them. What, if anything, should be disclosed back to the research participant, or participants' physician, or in the case of minors, parent or guardian?

Prospectively, what should protocols and consent forms say, and of course, this big one at the end, what about biobanks and archived data?

Turning to individual research results, here, just some examples. You've heard others. You heard a BRCA example earlier today. These are taken from the recent Science article. Should researchers offer these back?

Now, here is where I want to argue what a big deal this is, both in bioethics and law, that the problem of incidental findings and individual research results fundamentally challenges a foundational dichotomy we've built in to health law and bioethics.

By asking, do these researchers, who thought they were doing human subjects research and not clinical care, actually owe some duties to return clinical information and address clinical issues?

These research participants, who we thought, in the role of research, were over here in the bucket, doing research, what about their entitlement or interest in clinically important information?

Here is a quick slide, trying to schematize what foundational literature in both fields tells us, that there is a difference between how we think about the doctor/patient relationship and the researcher/subject relationship. I'm going to stay at the top of this. It gets more legal, toward the bottom.

But the idea, traditionally, is that a physician owes a broad duty of clinical care, to address all of the clinical issues that present.

The word incidentaloma, if you look in medical dictionaries, is defined clinically. It's a common phenomenon in clinical care, that the patient comes in complaining of 'x' and you find 'y', and you sure do have a duty to address 'y', not just 'x'.

The duty of the clinician is to serve that patients' interest, and the physician is accountable in law, as well as ethically, for failure to do so.

On the researcher side of the ledger, it's a totally different ball game, as we've conceived it, but the researcher owes little clinical care and the duty is not to the individual participant, first and foremost, but to seek generalized knowledge.

Indeed, research subjects generally may not sue, do not have a recognized individual cause of action for failure to do right by that individual subject, though of course, we've had some important legal cases that I'm happy to talk about.

Why? Why have we built bioethics and health law this way? Well, I think we've thought traditionally of research as asking narrow circumscribed questions, as — in the business of advancing aggregate knowledge and welfare, as time limited and as often conducted by non-clinicians, by PhD's and others.

The new research realities actually challenge all of that. Research now asks broad questions. Indeed, GWAS can proceed inductively, in what's called discovery research. It may no longer be time limited, with archived data sets and samples.

The research technologies are so powerful, they routinely generate findings of potential clinical and reproductive importance, so researchers do acquire data, highly important individual welfare.

So, given this attack on the traditional dichotomy, where do we go to figure out where to go next? This is a brief schematization. I could go on, and have at greater length, about where we would look in regulatory theory, at ethics theory and legal theory.

None of these, the Common Rule, for example, on the regulatory front, says nothing explicit about incidental findings. There have been no litigated cases on incidental findings, but there is a lot out there, very suggestive.

Consent has to address risks and benefits. These findings are potentially both. They can save your life or they can send you down a long pathway, to no avail of expensive and burdensome testing.

Ethics theories. I want to acknowledge that Henry Richardson at Georgetown and his colleague, Leah Belsky, have talked about limited duties of clinical care, ancillary care, that may devolve on researchers.

Illes et al., I was on this paper in Science, participant autonomy, interest respect for them, duty of reciprocity. Zak Kohane and others talking about withholding data at this point, as being excessive paternalism, and some nascent legal theories.

We did come up with recommendations, consensus recommendations, in our first project, arguing that researchers, indeed, bear a duty to address incidental findings and to return them.

This was a three-part schematization of which ones should they return. Dis-aggregating strong net benefit, possible net benefit, unlikely net benefit and arraying the duty to disclose, according to which of those buckets you're in, and really, analyzing this from the participant perspective.

That was one of the big ethics moves we made in that paper, not from the researchers perspective of, what can we fix, but from the participants perspective, what might I want?

This compares views on returning individual research results. NBAC looked at this. One of your predecessors Commission, but narrowly, a bit over 10 years ago, focusing on archived information.

This is a very dated treatment now, of this problem, which has yielded a great deal of work since, and yet, look, as you look at NBAC, as you look at the 2006 NHLBI, some of the themes are emerging. Do we know what we're talking about? Is there analytic validity?

Is this a significant problem? Is it actionable, though, look at NHLBI expands at significance to reproductive, significance there at the very bottom.

A recent paper was a re-look Fabsitz et al. I was on this paper, Ellen, some others, actually, a long list, and this separated researchers should, from researcher may.

Researcher should is still at valid, significant actionable, where actionable is actually defined very broadly, even surveillance, would heightened surveillance potentially be important?

Researcher may is when you're not and should, but it's significant from the participants perspective.

The last thing I want to talk about is biobanks. The big graphic is from NCI. It's an anticipatory graphic of a biorepository. They're putting together a very important one called caHUB.

All I want you to see from this is, there are three stages to this. Stage one, the collection, where research, itself, can be done on the left. The mother ship, this hexagonal purple, where it's held, and where research may

continue, and on the right, secondary researchers and other people accessing it.

All stages can produce incidental findings. All stages can produce individual research results. This suggests how.

In terms of what biobank should do about all of this, everyone is pretty much in agreement, research participants have to know what is going to happen to their material. Sometimes, consent is very open ended. They also need to know about this return of research results, and incidental findings.

But new issues, the conventional view has been that the full burden of handling this is on the collecting sites because only they hold the codes to re-identify. All of that is under challenge. Look at the bottom bullet.

Very important discussion workshop, held by NCI this summer, where a lot of the participants pushed back and said, "Biobanks themselves should be holding code, or entrusted in intermediary and get in the business of returning these." So, sum up.

Research technologies generate incidental findings and research results all the time. Advancing technologies is only going to heighten this. Current guidance and approaches are inadequate. We have a few consensus recommendations out there, but no decisive guidance.

The only way to handle this is in advance, by anticipation. We've got some serious retro-fitting problems with biobanks and collections already in existence, where this wasn't anticipated.

I think there is a fork in the road, in deciding whether return-ability should be by expert standards, Ellen forecasted this, or by the participants own standards. I would argue, there is a lot to support the latter.

All of this is going to require inclusive deliberation, reconsidering the entire researcher participant compact. What is our deal here, in terms of return of information?

Last slide, the traditional line between clinical and research work is under-challenged here. I will tell you right now, what I'm going to say at the roundtable, I think you should take it on.

This is a deep challenge. It's ethics. It's law. It's politics. It's science. It's medicine. The research paradigm is shifting. It's going to exacerbate this problem and it requires, my last bullet, new approaches to bridge research and clinical care. Thank you.

DR. WAGNER:

Susan, thank you. Let's now turn to Professor Erik Parens, Senior Research Scholar at the Hastings Center, who investigates how we use new technologies to shape ourselves and how emerging science shapes our understanding.

He is principle investigator on a project investigating the difference between reasonable and unreasonable claims, based on neuroimaging technologies, and Dr. Parens is a former consultant to several Government and non-Government bodies, including National Bioethics Advisory Commission and the AAAS, American Association for the Advancement of Science. Welcome, Erik.

DR PARENS:

Thank you very much. It's an honor to be here. We're going to switch gears, in a couple of senses.

I would like to offer a friendly challenge, and that is that you should help citizens recognize a couple of basic points.

One is just how incredibly fascinating and complicated the results of the new sciences of human behavior are A) and B) how important it is to continue asking what those results do and do not mean for fundamental ideas, like freedom and equality.

Now, to try to sure up my claim that the results are complicated, I'm going to tell you a one-slide history of behavioral genetics, actually, I am going to tell you — can offer you a one-slide history of schizophrenia genetics, but I think it's a fair enough emblem of the field, as a whole.

In 1966, Leonard Heston published a very elegant, simple paper. What he did was compared foster children born to mothers with schizophrenia and foster children born to mothers who were psychologically normal, and he was able to show, low and behold, that genetic differences helped to explain why some children developed schizophrenia and others did not.

Now, some of you are sitting around the table, like John over there, and saying, "Duh," but this was 1966, and in 1966, there were a lot of very smart people, people as smart as all of you, who thought that the primary cause of schizophrenia was bad parenting, and in particular, bad mothering.

So, this was a radical important result, and at the time, many people wrote many similar papers, demonstrating the same point, regarding many common disorders and regarding many common behaviors.

Fast forward about 25 years, almost 25 years, and the human genome project gets funded, and so, with the human genome project, there was this aspiration to get from showing that genetic differences make a difference in explaining why some people develop some traits and others don't.

The aspiration was to get from showing that genetic differences matter to showing which genetic differences made a difference.

So, way back in 1990, many smart people hoped that there might be the — they might be able to discover the gene for schizophrenia, in just the way they had found the gene for PKU or CF or Huntington's or Tay-Sachs.

In the early 90's, though nobody will admit to it now, there were some people who thought that we would find the gene for aggression, maybe.

Well, fast forward to the early 2000's and as all of you know, now, it turns out that the picture that the human genome project was painting was vastly simplified.

Two lead — I am quoting here, two leading lights of behavioral genetics are of Gottesman & Pertonis, who in 2003 wrote, "Around the start of the human genome project, many optimists could envision the imminent identification of genetic causes for common human diseases, such as schizophrenia."

The truth is exactly the opposite. The truth is a lot more complicated and a lot more fascinating.

As we heard just a moment ago, I believe, most genes don't code for one product or have just one effect. Indeed, it's not unfair, I think, to say that the central dogma, one gene, one RNA, one protein is in the throes of a radical, radical revision.

What is exciting and fascinating and perhaps, in a way, a relief of a kind, it turns out that the understanding of single genes requires understanding how genes interact with genes, how they react with — in the cellular environment, in the intra-uterine environment, in the family environment, in the social environment, and in the environment.

If you want to understand genes, most genes, the action is understanding interactions in environments.

So, it turns out, as a number of people have already said, everything seems to matter when it comes to understanding the emergence of

complex behaviors. Genes matter and neurons do and hormones do and nutrients do and reasons do and stress does and social status does and toxins do, too.

DR. GUTMANN:

Add that to your slide.

DR PARENS:

Okay, now, I'm trying to make good on my assertion that the science is interesting and complicated.

Now, I want to try to make this pitch, regarding meaning questions, and to do so, I want to make a tripartite distinction, a crude one.

For the sake of this conversation, I think we can distinguish between questions regarding the practice of behavioral genetics and questions concerning the meaning of results from behavioral genetics research.

Now, of course, those are not mutually exclusive categories, by any stretch of the imagination. In fact, I'll talk about a way in which there is interaction between them, but for now, we can distinguish, for the sake of conversation, those two kinds of questions.

And I think it's worth mentioning, in passing, that increasingly, natural scientists and social scientists are increasingly interested in something really different, and that is the causes of bioethical views.

That is, why some people tend to have some kinds of views about practices, why some people are utilitarians and some people are deontologists, and certainly, some day, somebody is going to be interested in why it is that some people tend to emphasize some kinds of interpretations and others emphasize a different kind.

What is different about what I am saying here is that I want to thump here, for questions regarding the meaning of behavioral genetics, findings.

Now, let me try to flesh that tripartite distinction out. When people think of bioethics, I think they think primarily of questions regarding practice.

Indeed, in your mission statement, you say your goal is to identify and promote policies and practices that ensure that scientific research, healthcare delivery and technological innovation are conducted in an ethically responsible manner.

Bioethicists are accustomed to, have a lot of practice answering questions like, how should researchers handle incidental findings, from

behavioral genetics research and how should policy makers prioritize offer — the offer of behavioral genetics tests?

Now, because patients need protection and because researchers need guidance, and because policy makers need to make budgets, practice questions require answers. No matter how tentative they might be, that's what they demand. Meaning questions are different.

By definition, behavioral geneticists investigate human behavior, which very quickly takes us to very old, old questions about the meaning of things like human freedom.

Indeed, what do we mean, when we say that someone is free? How could it possibly be the case that I am a natural object, like all of the other natural objects in the world, subject to all of the same laws, as all of the other natural objects in the world are, and have this experience of responding to reasons, or choosing?

Behavioral genetics also investigates genetic differences. That's the whole idea, is to establish correlations between how people are genetically different and how their behaviors are different.

In so doing, behavioral genetics raises very old, old questions about the meaning of moral equality. What, indeed, do we mean, when we say that persons are equal? How can we be physically, emotionally, cognitively different and morally equal?

Those kinds of questions do not admit of answers, the way practice questions do. What they demand is more conversation and more questioning.

Now, how we handle meaning questions may affect how we handle some important practice questions.

Can we investigate genetic differences between groups, while maintaining our commitment to moral equality or does such research ineluctably lead to discrimination? Can continuing to investigate the determinants of human behavior support our efforts to more humane — to act more humanely toward people, who act badly, or do the results of such investigation ineluctably lead to de-humanization?

But what I want to suggest, and this is the limb I'm going out on, I want to suggest that even apart from the potential practical pay-offs of asking meaning questions, we should be asking them, because as human beings and as citizens of a democracy, we care about what freedom and equality mean.

Quickly, the causes question, causes regarding bioethical views all together.

In the late 60's, when bioethics got off the ground, bioethicists leaned in this heavily cognitivist direction. When they thought about what they were doing, they explained their activity, primarily in terms of the application of disinterested reasons to questions regarding practice and policy.

The emerging field of moral psychology invites a more complex view of bioethics. Moral psychologists seek to explain why human beings vary in their responses to the same ethical question.

There has been a lot lately, about neuroscience and its contribution to moral psychology. I would suggest to you that evolutionary biology, developmental biology, developmental psychology, social psychology, even behavioral genetics, in however small a way, can in principle, contribute to causal explanations of bioethical views.

Clearly, I'm saying that's interesting, but hardly sufficient.

Questions about the causes of our views admit of scientific answers. Questions about practice require actionable answers. How are the behavioral genetics researchers going to help? How are we going to help the behavioral genetics researchers to decide how to handle incidental findings?

Again, the meaning questions demand more conversation. They demand more questioning. What do we mean by freedom and equality? What do and don't behavioral genetics findings mean for those fundamental values?

Now, I submit to you that we live in a culture that is ever less patient, with meaning questions. It seems to me that some of our great universities, not yours, but some of our great universities are flagging in their commitment to asking such questions, because doing so does not seem to grow the economy or protect anybody from harm or improve anybody's health.

It seems to me, nonetheless, that human beings and citizens care about meaning questions. They don't only care about growing the economy and protecting us from harm and improving our health, though we all care a whole lot about those things, and for a good reason.

So, again, the challenge is this. How can you, how can we facilitate a conversation to help citizens recognize A) how fascinating and complicated the results of the new human sciences of human behavior

are and B) how important it is to ask what the results of those sciences do and do not mean for fundamental values, like freedom and equality? Thank you very much.

DR. WAGNER:

Thank you, in fact, thanks, all of you.

You've given us quite a range of conversations. Actually, it's interesting, I don't know if you got together in the back, before you did this, but we had a conversation about citizens and the general public.

We had a conversation about researchers and a conversation about the medical healthcare community, and all of those are valuable. I've got copious notes and I look forward to getting back to your slides, to fill in some of the blanks.

Susan, your charge to us, I think, was pretty direct, about wanting to address — have us spend some time addressing incidental findings and individual research results.

But Ellen, back to you. There was a sense of, for lack of a better word, frustration and — in your message to us, and maybe this is a question for all three, about a clear understanding of what some of the issues would be, are and would be.

But the frustration seems to be about how best to address those. I wonder, is there — do you have in mind, what kind of guidance would be most welcome, from a Commission like this?

I know that in the healthcare community, in particular, I know that, you know, physicians bristled, in some ways, around HIPAA requirements.

On the other hand, they provide a firm back-stop to the way certain information will be handled.

Is there something like that, that you have in mind, to help address some of the questions, particularly in the middle, your middle point, about policies and access issues and views?

DR. CLAYTON:

Yes, here is where I think we need guidance.

I think we need very clear understanding about how we're going to use the information and what kind — what sorts of medical interventions are going to be provided in response to certain genetic variants and what medical interventions are not.

I am concerned this will be deeply unpopular, but I think it's absolutely essential.

DR. WAGNER:

Comments from the others of you? Well, let me go to — go ahead.

DR. SULMASY:

Thanks, Ellen. I was going to follow on that, because you sort of expressed a kind of pessimism about, you know, controlling the information and this sort of sense of almost an optimism about, you know, controlling the expenditure of healthcare resources, regarding the findings of these things.

You know, there are three propositions, it's been said, that govern, you know, our healthcare system, which is that everybody wants everything. Nobody is willing to pay for anything and no one is willing to tell anybody `no`.

This gets us — has gotten us into huge amounts of trouble, even beginning to try to have a conversation about controlling, you know, healthcare costs.

How is it that you really think it's going to be different in genetics?

DR. CLAYTON:

Well, I actually would go so far as to say that I think the healthcare system actually has to take the bull by the horns and start saying `no`.

Now, frankly, I don't think it is start, it's continuing, saying `no`. I mean, the example I give of the parent who wants amoxicillin for their child with a virus, I mean, it's my job to say `no`, and I think that the question that we really have to ask is, what is the scope of why we should say `no` and what is the justification for that?

I think that actually, defining that scope of justification is a real challenge for us, but that, in fact, has got to be the key to the answer, that — and so, because the information is absolutely going to be out there. The demand is absolutely going to be out there, although what people say they want and what they actually want are two radically different things, a lot of the time.

We have a lot of information about that, but I think that there has to be a fundamental question about what it is that healthcare providers and the healthcare system are suppose to do and what they are not suppose to do, and I think that we, in light of this science, have to answer that question directly, and so, I think that's the fundamental challenge.

DR. WAGNER:

Susan?

DR. CLAYTON:

And by the way, Susan and I completely disagree about this, which is fine.

MS. WOLF:

That is not where I was going, Ellen.

I'd like to coin a new term, public informatics. I think part of the problem, Dan, is that we've thought about information return and clinical decision making in an old fashion way. Here is what we've found. What should we do?

The challenge of genomics, and I think we would agree on this, is that suddenly, you're talking about a fire hose of information, potentially, coming at this individual, whether it's in a research or a clinical context.

It has to be sorted, in some way. There are colleagues at Harvard who are working actually with online systems, for offering information back to research subjects in that context, that would give them a sense of what is this? How well validated?

There are ways to return information that can help structure the, what are we going to do about it, side of it.

DR. WAGNER:

John, you had a question. I'll tell you what, hold on, I've got John, Nita, actually, I've got Amy, Nita, Barbara.

But while we're doing this, why don't we ask if anybody in the audience wants to cue up behind the microphone, and this would be a good time to do it. John?

DR. ARRAS:

Okay, I want to thank all of you. I think this is one of the best panels we've ever heard. So, thank you.

Erik, I'll take the bait, okay. So, suppose we want to go down this road, of really scrutinizing meaning of freedom and equality and so forth.

Now, as you know, I mean, philosophers have been battling these issues around since forever, right. As graduate students, we cut our teeth on exactly, these sorts of issues.

Do you see these new emerging technologies as changing the nature of these traditional discussions about freedom, determinism, equality difference? You know, have they posed a different sort of challenge that requires different sorts of answers, or what do you think?

DR PARENS:

I tried to make clear, that I think there is absolutely nothing new about the fundamental philosophical questions.

The new technology raises the old questions, anew. Indeed, there are many senses in which I think genetic technology saved the life of philosophy.

It is the case, that geneticists study genetic variation, and we are a culture that has trouble wrapping our minds around the fact that we are genetically different and moral equals.

That question may have some practical pay-off. I was very careful, to say that I think you should figure out how to help citizens recognize how important these meaning questions are, which is to say, I don't have a simple answer, how to do this.

Now, there are, of course, many efforts to do this sort of thing. One might argue that the MacArthur Foundation has supported this sort of effort, in the context of neuroscience and freedom, or I mean, they say the law, but I think it's neuroscience and freedom.

I don't know if it would be useful, for somebody, with your help, to start focusing on the human sciences and equality.

Now, again, I understand the respect in which this is a quixotic injunction or request of mine, but I do want to be on record, as thinking, this is something bioethicists should be thinking about.

DR. WAGNER:

I would agree. Actually, yes, we do need to hear that, I agree.

I'm going to go to Amy, and then to you, Hank.

DR. GUTMANN:

Let me pull one thread together, about what the three of you have said, and then, see what your reaction is.

So, and it's a thread that I'll tell you, I agree with, but it leads to an interesting question and dilemma, with some answers and some need for further conversation.

So, the monopoly of information, genetic information, or any kind of health related information, by clinicians, is gone, Ellen said. It's been gone for a long time. The internet made it gone, a long time ago, even before where we were talking about genomics and neuroimaging.

So, it's gone. There — researchers have an obligation to share information, under some circumstances, and Susan, you've laid out some of the criteria for that.

Now, Erik, there are — when you get — when people, who are not experts in an area, get information, particularly, information about themselves and their family and their children and so on, especially when the information is as broad as the information that is available on the internet or available when you get — you know, you learn about gene sequencing, there are a lot of questions raised about what you should do with it, what you, as an individual, should do with it.

Some of those questions have answers, and some need to lead to further investigations, right, and one of the things we're trying to deal with are the hard issues of when you get information that doesn't have a clear answer. What happens next?

Do you have access to clinical expertise? Where do you go — and counseling?

So, that's what I want to ask you, as to what you think are the open issues that raise ethical issues here?

Not everything — not every ethical issue lacks an answer. Some do and some don't, okay. So, we tried to —

DR PARENS:

I tried to say that.

DR. GUTMANN:

Okay, okay. So, where do we go from — if we can agree on that, where do you go? What are the hard issues that — or a hard issue that follows? Put your microphone on.

DR. FARAHANY:

Ellen, you mentioned, just as a dichotomy, access versus the action that we take on the information, and it seems to me like there may be some things in between, right?

So, just as Amy says, I think access has been out there, for quite a long time. Neuroimaging and genetic information doesn't necessarily introduce new wrinkles, except in between those things, we might have

things like the manner in which the information is collected, whether it's explicit or if it's covert, or the manner in which it's stored.

So, I know that Hank might speak to some of the re-identification issues, that are currently happening and ways to make sure that the data is strongly protected or consent to the use of the information and the extent to which people can consent in advance, to the broad uses.

So, I wonder if there is something in between access and action that you might think would be an open ethical issue.

DR. CLAYTON:

I will take those in a couple of things.

I think first of all, there is a huge distinction between imaging and DNA, at least at present, in the sense that at least at present, you have to — I mean, you know you're getting imaged. I mean, something happens to you. Getting DNA is a completely different ball of wax.

And so, you know, for the most part, you know, but you may not know, and so, I think that's going to be — that's a distinction that's going to have a huge impact, I think, in how we think about this.

The issues about, you know, about the kind of research people do, I mean, we have to recognize that there is a tremendous amount of research, particularly in the area of epidemiology and more particularly, epidemiology — genetic epidemiology, that's done without individual consent, I mean, and that's just true.

So, and so, unless you plan to change that, that's — I think that's — I mean, that's out there.

I think the fundamental issue that we really are going to face here is the idea that just because Francis wants to go out and get, you know, expert ideas about — I did 23andMe, too, and you know, and so, when I do 23andMe, I, of course, bring to bear, all the stuff that I already know about genetics, to explain away everything that might be potentially worrisome, and if I actually did have some worry, I, too, can access anybody I want.

But the fact is, most people aren't going to have that. I mean, there is not going to be a kindly genetic counselor, even a kindly geneticist talking with you about this.

And so, it's going to be, you know, the best you're going to get is, you know, is diagnostic tools that are embedded in the electronic medical record, that are going to try to help your clinician.

But the idea that you're going to have something that looks even remotely like genetic counseling for most of this, I believe is illusory.

DR. WAGNER:

Let me — let's go, real quick, yes, let's hear your comments, real quick, and I need to go to the — you need to go to the microphone, it will go to Hank. Erik, did you have one?

DR PARENS:

I just wanted to try to respond to this —

DR. GUTMANN:

No, let Erik — okay, yes.

DR PARENS:

Let me try to respond to the distinction.

I think it would be helpful for all of us to get clearer, about the difference between reasonable disagreements about what to do with probabilistic information and outright mistakes about the significance of the information.

I think it's really important to recognize that both of those things can go on and surely, a regulatory body can help people avoid mistakes, and has to facilitate reasonable disagreements.

DR. GUTMANN:

All right, so, I like the quote from — which became quite famous, from Daniel Patrick Moynihan. "Everyone has a right to his own opinions, but not to his own facts." There is a difference.

DR. WAGNER:

Susan?

DR PARENS:

Right, but we — so, it's important to remember that we're not doing anybody a favor by giving them access to partial useless facts —

DR. WAGNER:

And there is a big question in the useful —

DR PARENS:

Where is threshold?

DR. WAGNER:

Yes.

DR PARENS:

There is a threshold, but there is a difference.

DR. WAGNER:

The data are far more useful to Ellen than they are to maybe, a number of us.

MS. WOLF:

Let me just add that I actually don't think we're over the access hump in genetics.

I mean, there is a lot of stuff you can find out about genetics, generally, out there on the internet, but getting access to your own data and particularly, sophisticated data, you know, a copy number variance, analysis of your genome, that's still a really big issue.

In terms of action, I think we're going to strive, through research, for evidence based responses to that. I've been part of studies, trying to track, so, then what do people do with this information, and then ultimately, you want to ask about outcomes with this information.

DR. WAGNER:

That gets back to the utility question, that I think you made. Hank, you've been patient.

MR. GREELY:

Sure, I'll be happy to fight with my old friend Ellen about re-identification —

DR. WAGNER:

If you could take that outside, that would be great.

MR. GREELY:

Or maybe another place and time, but I want to agree with her third point, about how this critique throws into question, a lot of epidemiology.

I think it does, but I think that's a problem that this Commission might want to deal with.

The problem comes when scientists are doing things with data derived from people, that the people that the data was derived from didn't realize or don't think is going to happen.

When you've got that mis-match between the action and the popular belief, you run the risk of things like the Havasupai suit and the suits against the use of blood spots, in both Texas and Minnesota.

So, I think one thing this Commission might usefully do is try to narrow that gap, and you could narrow it in either direction. You could change the consent process, so that people knew it, or you could come up with other ways for people to know that things are going to be used without their consent. Either one of those logically works.

But narrowing that gap, I think, would be potentially, a good use of the Commission's time.

DR. WAGNER:

Chris and Barbara, can you ask — can we wait for the break — can we go to the break, or do you have something that would benefit us all, maybe, quick?

DR. ATKINSON:

Mine might be a real, fast, quick.

DR. WAGNER:

That's great.

DR. ATKINSON:

Okay, it's for Susan and it's the, who pays?

I think the problem with the whole area that you're talking about is, is it the research budget? Is it the insurance carrier, after it's found? Is it the doctor, who doesn't get paid? Is it the patient, him or herself?

MS. WOLF:

The recommendation to date has been that research budgets, direct budgets should be expanded, so, this falls on funders, to allow the researcher to identify, and then get a consult, does this look like a finding of concern?

After that, it goes back to the research participant, and further pursuit of its meaning and treatment is in the treatment sphere, with treatment payers.

DR. WAGNER:

This has been a very rich session. Thank you, thanks to the three of you. We'll reconvene at 2:30 p.m. Thank you, all, very, very much.

