This transcript has been edited for clarity

Thursday, November 16, 2006

President's Council on Bioethics

Session 4: Overview: Genetic Ethics and Public Policy

CHAIRPERSON PELLEGRINO: Next, this is an overview of genetic ethics and public policy. We have the privilege of hearing Dr. Kathy Hudson, the Director of Genetics and Public Health Policy at Johns Hopkins University. She knows we don't give long introductions and she's pleased with that.

So I'll ask you to jump right into the matter at present.

DR. HUDSON: Thank you very much for the invitation to be with you today.

I have a narrow subject about genetics ethics and public policy, and what I thought I'd do is divide my remarks into three sections and talk about ethics and policy issues in genetics research, in clinical practice, and in non-medical contexts.

So first, in talking about genetics research issues, there are a number of policy issues and ethics issues which are really garden variety issues and are common to all biomedical research and really don't pose immediate problems in genetic research, and some examples are given there.

Then there are issues that are special but manageable issues in genetics research, including impacts on family members, including non-paternity, ownership of specimens and data, and intellectual property issues which, while present in all biomedical research, are particularly acute, I think, in genetics research.

And then there's the really tough issues, and I think some of these really tough issues are emerging as a consequence of the rapid proliferation of very large cohort studies with large biobanks and databases.

So Bob has talked a little bit about the intersection between genetic factors and environmental exposures and lifestyle and behavior. And in order to dissect out the weak genetic contributors—probably numerous genetic contributors to any specific health outcome and the numerous environmental exposures lifestyle and behavior inputs, it has been proposed that in order to unknot that problem, that we do a large scale, population-based study where we collect information about all of these inputs.

So the proposal has been made, but not funded and probably won't be funded for some time, to study a very large cohort of people in America. And I should mention that this has already been underway in a number of countries around the world, including Iceland, which is where the

diabetes allele that Bob mentioned was found.

So in the U.S. it has been proposed that half a million people be followed, that DNA and biological specimens be collected, that clinical data be collected, lifestyle and behavioral information be collected, environmental exposures, and that folks be followed over a decade. And this is all to provide a very large research resource in which people can use that resource in order to be able to identify weak genetic, environmental, and behavioral contributors to health outcomes.

I should mention that in terms of the technologies for being able to do this, the genetic technologies are really ripe to be able to do the genetic component of this. The technologies for accurately assessing lifestyle behavior and environmental exposures, I think, are really sort of akin to where we were in the '80s with genetics, where we really don't have very precise measures of some of these things. They are coming along. So, sensors that can be worn that measure air quality, for example.

So what issues are raised by such a study? There are issues in terms of whether or not the primary data is returned to the individual research participants, and if information is revealed that places that participant at high risk, imminent risk, what is the obligation of the researchers to provide immediate care?

What kind of research or what kind of consent is provided for this secondary research, with this very large database?

As Bob in the discussion mentioned, the personal and social reactions to potential group findings, findings that are relevant to different social groups. And then, of course, how do we protect the participants in terms of privacy and discrimination?

And certainly within the study, information will be collected about people's participation in illegal or stigmatizing behaviors.

So in many large DNA studies oftentimes the samples and the information is de-identified and thereby it becomes no longer subject to some of the rules and regulations that guide human subjects research. And just to remind you that human subjects research guidelines define a human subject as somebody who's alive, somebody from whom data is collected through an intervention or interaction, and it contains private identifiable information.

The office at HHS responsible for implementing and enforcing these rules has said that it doesn't consider coded private information to involve human subjects if the information was not initially collected expressly for the purpose of the second study or third study or 105th study, and if the investigator cannot readily assess the identity.

So it's not that anybody can't ascertain the identity. The investigators can't readily identify the individuals. And I think that raises some issues for us collectively, whether severing the link between researcher and participant is a good thing or a bad thing. Is DNA ever really not

identifiable?

Amy Maguire and Richard Gibbs have published a paper recently in *Science* in which they argue that we might need to reconsider the rules governing the use of de-identified samples in the absence of consent.

Specifically, in a proposed large cohort study severing the link between the participant and the researcher may, in the end, sever the ability of individuals who participate to receive information about that study that may be relevant to their own health.

So I'm going to move now to clinical genetics issues, and I'm going to just give three little tidbits of information, I think, that are relevant to the clinical genetic situation in terms of policy and ethics.

And the first--and just to remind everyone--the number of genetic tests is increasing steeply. Most of the genetic tests prior to the present day were for rare Mendelian genes and mutations.

More recently, they are for more common variants that contribute to complex diseases and for pharmacogenetic tests, and you can see that the slope is getting steeper on this line, and I think that's likely to continue.

And there have been projections that we'll have handy-dandy devices that can read out our entire genomes within the next few years. This is an article by George Church that was in a recent *Scientific American*.

So this committee has considered the issue of preimplantation genetic diagnosis in the past. To remind you, embryos produced through *in vitro* fertilization have a single blastomere removed. Genetic analysis is performed, and based on that analysis embryos are selected for transfer back into a woman's uterus.

This committee, when it issued its report, "Reproduction and Responsibility," said, and I quote—or maybe I'll paraphrase— that there really wasn't enough information about PGD to help the committee or other policy makers formulate policies to govern this area of clinical practice and research, and the committee recommended that studies be undertaken to really get a good handle on what was going on in terms of preimplantation genetic diagnosis.

In the wake of that recommendation and our own work, we conducted a survey that I would like to share just a couple of top line results from. We surveyed 415 assisted reproductive technology clinics in the United States, had a 45 percent response rate, and what we learned was that three-quarters of the IVF clinics are performing preimplantation genetic diagnosis.

We ask them to estimate the number of cycles of PGD -- this is not babies, this is cycles of PGD -- in 2005 and had among our group 3,000 cycles reported, and we estimate that that's about four to six percent of all the IVF cycles in the United States.

This committee has talked a lot about for what purposes preimplantation genetic diagnosis is performed, and so we asked clinics whether or not they offered PGD for these different purposes: aneuploidy testing to look at abnormalities in chromosome number, autosomal disorders, chromosomal rearrangements, X-linked diseases, non-medical sex selection, adult onset disease, HLA typing in combination with a single gene test, and HLA typing in the absence, and finally to select a disability.

As you can see here that overwhelmingly, aneuploidy testing is the most common. Most clinics that are performing PGD are offering PGD for aneuploidy.

Of interest, of note is that 42 percent of the clinics indicated that they are offering preimplantation genetic diagnosis for non-medical sex selection.

We also asked them about how many cycles they perform for each of these purposes, and you can see that there's a big drop, notably in everything except for aneuploidy. You can see that while 42 percent of the clinics are offering non-medical sex selection, this use constituted only nine percent of the cycles performed in 2005.

There have been a number of really heartbreaking stories about misdiagnosis in preimplantation genetic diagnosis. We asked clinic directors about their awareness of inconsistencies between PGD results and subsequent genetic testing. And nearly a quarter of the clinic directors said they were aware of such a circumstance.

That doesn't mean that 21 percent of the cases are misdiagnoses. It means 21 percent of the directors had been aware of such a case at some point. It may have been their own. It may have been another laboratory's.

So data I think are important, and this sort of reiterates your own recommendations, are needed for informed patient decisions, for quality improvement in PGD, and for evidence-based policy.

And as a result, we are in the process of putting together a voluntary registry for preimplantation genetic diagnosis, and we are working collaboratively with the American Society of Reproductive Medicine, the Society for Assisted Reproductive Technology, and the PGD International Society.

We have the data fields all collected. We know what we want to collect. We have the collaboration and cooperation of the leadership of these organizations, and are now seeking funding for this registry.

So moving to my second issue, one that's near and dear to my heart, which is the quality of genetic testing. We talked about the clinical utility of tests and focused on that, in Bob's remarks and the clinical validity of tests. I'm going to focus somewhat on the analytic validity, that of tests.

So as background, genetic testing laboratories are governed by the Clinical Laboratory Improvement Amendments, which were put in place in the wake of bad Pap smear test results going back to women in the '80s.

The responsibility for implementing CLIA is given to the Centers for Medicaid and Medicare Services, and CLIA was really intended to assure analytic validity. When a laboratory does a test and says there's a mutation there, you want to be quite confident that they're right-- analytic validity. Whether or not that mutation has an association with a health outcome and if there's something useful that you can do with it are the two other "-ities." I'm talking about the first "-ity."

So the law directs the government to issue standards to assure consistent quality performance, including a whole bunch of measures that you would expect would be in laboratory quality, including proficiency testing.

Of note, there is a special category for high complexity tests and all genetic tests are high complexity tests, and specific requirements can be developed for specific types of tests through the creation of a specialty area. For example, there are specialty areas for microbiology, toxicology, immunology, chemistry, et cetera.

There has been no specialty created for genetic testing despite the fact that I believe it is the fastest growing area of the diagnostics market, and creating a specialty area really is a prerequisite for mandating proficiency testing programs, which Congress believed was the best way to directly measure whether or not a laboratory can get the right answer consistently.

So we're not the first people to notice that this is a problem. Advisory committees over time have pointed out that there needed to be enhancements in laboratory quality for genetic testing. The NIH-DOE task force nearly a decade ago, and the Secretary's Advisory Committee on Genetic Testing in 2000, specifically recommended the creation of a genetic testing specialty. And in 2000 HHS said, "Yes, we're going to create such a thing," and create tailored standards for this complex set of tests.

After six years went by and no regulation came out, we looked at the comments that were submitted in response to that notice of intent and found, in fact, that most people were supportive, and we were pleased when we communicated with the Department that they said that they were planning to publish a proposed rule for genetic testing as soon as possible, and that was in January.

A couple of months later they put it on their regulatory agenda, which is their signaling “we're going to do this” in a formal way, but then there was an abrupt change within CMS they have first privately said and more recently publicly, indicated that they have no intention to create special standards for genetic testing.

And according to a CMS official earlier this week at another advisory committee meeting,

they said that genetics is moving very fast, and that's true.

They said that CLIA does not address clinical validity, and that's true.

They said that CLIA does not address all of the complicated ethical, legal, and social issues, and that, too, is true.

They said that there are not many samples available or formal programs for proficiency testing, and that is also true.

They said that there is not an evidence of a problem, which I do not believe is true, and that genetic testing laboratories participate in other specialty areas, the relevance of which is unclear to me. If you can do a blood chemistry test, it doesn't tell me that you can do a genetic test.

So we did a survey of genetic testing laboratories and found that there are deficiencies in genetic testing laboratories and that the more a laboratory participates in proficiency testing, the fewer analytic errors they observe.

So proficiency testing is doing exactly what it was intended to do. It's reducing analytic errors. CLIA was intended to reduce analytic errors so that when you get a test result and you make a profound decision based on that test, you know the answer is right.

We document this sort of sad history in a report that I think was included in your briefing book, and we also have formally requested that the agency move ahead with rulemaking along with Public Citizen and the Genetic Alliance, and we're awaiting a response to our petition.

So that's the laboratory end of things. What's FDA's responsibility here? Genetic tests can be done as home brews. That's a laboratory developed test where the lab makes all of the ingredients itself. They don't really buy anything except for general purpose reagents.

Then there's home brews using analyte specific reagents which are purchased, and then there are genetic tests using kits that are premanufactured. FDA regulates analyte specific reagents and they regulate kits.

So of the 1,000 or so genetic tests that are are available out there, only five have been reviewed and approved by the Food and Drug Administration. Actually a couple of these Bob talked about. CYP450 is a pharmacogenetic test. UGT1A1 is the test that will tell you whether or not you are at risk for an adverse reaction to Irinotecan for colon cancer.

So laboratories are not required to use test kits if they're available, which creates an unequal system in the marketplace, and there are two paths to the market. People for good reason take the path of least resistance.

FDA has recently jumped into this fray and has said that they will regulate one specific type of laboratory developed test, which they call *in vitro* diagnostic multivariate index assays, if you

can say that five times real fast. And so they've caused quite a lot of consternation, I would say, in the laboratories and in genetic testing companies and in the biotech industry and in the patient community because it's unclear where FDA is going here.

Why did they jump into IVDMIAs? The guidance is really based on the technology used and not the risk necessarily posed by these kinds of tests, and it's very unclear what the big picture plan is. How can we ensure quality and also ensure access as we move forward. What's the big strategy here for how we move forward?

So CMS has thrown in the towel and gone home. FDA has put its toe in the pool. It's not clear what the overall strategy here is, and so we all are getting conflicting signals or at last confusing signals.

So we need transparency. We need quality. We need a level playing field. We need to reward innovation, we need to ensure access, and we need a good plan for how to do that, which we don't yet have.

We talked -- you talked -- a little bit about direct to consumer testing, and I'm going to end the clinical chunk by talking a little bit about this, and not the specifics of the oversight system that's in place for these, but rather to give you a couple of examples of what's on the market.

There is a test available for women that can tell you whether your child will be male or female at five weeks of pregnancy by looking supposedly at fetal DNA circulating in maternal blood. There have been a lot of complaints about this. Some report that they get the right answer about 50 percent of the time.

(Laughter.)

DR. HUDSON: More disturbingly, the company has contacted women who have had the test and told them, "Your fetus has severe chromosomal abnormalities. You need to see a doctor immediately." People have gone through intensive testing and screening and then given birth to healthy babies with normal karyotypes. So there’re some troubling characteristics here.

DNA Direct offers a number of genetic tests — including for people who are desperately trying to have a child — fertility testing, where they look at chromosomes and do Factor V testing. Of course, the first thing you really should do is go to your doctor and make sure that you're producing the two key reagents, oocytes and sperm.

(Laughter.)

DR. HUDSON: Factor V testing they say is a common genetic variant. I think "common" in genetic parlance and "common" to the lay public has very different meaning, and they talk about women having recurrent miscarriages may carry this particular mutation. In fact, I think most of the scientific literature points to this mutation only being associated strongly with third trimester pregnancy losses, and the overwhelming majority of pregnancy losses are first trimester.

There's a stress gene test (and I know I've got it).

There's the Alzheimer gene test that's available, despite the widespread agreement that this is not ready for prime time.

And then there's my favorite, CyGene Direct, which can give you a genetic test for your athletic performance. Some of us don't need a genetic test to tell us that.

And then this test is no longer available, although the offer has popped up in a new company offering similar testing: "Are you concerned about your child's future? Does your child have a genetic trait that leads to disruptive addictive personality? DNA testing can help you understand and manage your child's behavior before it gets out of control. Imagene will test a panel of dopaminergic related reward deficiency syndrome genes."

And the physicians in the crowd, I'm sure, learned a lot about reward deficiency syndrome in medical school.

So we can talk about what we need to do or not need to do about direct to consumer testing in the conversation. I'm going to move quickly to the non-medical uses of genetics, and probably the most common use of genetics outside of a medical context is in law enforcement, identification of suspects with DNA presented as evidence, the Innocence Project having successfully exonerated a number of people who were wrongly accused and convicted.

More troubling, I think, or somewhat troubling, I think, are the increasing use of DNA dragnets where DNA is asked to be voluntarily supplied by people in a particular area or meeting a particular eyewitness description.

And then DNA profiling, where people — in fact, a company — will take the genotype and give you the probable phenotype of the suspect.

Although this hasn't happened much lately, there's some reasonable chance, I think, that genetic information will be used in the courtroom, especially in the sentencing phase in determining culpability.

So to talk about the other non-medical issues, I want to tell a little story of this family, and we're going to call this woman down here Beth. Beth's father has pre-senile dementia and is now being principally taken care of by her mother. Her two brothers, who are older than her, have early symptoms, very similar to what her father had in earlier years.

Her mom learns about a test that's available for presenile dementia. This is one of those cases where there's nothing you can do about it, like ApoE4. In this case the gene is presenilin-1, which is a real gene which also leads to presenile dementia.

So the family gets tested except for Beth, and in fact, the affected family members are found to have a mutation in the presenilin-1 gene. So Beth is thinking, "Should I get tested, too?"

So if there were an intervention, the whole equation would change, right? If there were something she could do to prevent the onset of dementia, I think what she would be thinking about and the magnitude would be very different.

One thing she might be thinking about is whether or not this information might be used against her, specifically in the health insurance context, but luckily Congress, with some foresight in passing the Health Insurance Portability and Accountability Act, included genetic information among the factors that group health plans cannot use to deny coverage or increase rates. So if Beth is in a group health plan, she's protected.

What else might she be thinking about? Well, she might be thinking about whether or not her employer can get this information.

There has been a debate over the last decade about whether or not the Americans with Disabilities Act provides sufficient protection for predictive genetic information, and specifically, the Equal Employment Opportunities Commission has said that predictive genetic information would be covered under the so-called third prong of the ADA and that people with predictive genetic information, if they were discriminated against, would be regarded as having a disability.

There have been some cases that called that into question, and most courts are now very narrowly construing what meets the definition of having a disability under the ADA. And so in the wake of that lack of clarity, in 2000 President Clinton signed an executive order which remains in place today that the federal government as an employer cannot deny jobs or employment benefits based on genetic information.

And when he signed that order, he said, "I'm trying to set an example for the private sector," and he called on the Congress to pass an equivalent law.

Unfortunately his example was not followed, and one year and one day later there was a case at Burlington Northern-Santa Fe Railroad where they were surreptitiously testing employees for whether or not they had a genetic predisposition for carpal tunnel syndrome.

There has been a bill pending for a long time in the House and the Senate. Its most recent iteration would prevent genetic discrimination in employment and in the individual health insurance market. It passed in the Senate by 98 to zero, not much opposition there. It has been stalled in the House despite the fact that it has 244 sponsors. It's very likely that in the next Congress this bill will be reintroduced in both the House and Senate and pass pretty quickly.

So that means that when Beth goes to make her decision, her doctor can tell her with absolute clarity that this information cannot be used against her in health insurance and employment, something that right now is having a very negative impact on genetic research and clinical practice.

My last little example here is assuming that Beth is in the military, she joined up to serve in

Iraq and she has this mutation or she may have this mutation. Would she be protected?

The Department of Defense provides benefits to our Armed Service men and women, including providing medical and disability benefits for retired service men and women, but they have this funny little policy that any injury or disease discovered after a service member enters active duty is presumed to have been incurred in the line of duty, with the exception of congenital and hereditary conditions.

I met this young man, Jay Platt, a number of years ago. He had served in the Marines on two tours of duty in the Gulf War, had been diagnosed with a number of cancers, and was diagnosed with von Hippel-Lindau disease, which is a cancer syndrome.

He requested a medical discharge. It was denied, which meant he would not receive benefits, and only because of his perseverance and only because the NIH intervened on his behalf and argued a technicality, frankly -- we argued that he lost function in the other allele, maybe because of something he was exposed to in the war -- and he got his benefits reinstated.

Most people aren't as clever as Jay is. I think that this policy is not viable over the long term, and it's certainly not a just policy if you think that the people whose genetic contribution is known today don't get benefits, and if your genetic contribution is not yet known, you do get benefits. It doesn't make sense to me.

So what do we need to do for Beth? There's a lot of stuff we need to do for Beth, and the most important one is to develop an effective intervention. That's thing one.

So we need to support a robust research pipeline. We need to make sure that she and other members of the public are confident in the research enterprise and confident in the medical enterprise.

We need to demand that genetic testing is of exceptionally high quality by creating a genetic testing specialty, rationalizing the FDA system, tracking outcomes over time which can then feed back into the clinical utility question. It would be much easier if we had electronic health records.

We need to provide health provider tools so that health care providers know who to test with what test and what to do based on that test. We need to protect against privacy and misuse of genetic information, and perhaps reconsider the standards for research using de-identifying samples.

I'm going to close with a word of caution. I'm not sure exactly what the discussions have been about this Council taking up issues in genetics more broadly outside of the reproductive context where you have done such great work in the past. But I want to remind you that there are a number of other committees who take genetics issues quite seriously.

Most of these are within the Department of Health and Human Services, and they are listed

here, some with quite unpronounceable acronyms. If anyone can pronounce that, I'd be interested in hearing it. These are all committees that are focused — this one is newly created actually this week — all four of these committees are focused expressly on genetics issues, and then the Advisory Committee on Human Research Protections focused more broadly on biomedical research issues.

And so with that, I'd like to thank you and look forward to the discussion.

(Applause.)

CHAIRPERSON PELLEGRINO: Thank you very much, Dr. Hudson.

Dr. Schaub, would you be kind enough to open the discussion?

PROF. SCHAUB: Thank you very much for that presentation.

My remarks and questions are based on the two advanced readings that we received from you, and I think I'll leave it to my colleagues to follow up on some of the new information and policy proposals in your talk.

The first report that you supplied to us calls for the creation of a genetic testing specialty under the CLIA, arguing that it's critical to the public's health.

The second report suggests, in addition, that the FDA expand its purview to insure that all genetic tests are analytically and clinically valid.

It would certainly be odd to say that one is opposed to folks being competent at their jobs. So if a designated specialty with standard procedures and ways to test both the tests and the tester would improve the accuracy of genetic information being supplied to individuals, then that seems like a good thing.

However, accurate genetic information is only a good thing to the extent that genetic information itself is a good thing, and I guess I think that in addition to these policy options that you put before us, there are some prior inquiries that our council may want to take before joining in the quest for accuracy.

I would want to ask whether and in what cases and for whom the information is desirable in light of the fact that our ability to test for disease or increased risk for disease is so far in advance of our ability to actually treat or cure these diseases. I'm not certain that better information about ones future fate is better for the human beings concerned.

Know thyself is a human desideratum, but I have some doubts as to whether individualized genetic information contributes to self-knowledge or happiness.

Indeed, I'm not even sure that it contributes always to health. Both reports assert that reliable

tests are critical to the public's health, and you give five, in one of the reports, you give five illustrative instances of the serious consequences that laboratory errors can lead to.

Two of those involved prenatal genetic testing and a third one involved parental testing with a view to procreation. In each case parents were wrongly informed that their child would not have a particular disorder.

The implication is that had they had the correct information, they would have aborted the fetus. I'm not sure where precisely the threat is here to the public's health, unless we mean that allowing unhealthy individuals to be born is the threat.

In other words, genetic information pretty quickly lends itself to eugenic uses, fueled in these instances not by government mandate, but by the longing of parents for unblemished offspring.

You know, if your insurance company finds out what you're going to develop certain genetic diseases, it won't insure you. If your parents find out, they may not welcome you into their arms.

I was very struck by what we learned at the last Council meeting about testing for Huntington's and the efforts that are made to protect the privacy of the young, at least once born, even against the parents by not permitting testing until age 18. So I think there are some real questions to be raised about the ethics of testing not oneself, but another, although another who is, in the case of parents, admittedly also one's own.

Can you tell us what proportion of the genetic testing being done today is prenatal?

In the examples that were given, the errors all led to individuals being born who otherwise might not have been. I suppose that the errors also occur in the other direction. A fetus is diagnosed with a genetic disorder. The fetus is aborted, and then perhaps found to be quite healthy.

Does that happen or do we not know since follow-up testing is not done?

In the second reading, you suggest that a focus on the quality of testing could actually help us to answer questions about who should have access to which tests, along with these questions about advertising and commercialization.

If we went that route right now, and required greatly increased federal regulation and oversight, would the effect be a dramatic scaling back in the availability of genetic testing, at least a temporary dramatic scaling back, since at present only four of the 900-some genetic tests have FDA approved test kits, would laboratories have to close off access, especially this direct to consumer access until FDA approval is secured and appropriate guidelines are developed?

Finally, I want to just say something about the art work by Dennis Asba which accompanies the article in *Issues in Science and Technology*. I thought the paintings were very beautiful and the colors were very beautiful, but they seemed to me to illustrate one of the perils of genetic

testing. To me at least the paintings displayed a form of misreading that goes beyond the misreading committed by insufficiently trained technician.

The misreading that I'm worried about lodges in the popular imagination. Dennis Asba say that the point of his DNA paintings is to "reveal the inner code beneath appearances." And on page 64, there's a reproduction of a painting entitled "Son of Sam." Presumably it shows a section of the notorious mass murderer's DNA.

And while the scientists might assure us that Son of Sam was not coded for mass murder and while a scientist might tell us that the relation between the genotype and the phenotype is more complicated than the inner code beneath the appearances, I suspect that non-scientists will not really get the message.

Indeed, we've been told that even physicians often have a very sketchy grasp of the meaning of genetic test results that are, you know, returned to them.

Human beings have always sought knowledge of their individual fate. The Greeks visited the Oracle at Delphi. Other peoples looked to the stars and astrology for predictive power. Yet others have turned to evidence supposedly offered by the body itself as in palm reading or phrenology.

I certainly don't mean to suggest that genetic testing is fraudulent in the way that these earlier fortune tellers were. Not at all. Part of the danger today may be that genetic testing will be embraced by the public not for its real, albeit limited, value, the sort of thing that was sketched out for us by Professor Nussbaum in talking about pharmacogenic results, but rather that it will be embraced as a scientifically valid version of palm reading.

Is seeking more detailed information about our bodily fate, in doing that, will we become a nation of fatalists?

Even when genetic information is sought in order to stave off or to avert one's fate, one is nonetheless obsessed with fate, and in that sense a fatalist. Alexis de Tocqueville predicted that democratic peoples would be strongly inclined toward both fatalism and materialism. And he argued that it would be important for democratic legislators not to contribute to this doctrine of fatality.

So in the Council's consideration of the ethical meaning of genetic testing and the public policies to be adopted, I would hope that we would remember Tocqueville's warning that it is a question of elevating souls and not completing their prostration.

CHAIRPERSON PELLEGRINO: Thank you very much.

DR. HUDSON: Thank you very much for those comments.

So this committee has previously dealt a lot with the reproductive uses of genetic testing, and

I think that while I'm not aware of any concrete data on the proportion of all genetic tests that are performed in the reproductive context, I'm fairly confident that it represented the majority of testing, certainly up until the present time.

And part of the reason for that is there's sort of a range. But genetic tests provide information only about which you can do nothing, to genetic information where you can intervene, such as we hope for in Beth's case, but she doesn't yet have.

And so in the absence of being able to do anything for the individual, reproductive uses of this technology, whether to prepare for the birth of an affected child or to terminate a pregnancy, have been very commonly used.

One would hope, and maybe it is but a hope, that as we move forward and understand the molecular mechanisms underlying some of these diseases that we can develop interventions whereby we're treating the individual as a living person and there will be less focus on the reproductive context.

So certainly today we are doing genetic testing for Coumadin dosing, for example, outside of the reproductive context. The CYP450 that I listed as one of the FDA approved tests is testing for enzymes that are involved in the metabolism of a huge proportion of prescription drugs and presumably could decrease adverse drug effects, and the cost of those, substantially.

So it's my hope that we move outside of the reproductive context for most of our focus in genetics. They're hard choices no matter how you feel on the pro-life/pro choice question.

The issue of quality and whether or not our focus on quality would reduce access, I think is something important to keep in mind. We certainly would not want to suddenly have a reduction in the access of patients to get tests that are so vital to their futures.

There are some proposals that are being developed. Senator Kennedy has a draft bill that has been circulated now where -- and I haven't read the most recent draft carefully -- but where he proposes allowing genetic tests to remain on the market, and therefore accessible, while everybody lines up and goes through a review. And so once your number is up and you go to the deli counter, you can no longer be on the market if you don't pass FDA's seal of approval.

But until that time, nothing is taken off of the market. I think there may be an exception in the bill for direct to consumer testing. There are, as I showed, some very questionable tests that are being offered as the intersection of the Internet and genetic technology give rise to this new business model.

Dr. Nussbaum suggested that the Federal Trade Commission has a role here. I think at a minimum if we could guarantee that people had access to information about what those tests can do and what they can't do, then at a minimum people have appropriate information.

A lot of these tests that are being offered on the Internet and even by laboratories not over the

Internet, it's very hard to get information about what is the gene, what is the variant, what is its prevalence, what's the positive predictive value, how many people were in the study that demonstrated that there is this correlation. It's very hard to get at this information.

And so at a minimum if we could get some transparency in the system, I think we could facilitate good provider decision making and good patient decision making.

And with regard to the art, we didn't pick it. We didn't see it until it came out.

CHAIRPERSON PELLEGRINO: Thank you.

Any comments? Yes, Janet.

DR. ROWLEY: Well, I'm sort of surprised that you think that most genetic testing is related to reproduction. I guess I would have thought that most of it is Guthrie type testing or maybe you don't.

DR. HUDSON: Newborn screens.

CHAIRPERSON PELLEGRINO: Dr. George.

DR. GEORGE: Yes, just to be clear and to follow up on what Diana was saying, when you say in the reproductive context, does that mean predominantly for eugenic purposes?

DR. HUDSON: Without commenting on what is and is not eugenic --

DR. GEORGE: Well, I mean with a view -- well --

DR. HUDSON: -- so the most -- so in 2001, for example, the American College of Obstetricians and Gynecologists adopted a guideline, health professional guideline, that indicated to obstetricians and gynecologists that they should offer cystic fibrosis carrier testing to all couples of a reproductive age.

As it turns out, in practice that test is most frequently offered after a couple already has a pregnancy underway, when, in fact, it makes much more sense, and was the guideline's intent, to do that testing prior to initiating a pregnancy.

So I don't think there's any concrete data on the absolute number of CF carrier tests that are being performed today, but it has got to be a vast, vast number now, not to the extent of newborn screening, but it's a big number.

DR. GEORGE: Do you happen to know why things went awry in that one example that you used? Why did it end up being the case that most testing was done after conception rather than before?

DR. HUDSON: I'm not a medical doctor.

DR. GEORGE: It wasn't anticipated?

DR. HUDSON: Yeah. I think part of it is that when a woman shows up for her first prenatal visit, obstetricians are accustomed to offering a series of tests, and that's the time when they do that test. When in fact women, many, many women go in for their annual Pap smear and that's the only doctor they see. In theory it should be at those visits that the gynecologist says, "Hey, are you thinking about -- let's talk about -- let me give you some information about…"

Unfortunately, that's not yet happening, and maybe testing will move earlier. Certainly ACOG is making every effort to see that happen.

DR. GEORGE: What's the normal way that that information is communicated so that changes in practice actually take place?

DR. HUDSON: Well, professional guidelines, and actually the CF testing guideline is a rarity; so with 1,000 genetic tests out there, increasingly for common diseases and conditions, there's only a tiny handful of professional guidelines that are available right now.

There are some efforts underway, funded by CDC, to develop the evidence base that would facilitate health professional guideline development, but it takes a lot of resources and intensity for those guidelines to be developed. The CF guideline was supported by federal funding from the NIH, and I think that there is data about how long it takes from the time that a health professional guideline comes out to when a majority of practitioners are actually following it, and it's a fairly substantial lag time. It's sort of just the normal diffusion time.

CHAIRPERSON PELLEGRINO: Rebecca.

PROF. DRESSER: Kathy, I was wondering about CF and these home brew tests. would the Kennedy bill get any jurisdiction over that?

And do they say they don't have jurisdiction because there isn't interstate commerce or I don't understand.

DR. HUDSON: Yeah, yeah. So they — actually years ago, they said in the preamble to some regulation — they said we believe that laboratory developed genetic tests are medical devices, and they are subject to the Food, Drug and Cosmetic Act devices amendments.

But we are using enforcement discretion and saying we're not going to pay attention to them. So for years and years and years they said, "We're not paying attention to them, but we have jurisdiction." There was sort of a silence for a period of time when the General Counsel at FDA was rumored to believe that they were not under FDA's jurisdiction.

At a hearing in July, on direct to consumer testing, an FDA official shocked us all when he said, "Not only do I believe we should have jurisdiction, but we do have jurisdiction," and shortly thereafter they put out this draft guidance which would cover one subset of laboratory

developed tests. This sort of shook up the world.

PROF. DRESSER: Did they explain anything about why they chose that limited kind of a test?

DR. HUDSON: Yes. These are tests that are looking at multiple analytes at one time. So think of a microarray either looking at DNA variants or expression patterns where it's not just a binary answer. They're using some sort of computer algorithm to develop a risk profile, a recurrence risk profile.

One of the companies that's out there that would presumably be an IVDMIA is Genomic Health, which looks at gene expression from a number of genes and calculates a recurrence risk for breast cancer. So they view this algorithm as being sort of a black box where no well trained health professional would be able to understand really how they got the answer, and so that's sort of their hook.

Whether or not that's higher risk than getting the wrong result on a Huntington test I'm not sure.

CHAIRPERSON PELLEGRINO: Dr. Rowley.

DR. ROWLEY: Well, I just wanted to make a comment about this de-identified samples, and I don't think that the general public really understands what a serious medical problem this is.

Well, let me give you two examples. One is from a very well respected investigator at Harvard who could get DNA samples from women de-identified, and he found five of 100 women had BRCA-1 mutations.

Now, because the samples were de-identified, he didn't have any idea which of the five women were actually at risk, and in order to find that out, one would have to go back and do the tests all over again.

So I think that de-identified samples are a bad idea, and particularly in cancer as we're trying to associate genetic abnormalities in tumors with survival. If you are given de-identified samples, you have no idea once you find the genetic abnormality what its consequences are.

So we've talked a lot about patient privacy, but I think there are a number of very important examples where patients are actually done badly by having de-identified samples.

DR. HUDSON: I don't know that I have a formulated opinion yet about the costs and benefits of de-identification, but I agree with you that severing that link does deny the ability to get back with important health information.

It seems to me that with information technology and the Internet, that some process of sort of

an ongoing, rolling consent model might be preferable to just absolutely severing this link and the set of responsibilities that researchers and participants have towards one another.

CHAIRPERSON PELLEGRINO: Dr. Kass.

DR. KASS: Thank you very much, Kathy for a very fine presentation.

I have a couple, maybe three questions. One, you cited the Council's reproduction responsibility report and the call for, among other things, longitudinal studies, the effects of PGD on the children born. In your own study that you cited then, the word "outcomes" appears, and it's a collaborative study involving ASRM.

How are you going to get the ASRM people to pay attention more than just a live baby was produced here? I mean, the really interesting things I think one needs to have evidence for are pediatric studies and things going further on. I'm wondering if that has been taken into account. Okay?

The second question, I was very struck as you pointed it out, the percentage of the IVF clinics that are offering PGD for non-medical sex selection. I think the number was 42 percent, although they haven't at all done it.

This ought to raise some further doubt in case one didn't have it already about the efficacy of the practice guidelines because the ASRM is on record on this subject. They are also on record not enforcing these guidelines, and I wonder whether -- I mean, one would like where possible to rely on professional self-regulation, but I wonder whether or not the experience there is a kind of warning to us if we're sort of thinking about the degree to which we can rely on practice guidelines unenforced, especially where the commercial interests become very, very large to do the job of protecting the public.

Finally, and this is just a factual question, you put up a slide of the things that the CMS said when they sort of drew back from where you thought they were going. Four of the items you said were true, and the fifth most important one, they deny that there's a problem. It seemed to be false.

Do you know -- this is a political question -- do you know what happened and is there powerful, organized economic lobbying, that if one wants to think about public policy in the area of testing that one should address, we certainly met these lobbies with respect to other things that we were engaged in?

And if you could help us think about that, I at least would be grateful.

DR. HUDSON: In terms of the registry and how it might help track and assess children over time, we know and you certainly know that IVF clinics currently really have no reach into the family with the baby and so, for example, the data they collect on malformation rates among children of IVF are lower than in general population.

So the data is of very poor quality on the health of the babies born after IVF. So what we are proposing to do here is that when data is entered into the registry, there will also be entered whether or not the family is providing their consent for recontact for subsequent studies. The registry would provide a research resource for subsequent investigators to actually construct, devise, and carry out studies of the sort that would be needed to really assess the children's outcomes.

Now, there are not that many PGD babies in the United States, and there have been studies that have been designed in the past where children have been assessed from various different technologies and where people have gotten in their vans and driven around the country and actually done direct health assessments of children.

So this would enable that. It would not in itself do it, and the registry we would propose would have a set of research priorities so that entry into being able to access the information and the patients would be based on the priorities that the registry governance body had created, and this is the number one priority.

Oh, and then in terms of the non-medical sex selection and whether or not professional guidelines are sufficient in the absence of a big stick, I'm going to quote Joe Lee Simpson here, who I think has spoken to the Council in the past, former president of ASRM and a prominent geneticist. And he has recently published an article where he has talked about the PGD registry and proposed that it may be a means of identifying and eliminating, quote, outliers.

Whether or not that can actually come to fruition and how that would come to fruition, I'm not sure, but I just put before you what Joe Lee Simpson has proposed.

And then lastly, what happened with CMS? A mystery, somewhat of a mystery. The personalized medicine coalition — which is pharmaceutical companies, biotech, academic organizations, large organizations — has supported the creation of a specialty. The American Society of Human Genetics has supported the specialty. The majority of our survey respondents, the regulated community, has supported the creation of a specialty.

Apparently it got yanked at CMS. So it never went to the Office of Information and Regulatory Affairs at OMB, it was somewhere else. I have heard it was within CMS that the decision was made, and that it was based on their competing priorities. So it was viewed within the agency as not that important.

CHAIRPERSON PELLEGRINO: Dr. Hurlbut.

DR. HURLBUT: Kathy, can you say a little more about the issue that's brought up in one of your reports of surreptitious testing and also the need for required counseling?

This strikes me as a very worrisome -- very, very worrisome, and then I have a follow-up question.

DR. HUDSON: Thank you very much for raising the question. There's an interesting issue which has not been real enough until recently to really worry about, which is that you leave DNA everywhere, right? And there are now companies that will test various clothing to tell you whether or not you might have had infidelity in your family. Parents — perhaps disgruntled parents — can test their children without their permission or consent to find out whether or not that child is actually theirs.

So there is this non-permitted, non-consented taking and examination of DNA that is permitted right now, and it may be that we are approaching a time where we need to think very seriously about whether or not there should be some limits on whether or not it should be permitted — lawful — to do genetic testing without consent except under certain circumstances — for example, at a crime scene.

I can't read my handwriting. So I can't remember just --

DR. HURLBUT: Required counseling.

DR. HUDSON: Counseling.

DR. HURLBUT: I know of a case where an elderly woman was told that she carried apoeliprotein E4 allele, and she told me that she went through over a year of waking up in the night every night crying and worrying about arranging her whole life around the reality that she was going to get Alzheimer's disease, and then finally just mentioned something from the doctor about when is it going to come on.

I mean, it just strikes me as an amazingly tragic potential out there, and especially combined with what Dr. Nussbaum mentioned about the over interpretative determinism of these tests.

By the way, just to add a little element, you were talking about tests not to do. I do think we ought to do tests in this, but it struck me that just think of the impact of not just tests like Huntington disease, which by the way sometimes people who have gotten results that said they weren't going to get the disease have had decompensations that were quite severe.

But it strike me that there are quite a few grayer zones with polygenic traits like depression, for example, that -- I mean, if you're already susceptible to depression, hearing a depressing result might not do you much good.

(Laughter.)

DR. HURLBUT: And counseling seems to me to be really crucial here.

DR. HUDSON: Yeah, particularly for serious diseases for which there is no intervention. I think the standard paradigm of pre- and post-test counseling really needs to be adhered to, but it's really about what's the content of that counseling, and how much are counselors really able to get the individual to think about "what will you do with the test result if it's this way and that way."

And even with that, I think there is the reality that what you think you're going to do when you have a piece of information and what you actually do when you have that piece of information don't always line up, and that's just the reality.

Because genetics — we've been in this state, this sort of uneasy state for such a long time with being able to, you know, tell parents what their recurrence risk is for having a child with a specific genetic disease. Now we're entering a different phase, albeit slowly, and so in some ways it's time to sort of question the paradigm of genetic counseling. Do you really need pre- and post-test counseling to tell you that you're a fast metabolizer, for example? Do you need to think about the implications for your family of you being a fast metabolizer?

So we need to sort of realize that genetics isn't all on that one end of the spectrum anymore of serious diseases where you can't do anything about it, but across the spectrum, and sort of attenuate our expectations for what health care providers do.

The one other thing I'd say is people who provide genetic counseling, which are often not genetic counselors, don't get paid for what they do really. The time — you know, you can't evaluate with somebody what are you going to do if you find you have the ApoE4 allele in 15 minutes. And so how we are coding and reimbursing for genetic services and genetic tests is, I think, a significant issue.

DR. HURLBUT: Can I have one follow-up on that?

CHAIRPERSON PELLEGRINO: Yes, yes.

DR. HURLBUT: Kathy, from what we heard earlier, it seems realistic that there might be the $1,000 genome in the future, and actually you could do much easier and quicker and cheaper analysis of 100,000 or 200,000 sailing at alleles or locations, coding zones.

And it strikes me that all of this individualized testing may be outmoded in a couple of years, not a couple, but maybe ten or 12 years, and our policies might just be coming into place then.

It strikes me we need to anticipate that possibility, and by the way, what a nightmare scenario for counseling because now you're looking at 20,000 genes with various percentage probabilities. Do you see what I'm saying?

DR. HUDSON: Sort of to reinforce that, I have heard that there is a company that's going to be launching soon that will be looking at a large number of variants, in the thousands, and be providing that information back to people and then providing them sort of a Web portal to do their own investigation about what each of those variants means.

So stay tuned and get ready.

CHAIRPERSON PELLEGRINO: Dr. Carson.

DR. CARSON: Thank you for that presentation.

You know, the thing that worries me a little bit is the whole concept of mission creep. You know, as a pediatric neurosurgeon, I remember many years ago I would get referrals of babies who in utero were diagnosed by ultrasound with anencephaly. Well, you know, that was pretty easy.

And then it was hydroanencephaly. You know, they had a little bit of a cordicomatter, but not much function, and then it just became, you know, hydrocephalus, and then it became questionable ventriculomegaly.

And the question at each stage was, you know, what should be done with this baby, and you know, what recommendation would you have to keep the same kind of mission creep from happening as we develop more of this genetic information and people not wanting to risk, you know, abnormalities?

DR. HUDSON: I'm afraid I don't have a concrete answer. I will reinforce the problem by sharing stories that my genetic counseling friends have shared with me, which is that during amniocentesis when you just look at the chromosomes, you look at a karyotype. When you find a chromosomal rearrangement, a little tip of a chromosome that's sitting on the tip of another chromosome — for example, a chromosomal rearrangement that you haven't seen before. And so the family, you know, -- you tell the family that there's this chromosomal rearrangement, and they say, "What does it mean?"

And you say, "We don't know," right? What do parents do in that circumstance? And that's the nature of the analysis, the information that you get and the information that parents get and make decisions on.

Sort of related to this, there was a bill that, well, is still a bill, a bill introduced by Senator Brownback that suggested that parents when making the decision to have prenatal genetic testing be given better, more comprehensive information about the conditions that are being tested for, specifically Down Syndrome.

And it's no doubt true that in genetics because it's easier to identify the extreme phenotype that that's how we define things, right? We define things by the extreme phenotype and not so much by the gradations in phenotype, and so the emphasis there was how can we provide more complete information about what this really means, hooking parents up to families that have children with that condition as a means of trying to help people make informed decisions and not sort of glump everything together.

And I didn't understand what any of those terms were that you said.

CHAIRPERSON PELLEGRINO: Any other comments?

PROF. LAWLER: At the end of the day, given all of the problems you talk about, given the

need for more federal leadership, does this Council provide any of this federal leadership or should these problems we addressed somewhere else?

DR. HUDSON: I think that there are a number of these issues that are being seriously undertaken by others, some of the issues that I talked about that were seriously undertaken by others, and yet there are some where — especially, I think, sort of the more anticipatory issues, the ones that aren't here right now but that might come to become more prominent. Like Bill mentioned, the sort of unauthorized taking and testing, I think, are potentially some issues here.

And it might be worth reviewing what's on the agenda for those committees who are currently focused on genetics issues to see whether or not there are issues that the Council is interested in that are not being considered or not on the prospective agenda for those groups.

CHAIRPERSON PELLEGRINO: Paul.

DR. McHUGH: I, too, thank you for what you've done, and I'm raising just really two issues to get your information on this.

The first one is what I tend to refer to as materialism in the woman, and that is being pregnant today is a much tougher task and a more frightening task for women than it ever was before, primarily because of the information we've given about the material.

And at this Council meetings and at other meetings, I've protested about the psychological burden that women bear with the triple test that gets them to change their odds about Down's Syndrome, and the failure of genetic counselors and the like to help these women even when they've had an amniocentesis and they've got at least that test that shows that they don't have a Down's Syndrome child.

But the encouragement that they get to press on in these ways, and their sense of defect which seams to be a real frightening burden that women carry, and I'm really surprised that our government and our Public Health Services haven't been studying this matter more carefully and seeing the burden that's come for women in this matter. So that's the first thing I wanted to ask you, if there's anything going on there.

The second thing that was interesting to me, you pointed out that we have made great advances in genetics but we may not be making any advances or we may be back in the 1980s on our studies of behavior and life styles, and you put it, and I think quite correctly, that part of the reasons for being in that is the difficulties in maintaining privacy and the like.

But I wondered whether you had looked into the work, particularly done in the Nork Center at the University of Chicago, where they have worked out ways with interviewers to interview people about the most intimate matters of their life in kind of dueling computers, have been able to take that information in and then disperse it into a body so that the people can be assured not only are they private, but they're even private in the interview itself, which is very hard, which is a very important thing to get the information.

I just wondered whether those things were coming to the fore. So those are the two questions.

DR. HUDSON: I think you're quite right that there is a real burden of information on women. There was a beautiful article in the *New York Times* ten years ago by Natalie Angier where she talks about the burden of information on women as they're pregnant, and it was beautifully, beautifully written.

And at the time I was actually pregnant and I had chicken pox during my first trimester of pregnancy, and that is ostensibly linked to various forms of birth defects, and you know, when you know too much you can know too much. So I knew way too much and had the phone call from my doctor after a sonogram telling me to please call the office. There were abnormal results.

That was 6:30 at night when I got the message. You can imagine how much I slept. He later indicated to me that there was an abnormal interocular distance in the fetus, and I said, "Well, what does that mean?"

And he said, "We don't know, but we need to do more testing," which we politely declined, deciding that if our son looked like Lyle Lovett that was okay with us.

(Laughter.)

DR. McHUGH: By the way, I'm surprised that you got just this information at 6:30 and by not responding 'til the next morning you didn't get ten more messages between 6:30 and 5:00 a.m. because the obstetrician is so fearful that if he doesn't let you know this, he'd be sued.

DR. HUDSON: There's going to be a lawsuit, right.

And then in terms of the privacy technology, I think there are wonderful ways of getting accurate information from individuals, and particularly, you know, there is an effect when you actually see a human being. You give them the response that you think that they want to hear, and so you get very different responses from people when you actually take the other person out of the room.

So Internet based or paper based surveys and information collection devices are much more effective than actually having a person sitting across from you because I want to give you the answer that I think you think is okay.

In terms of the privacy though, when you link that with DNA it's still kind of identifiable, and I'll give you an example of how it can be identifiable.

There was a case of a man whose father was a sperm donor, and he wanted to contact his father and find out who his biological father was, and so he himself put his DNA into one of these genealogical databases where you can trace your ancestry and who's related to whom, and

he found out that there were a group of people who were genetically related to him in a certain part of the country. He contacted those people, asked if there are any young gentleman family members who happened to be in the Boston region or whatever city it was in the year that he was born, and managed to locate his father.

DR. McHUGH: Good for him.

(Laughter.)

DR. McHUGH: By the way, as I was saying, the Nork thing, although it is face to face, the dueling computers made it possible. There are advantages, of course, to having somebody speaking to somebody and at the same time having that somebody not have any clue as to what your answer is.

So this kind of development of technology and appreciating the data I'll follow with great interest, and I'll look up that article in the *New York Times*.

CHAIRPERSON PELLEGRINO: Any other questions or comments on this subject?

(No response.)

CHAIRPERSON PELLEGRINO: If not, let me thank you, Dr. Hudson, for again a very, very excellent presentation.

(Applause.)

CHAIRPERSON PELLEGRINO: And let me ask the Council for a moment tomorrow morning we'll be going over a paper by Eric Cohen and Sam Crowe with suggested policies having to do with some aspects of organ transplantation. I'd like to be very specific about that tomorrow and have us concentrate on it, and so I would suggest just for that if you could some time look at page 1 and 2 for the guidelines that are now being used in organ transplantation and then look at the recommendations that are being made, and I'd like to find your opinions and get your opinions specifically on those you think that are important, those that may not be of significance.

Speaking now of the specific recommendations made by Sam Crowe and Eric Cohen rather than the guidelines that are current, except as to background against which you would want to think about the proposed policy changes.

Thank you very much. Have a good evening.

(Whereupon, at 5:06 p.m., the meeting was adjourned, to reconvene Friday, November 17, 2006.)