Ethical, Legal, and Social Implications of Genetic Technologies

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DR. McCABE: Our next speaker is Dr. Eric Juengst, whose topic is ethical, legal, and social implications of genetic technologies. Dr. Juengst is Associate Professor of Biomedical Ethics, Case Western Reserve University School of Medicine.

DR. JUENGST: Thank you, Ed.

It's an honor to be invited to address you at your inaugural meeting. I also had the honor to work with Bruce on the DNA advisory board for a couple of years, and I learned that he's considered a very lucky guy within the agency because he not only gets to look into the X Files but the Y Files as well.

(Laughter.)

DR. JUENGST: I want to give, like my predecessors, a survey of issues that I think will be on your plate, or could be, and with an eye to the future, what's coming down the road, and an eye on issues that are ripe for public policy development at the federal level.

This is an auspicious time to be launching this commission because, as Francis said, we have just celebrated the completion of the Human Genome Project, achieving what Walter Gilbert, Harvard biologist, said early on in the late '80s was the holy grail of human biology. Well, we've achieved the grail, and now we've got to live with it. The question is, once you've achieved the grail, what are you supposed to do with it? The legends don't tell us that. It's all about the quest.

But we do have to face living with the grail. Here is a paraphrase of Francis' famous chart. I've turned it upside-down to emphasize that grail-like aspect to it.

(Laughter.)

DR. JUENGST: The three sets of products, fruit, that the Genome Project will yield, going through three further areas of research are the technology development that will give us the microarrays and DNA chips that will improve our testing capacity to do genetic risk assessments of multi-site problems of complex traits of polygenic diseases; secondly, the research track through functional genomics, working out how the genes are regulated and expressed in cells that will underlie a new generation of gene therapies, gene therapies that are actually grounded in knowledge about how genomes work; and finally, the study of genetic variation, the population genomic studies that will bring us to a sense of our individual susceptibilities and how to tailor pharmaceutical interventions to individuals.

Well, I think each one of these tracks raises issues for us as a society, so I want to go through each one briefly.

This is the most familiar set of issues, the one that the research funded by the ELSI program at NIH has been preoccupied with for the most part over the last decade, the questions that spin out of new generations of genetic risk assessments of various kinds. Here's another prediction about the fruit of the

Genome Project from President Clinton in his campaign for reelection in '96: "I think it won't be too many years before parents will be able to go home from the hospitals with their newborn babies with a genetic map in their hands that will tell them, here's what your child's future will be like."

Well, this illustrates what to me is the driving issue behind almost all of the specific issues having to do with the integration of new genetic tests into society, which is our cultural tendency, not totally irrational, to over-interpret the meaning of genetic test results. Increasingly we're learning that genetic risk assessments that will be coming along will not have occult powers to tell the future of our experiences in life. But that's still the image, the occult magical ability to predict the future, that drives a lot of the fear and the issues in genetic testing.

What sorts of issues? Well, every time we launch a new genetic risk assessment test into the otherwise calm pond of our lives, we do get these concentric ripples of questions, questions for the families and individuals who might avail themselves of this information. Am I comfortable living with uncertainty? Do I want to know my downstream risks? What are my obligations to warn those cousins in California we no longer speak to about our familial risks? What are my obligations to protect the next generation from our familial risks? All those frank and tough moral questions that individuals will face.

It's hard to write public policy on those sorts of questions. We don't have a good uniform theory of moral dynamics of family life in our culture, so a lot of the discussion of those questions quickly flips over into the discussion of professional issues. The ethical issues that health care professionals face when they're trying to help these families and individuals work through those moral quandaries. Often it is the genetic counselors and the clinicians, as much as the pastors and the rabbis, who are helping them address these moral questions.

For the professionals, those moral questions translate almost verbatim into questions of professional ethics and policy. If they won't warn their cousins in California, do I as a professional have an obligation to breach confidentiality and a duty to warn in this context? What should be the standards of care in this area? When is a test ripe for prime-time use? And what should the limits of my service be? One of the hottest topics in that domain at the moment is a question of testing kids, pediatric testing at parental request for mutations that confer risk of late-onset disease late in life. I'll get back to that a little bit in a minute.

Finally, at the limits of those professional ethical questions are the public policy issues that we've already been talking about a bit, the questions about the regulation of commercial testing. It's the professionals' question about when a test is ripe for clinical use writ large at the policy level. And then the mechanisms we have to prevent genetic discrimination.

In terms of the criteria that get involved in evaluating tests, I'm picking up here in the fourth quadrant of Wylie's box, where she said that when you have a test with relatively little therapeutic prescription behind it and relatively poor predictive capacity, what do you do? Well, you do a careful evaluation of risks and benefits. What goes into that calculus? I call this the calculus of the eight P's, because there are these four alliterative categories that seem to me to make up that calculus.

The first is the predictive power of the test, and that is the heart of the issue about clinical validity that the Secretary's Advisory Committee or predecessors wrestled with a good bit. Working out what clinical validity and utility mean for genetic tests is still a task to dwell on. But secondly, there's the price of a genetic test, its psychosocial potency. What are its risks for stigmatization and discrimination? Not all genetic health problems are created equal. Some are tied to conditions that already carry a cultural burden of stigma, like cancer, whereas others would not carry that same level of stigma.

The third one is this interesting category of how to weigh in the patient's own autonomy and their privilege to decide what they want to buy or not buy from the health care system. The hottest professional policy issue at the moment is the question of what sort of criteria ought to govern predictive testing for kids. But there's another example that I'll tell you about in a new category of genomics that I call ego genomics or cosmeticogenomics.

This is the enterprise of a company called Lab21 which now has counters at Bergdorf-Goodman's and Saks Fifth Avenue. If you go in, you can complete their skin profiler questionnaire and let the beauty consultant take a small sample of skin cells with a tape off your arm. They'll send that off to the lab and genotype it for four markers that they feel are relevant to good skin, collagen markers and other sorts of things, and then whip up a customized DNA face cream with appropriate levels of active ingredients to help boost any measured deficiencies and ship that off to you. Direct-to-consumer genetic testing, in Francis' mode.

DR. LANDER: What are the markers?

DR. JUENGST: I don't have those, but I can --

DR. LANDER: Do they say?

DR. JUENGST: Yes, they say.

DR. LANDER: Can you get a different cream depending on your genotype, or do they just sort of send the same cream?

DR. JUENGST: No, it's tailored to your genotype.

DR. LANDER: They say that, but I'm just curious if anybody has done a mass spec on the stuff.

DR. JUENGST: How would you know?

DR. LANDER: It would be worth buying a few of them just to find out.

DR. JUENGST: Here are the markers: collagen, elastin, hyaluronic acid, and ceramidides.

Well, gee, caveat emptor, let the buyer beware. Why not offer this as a commercial service to people who want to buy it? It might be junk science, but a lot of stuff at the cosmetics counter might fall into that category.

(Laughter.)

DR. LANDER: Actually, Eric, is it really an RT-PCR machine, in which case they're doing an RNA analysis?

DR. JUENGST: Yes.

DR. LANDER: On dead cells?

PARTICIPANT: On dead cells?

DR. LANDER: Cool!

(Laughter.)

DR. WINN-DEEN: It's in your briefing book, Eric.

DR. LANDER: Is it? RNA analysis on dead cells?

PARTICIPANT: Is Roche developing the test?

(Laughter.)

DR. JUENGST: Well, that raises the question of regulation in a way we haven't talked about much because we've been so focused on the regulation of clinical genetic testing in the context of clinical laboratories. I don't know what the protocol is like at their labs. They're quoted as saying they don't have the capacity at their lab to test for any interesting disease genes. But if they've got the capacity to test for these markers, I can't imagine it would be too hard to build other capacities, and what their security precautions are, et cetera, at Saks Fifth Avenue for the chain of custody of these samples, I don't know.

(Laughter.)

DR. JUENGST: And that brings us to the topic that several speakers have raised about the need to have a fuller social conversation about regulation in this area, and I just show this to show the kind of drum beat of recommendations from previous groups, your predecessors, in this direction, with the latest being your predecessor advisory Committee, which you'll hear more about later.

Well, quickly then, the second line, through functional genomics to gene therapy. Gene transfer research has had a rollercoaster history over the last decade of promise, failures, and successes, at least one notable success with its own back-bite, a cure of a disease in a cohort of patients, some of which then succumbed to the cure by developing a health problem that was the direct result of the gene insertion.

But for generic policy purposes, the lines have always been clear over the last decade what the limits of gene therapy were. These are the kinds of boundaries that your sibling Committee, the Recombinant DNA Advisory Committee, has always been happy to live with. That is, we don't entertain protocols that are designed to go beyond therapy to try to improve on human form and function in some way, and we don't entertain protocols that are intentionally designed to affect the germline, affect the next generation of a patient's family.

What's interesting I think looking down the road and what may be a topic for you folks, since it is beyond in some ways the RAC's purview, are the ways in which these boundaries are both getting pressed. On the one hand, people are finding -- well, there was an announcement in the literature a couple of years ago from a hospital, a report of the first case of human germline genetic modification resulting in normal, healthy children. Oh, we've done it. We've crossed that line. What's going on? That was kind of a surprise to the RAC, because it certainly had never come before them.

What they had done was to find a side door into germline genetic modification that didn't involve recombinant DNA and therefore was exempt from the guidelines, didn't have to come through the normal regulatory routes. What they were doing was essentially transplanting mitochondria in early embryos to prevent diseases of mitochondrial origin. So the intent was to prevent a disease in a prospective patient,

the child that would grow from this early embryo. A side effect of it was that, of course, that child's children will inherit these new mitochondria as well, along with their DNA and the genes that they carry. The germline, in essence, in terms of a literal definition, has been tampered with, has been breached.

Now, whether that's a serious breach of concern to the world is a topic of conversation, but it does show you the way in which that boundary is starting to shake as we come up with new ways to influence the germline.

DR. LANDER: Eric, on that point, there's now a growing literature that mitochondrial haplotype is an associated factor with at least a small list, and I think it's going to be a growing list, of common diseases. So it's hardly a small point when you're talking about potential affects on neurological disorders, diabetes, et cetera, et cetera.

DR. JUENGST: Okay. Very good.

DR. LANDER: I wouldn't put this in the box of the rare mitochondrial disease, necessarily.

DR. JUENGST: Yes. So it's worth paying attention to.

The other pressure comes under the rubric of prevention. A lot of our reviewed and approved somatic cell gene therapy protocols are essentially aimed at treating and preventing disease by strengthening the body. There's a class of protocols called the cancer vaccination protocols which are designed essentially to genetically tweak the patient's immune system to seek out and destroy cancer cells more effectively. Well, that's great for the patients who already have diagnosed cancer. You can see it being used prophylactically. I could use an upgraded immune system myself. To that extent, I will have been enhanced compared to the rest of the species.

So one of the questions that's come up in the policy domain is do we care about enhancements that are clearly designed to strengthen our resistance to disease, to pollution, to other kinds of environmental insults? Are those worrisome in the same ways that the other sorts of genetic engineering fantasies we've had in the past are worrisome, or not?

One of the things going on at your sister Committee in response to the side door issue is a discussion, or was a discussion several years ago about whether to expand the scope of the guidelines that govern their work, the guidelines governing gene transfer research, and you can see the extent to which the simple phrase "experiments involving deliberate transfer of recombinant DNA" have had to be expanded in order to capture the range of new possibilities for influencing genetic traits in human cells.

Eventually, my last slide was circa 2020. Now we're at circa 2030. There will be some other pressures on these lines as well. If we get a functioning, safe and effective somatic cell gene therapy, we will find ourselves in the situation of contemplating families which continue to pass on the pathological mutations are cured in every generation by another bout of expensive somatic cell gene therapy, and somebody is going to raise the question, "Good grief, wouldn't it be more efficient to go ahead and do this gene therapy in the germline once and for all for that family line?"

That's an argument that at least one public policy shop has taken seriously. The AAAS, the American Association for the Advancement of Science, had a working group on this topic a couple of years ago that's produced a report you might want to hear about at some point on human inheritable genetic modifications, suggesting some interim steps towards getting ready for the day when someone makes that

efficiency argument persuasively. It's time to start thinking about germline gene therapy for therapeutic purposes.

At the same time, discussions are going on in other policy venues like the International Olympic Committee and the World Anti-Doping Association about the possible illegitimate and off-label uses of somatic cell gene therapies for performance enhancement in athletes. There's a class of gene therapy experiments for muscular dystrophy and other diseases that the athletic community sees as quite close to the kinds of blood doping they already do, and the World Anti-Doping Association has already begun to develop policies to address the day when athletes begin using these gene therapies off label, so to speak, to strengthen muscles, build oxygen-carrying capacity, block their pain, and speed their pace of healing from injury. Again, all uses that have perfectly good therapeutic and preventive applications in medicine -- we wouldn't want to stop the science that developed these interventions -- but which will have applications in other spheres that seem to cross that enhancement line.

Finally, a quick look at the issues raised by the third branch. The progeny of the Human Genome Project so far are all heavily invested in this third branch, being interested in doing comparative population genomics, studies of human genetic variation. All of them share this basic strategy of collecting DNA samples from members of different human groups for comparative analysis. Right, that's what we want to do.

The first question that you stumble on, though, is, well, what are the groups? Which groups? Are we going to fall back onto 19th Century color lines and say, oh yes, they're red, yellow, black and white? The genetics community has taken us a good way down the road towards obfuscating those lines, pointing out that as biological concepts there's not too much reality to that, and that makes population genomics a particularly tricky tool to use without hurting yourself in the process. We're used to double-edged swords in medical genetics. Information is power. This is at least, to my mind, a quadruple-edged sword because of the implications of the results of these kinds of variation studies.

On the one hand, we are interested in the diversity in the genome, because that's what's going to give us a handle on specific population group susceptibilities and tailored health care interventions that might help address health disparities. On the other hand, of course, along with that, to the extent that it's successful, comes the ratcheting up of all our worries about genetic discrimination to the group level from the individual level if particular socially identified population groups become labelled as vulnerable to particular kinds of weaknesses and stigmatized in the process.

On the other hand, population geneticists like to remind us this graphic is way out of balance. The similarity blade should dwarf the diversity blade because we're much more alike than we are different in our genomes, and maybe this can be used to enhance inter-group solidarity. On the fourth hand, for some folks their biological differentness, their lineage is pretty important to their social identity, and it's not doing them a favor to homogenize them into the rest of society, partly for good historical and social reasons.

So I think one of the challenges that's going to face this field is to explain to the world the kinds of categories we in genomics want to put people and explain to the world in a way that doesn't exacerbate existing tensions between different human groups.

Ken Kidd has said -- and this is a typical kind of statement from one end of the spectrum within genetics -- "There's a virtual continuum of genetic variation around the world. There's no place you can draw a line and say there's a major difference on one side from what's on the other. One is talking about discrete, identifiable populations. There's no such thing as race in modern homo sapiens." Clearly true. On the

other hand, just because you can't draw a line to distinguish day from night in the twilight doesn't mean you can't distinguish midday from midnight; and you could, by going to wildly separate parts of the globe, collect samples from people that would show genetic variation that seems to segregate into populations.

So what's the message we want to give the public about that? Ego genomics Part III, if you will. The world's first recreational genetic testing service is how they bill themselves, DNAPrint Genomics, a company in Florida that says it will measure your racial ancestry and racial proportions for you using DNA markers. Well, why would you want to do that? Perhaps for genealogy or to validate your eligibility for race-based college admissions or government entitlements. Here's some of their literature from their website. "Have you ever wondered if you're of purely Indo-European origin, or a blend of Indo-European or Native American or other ancestry? We can answer that. Capable of determining your precise ancestral proportions might reveal you're 80 percent African," et cetera, et cetera.

Who is interested in this test? Well, genealogists, the adopted. One customer used the test to hone his search for an organ donor. Another suspected he was of significant Native American heritage but had no way to prove it. The test gave him a sound basis by which to claim access to commercial opportunities reserved for Native Americans. "So whether you're just curious or your goal is to achieve social status of a particular group, we can help you do this."

Well, again, junk science? I personally don't know. There seems to be a lot of contention within the genetics community about whether this is realistic and meaningful or not. But it certainly feeds into our race consciousness in this culture, and you can see ways in which people's motivations for acquiring this test for themselves, for their children, for their potential spouses, would only go in the wrong direction. In fact, this is, again, luxury genomics that is a recreational service, but it has already been put to at least one serious use. They've used the DNAPrint testing procedures on a forensic sample to reorient a search for a suspect from one race to another.

So here we are. Here's my summary of the issues that I would like to put on your agenda. First is to continue our exploration of this calculus of the eight P's about how we validate genetic tests. Second is to continue the pursuit of good genetic protections, good protections against genetic discrimination. Third is to continue the discussion of the regulation of commercial genetic testing with an eye towards the direct-to-consumer uses.

If you're interested in going in the direction of gene transfer research and you can work that out with the RAC, then these questions about what to do about the side doors to germline intervention that are coming through the field of reproductive genetics and reproductive biology are interesting. Then how to regulate off-label uses of a medical procedure like gene therapy.

Finally, this question about the social uses of population markers and the meaning, the interpretation of those markers for the general public I think is going to be an issue that will preoccupy us for a long time to come.

So here's a cartoon that I've been using for over a decade now, and it's finally apropos. "We've finished the genome map. Now we just can't figure out how to fold it." Well, folks, you are our map folders. That's your job in some ways, to figure out how to fold this genome map so we can use it to get to where we want to go. Thank you.

(Applause.)