

GENETIC PERSPECTIVES ON POLICY SEMINAR

**THE MOLECULAR FULL MONTY:
PERSONAL GENOMES, PERSONAL HEALTH**

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(edited for clarity)

KATHY HUDSON: Welcome. Thank you for coming today to our Genetics Perspectives on Policy Seminar Series, or GenePOPS. Today our seminar is entitled, “The Molecular Full Monty: Personal Genomes and Personal Health.” My name is Kathy Hudson and I’m the director of the Genetics and Public Policy Center. And this seminar series is supported by The Pew Charitable Trusts.

In the last year, we have seen the advent of several services that can scan your genome, testing as many as a million variants across your genome. And if you have an extra \$350,000 burning a hole in your pocket, you can have a vast chunk of your genome sequenced. These tests are marketed largely to healthy people and don’t require a genetic counselor’s or a doctor’s involvement. These new companies are challenging traditional notions and traditional models of genetic testing and raise interesting and important questions, such as how well validated is the information that consumers receive from these genome services? Is it useful to know if you have a slightly higher or lower risk of a common complex disease? Do the results change people’s behaviors and in what ways? And where will this personal genomics trend take us?

To help us explore these questions today, we have a phenomenal panel. So we can all enjoy their presentations, I would ask everybody to turn their cell phones and pagers and buzzers and beepers to at least a silent position. I am going to introduce all four panelists briefly, and then they will each speak for about 10 minutes. Then we will have ample time to respond to your questions and your comments.

Our first speaker is George Church. He is a professor of genetics and director of the Center for Computational Genetics at Harvard Medical School. He has been a leader in DNA-sequencing technology, RNA structural analysis, and bioinformatics. His current research focuses on integrating biosystems modeling with the Personal Genome Project – which I hope we will hear about – and synthetic biology. He holds degrees from Duke University in chemistry and zoology, and a Ph.D. from Harvard in biochemistry and molecular biology.

He will be followed by Hank Greely, who is a professor of law at Stanford Law School. He is a leading expert and author on the legal, ethical, and social issues surrounding health, law, and the biosciences. He specializes in the legal implications of new biomedical technologies, especially those related to genetics and neuroscience. Hank earned his bachelor’s degree from Stanford, and his law degree from Yale Law School. He will talk about some of the reasons we might be concerned about some of these tests.

Colleen McBride is our third speaker, and she is the chief and senior investigator in the Social and Behavioral Research Branch at the National Human Genome Research Institute. Building on her behavioral epidemiology and genetics experience, she is investigating how genetic information can best be used to motivate people to behave in the most healthful ways. Colleen holds a bachelor’s degree from the University of Wisconsin, a master’s from the University of Arizona, and a Ph.D. from the University of Minnesota. Colleen, today, is going to

talk about an important study that she has underway about how garden-variety Americans respond to information about risks for common complex disorders.

Concluding our panel is Bob Green, who is the co-director of the Alzheimer's disease Clinical and Research Program and a professor of neurology, genetics, and epidemiology at Boston University. He has developed novel genetic risk-assessment strategies for individuals at risk for Alzheimer's disease. He is a graduate of Amherst College and the University of Virginia School of Medicine and subsequently completed a residency in neurology at Harvard. Bob is going to reveal more than the other speakers and will truly do the molecular Full Monty for us today.

I would like to invite George to kick us off with the first talk.

GEORGE CHURCH: I am thankful to these groups and also disclosing my connection to these groups, both governmental and corporate, that are in one way or another engaged or interested in the future of personal genomics, and not just genomics, but there are many new forces in medicine. We have the personalization of drugs and vaccines. We have the computer industry involved in electronically controlled personal health records. We have Web 2.0, kind of a sharing of communities involved in genomics and medicine. And then we have the home test-kit industry.

Just to put my technological update into context here – and we have the Personal Genome Project, which I'll mention – which was intended to get a little ahead of the curve and try to get prepared with an informed cohort before individual access to personal genomics happened, but some of my friends and colleagues decided that it was such a great thing that they wanted to get, not wait for. And then we have the other extreme, which is research access, where people don't typically volunteer without expecting access to some of their data. And some of these programs do give them back data, as we will hear from Colleen and Bob.

The Personal Genome Project has a technological component, which is number one on our list, which is to bring down to less than \$1000 not just getting a genome sequenced, but getting something that is highly informative and inexpensive and available, in principle, to everybody who is in the healthcare system. We want full subject participation. We want to not over-promise on ID, identifications, since we can be selective about who is in the project. So we ask them to take an exam to give some indication on just how informed they are on the subjects of disclosure and genetics and so forth. And, of course, nothing will perfectly prepare them.

We want this to be open access – or at least for them to imagine that it is open access – and correlate genes, environments, and traits via trait questionnaires. And we have IRB approval to scale this to 100,000 people, and there is no particular timeline for doing that. And then we have cell lines available publicly through Coriell for the 10 individuals on the side there already.

Now, technologically, I have been involved in some of these groups both producing chip-based methods that you may have heard of, which are .02 percent of the genome. That is a very small fraction of the genome. Sequencing, on the other hand, can and has delivered closer to 98 percent of the genome. No human genome has been completely sequenced.

As an example of one of the oldest direct tests of genetic predisposition, if you have a family risk, where, say, sisters and aunts have died of breast cancer, then either Myriad or DNA Direct might deliver – not a chip-based method, but a sequencing-based method, where you will look at these two genes. And it is something where the interpretation is fairly straightforward, but it needs to be considered very seriously because the sort of preventatives that you do, like bilateral mastectomy, are not something that you do take lightly based on just the G's, A's, T's, and C's.

Now, there are a number of chemistries that have propelled us from the sequencing technology that we used to sequence the first human genome to the sort that has really brought the price down by a factor of 1,000 already, and easily another factor of 100 within the next – well, a factor of 1,000 in the last couple years, and a factor of 100 possibly in the next year. And these are based on – I don't want to get too technical, but you have four different colors for four different A's, C's, G's, and T's, which are incorporated either by an enzyme polymerase or an enzyme ligase in a very sequence-specific manner. And there are a couple of companies for each of these methods. And this is basically a transition from separating DNA by this movement in electric field, which was very costly, to basically a microscope that looks at millions to billions of individual beads or small amplified molecules with these four colors at a time, as one of the main ways of delivering it. This is one that is near and dear to my heart.

We worked on this in an unusual format from most of the other instruments that I showed on a previous slide in that this is intended to be open-source hardware, software, and wetware to try to really get community involvement, to demystify it, and to make people feel like they can change the enzymes, they can change the cameras, they can change any piece of this and at a low cost. This is about 10 times less expensive than the most expensive of the next generation, and about four times less expensive than most. Now, that is the instrument. But what we really care about is what is deliverable to people. And this gives you some idea – in 2007, we – I'm talking about the entire community – brought the price down from about a \$3 billion genome, which we were pretty happy about in 2004, to a million-dollar genome in 2007, to a \$60,000 genome a few months later. Contrast with \$1000, which is the lowest cost for the .02-percent genome that the direct-to-consumer companies are offering – a very stark difference in amount of the genome and price.

And I am speculating here – this is on the aggressive and optimistic side of the spectrum, but there is no fundamental engineering problems preventing us from getting whole genome sequences -- I mean 98 percent of the genome sequence -- to less than \$1000, and then pieces of the genome for \$90 or much less. It could be as little as 1 percent, but it actually will be more like 10 percent. And then things that actually add value that are not directly mappable onto this, which is looking at RNA, how your genes are expressed, and looking at your response to the environment, for example, your microorganisms.

We can do selective sequencing – and I don't want to lead you through all the data here, but it is very precise. And we can look at RNA from multiple tissues. If you are a volunteer that is healthy, you don't want to give up multiple tissues. So one of the other things that happened that is really exciting in 2007 is we can now reprogram tissues from skin samples to a variety of

other tissues. And, again, this data is showing how you can get RNA readouts, which are both person-specific and tissue-specific for some of the – this is from one of the personal genome projects.

And finally, it is not just genomes that determine traits. There is an environmental component, which ranges from schooling to microorganisms. And here is an example of how we are looking at resistance – multi-drug resistance in individuals. And this is greatly accelerated by our technologies. There is a function of days over 140 days and 18 different antibiotics showing – the solid blue means a lot of drug resistance, then later, much less. Period, full stop. I have 30 seconds left. (Laughter.)

(Applause.)

GREELY: I'm a law professor. They keep us away from electricity as much as possible for our own safety and that of our students. So I don't have any PowerPoints and, as you may notice, I'm crazy enough to wear a sweater on a day like this in Washington. (Laughter.) So I promise there is no Full Monty coming from me. (Laughter.)

What I want to talk about, though, are some of the new consumer-genomics companies and some things we should be worried about, as consumers, as public-policy folks, and others with respect to those companies. Now, there are a lot of direct-to-consumer tests out there. And they fall into a lot of different categories. And it is important to pay attention to what kind of tests, what kind of company you are looking at.

They range from almost fraudulent – the things like DNA dating services that will fix you up with your ideal person based on your immune system alleles, really reckless and irresponsible companies – to those that will tell you something about your risk of getting bipolar disease based on one study from one group with one gene that doesn't involve that much risk, to bigger, well-established companies that will give you an honest assessment -- based usually from a doctor ordering it -- of what your risk is of serious disease. So there is a lot of variation.

But the particular niches I want to talk about are the consumer-genomics companies, the companies that are looking across the genome. These are the companies doing the SNP chips that George talked about that are giving you 0.02 percent of your genome. But it is thought to be a particularly useful 0.02 percent of your genome that is made up of the SNPs or single nucleotide polymorphisms – you can see why we call them SNPs – that you will get somewhere between half a million to a million of these for about \$1,000. There are three major companies in this field right now – 23andMe, Navigenics, and deCODEme. There are a number of other companies. I may be wrong on who is major, but those are the three that have gotten the most press that I know most about.

I think there are four things to be worried about with these broad consumer genomics companies. First, we have to worry about what they are not warning their customers about. They sell themselves, in part, as telling you family information and ancestral information, but not one of their Web sites warns you that maybe you'll get family information that you wish you wouldn't have had, particularly information about false paternity.

Now, as a male, I find very daunting the stories I hear from my geneticist colleagues about the rate of false paternity in our society, guess I'm supposed to call it misattributed parentage, to be politically correct. (Laughter.) But there are damned few cases of false maternity out there. You could easily end up doing one of these services and discovering that you are not genetically related to people you thought you were genetically related to, like your children or your parents or your cousins or others. Now, that is a risk, I think, people should be warned about. And it doesn't show up.

The privacy risks, also. I liked George's take on this. And his company, the Knome company, is doing sequencing, so they are a different sort of thing. They worry about how much people care about their privacy. And do they know that there are some risks because no one can guarantee your privacy for this information. And in fact, these companies can't even provide any useful protection against things like subpoenas for civil cases or criminal cases, let alone issues of if the company is sold, merged, if it goes bankrupt and its assets, which are mainly going to be that databank, get sold off, as well as all the day-in, day-out problems with confidentiality.

I work for Stanford University. I just got an email two days ago about how a laptop with information on everybody who has gotten a paycheck from Stanford since 1989 or something was stolen. My information is potentially up for grabs from anybody. That can happen to any of these companies as well. So I think people need to be warned more. People need to be warned more about the privacy risk, so a little bit more warning up front.

Secondly, I have real concerns about the power of the information that is being given versus what people expect. Right now these companies are not providing very powerful medical information. They are all doing roughly 30 traits, disease risk factors and other traits. They are pretty much the same traits for all of them, things like your risk of type II diabetes, your risk of Crohn's disease. I think one does whether you have wet or dry earwax. So a variety of genetic traits, but none of them is particularly powerfully predictive.

In fact, there are some genetic tests out there that are powerfully predictive for things like Huntington's disease, early onset Alzheimer's, to some extent breast cancer. Companies aren't doing those; in part because there are intellectual-property problems; in part because the more medically powerful the test they do, the stronger the argument that they're practicing medicine without a license or otherwise running afoul of doctor-patient relationship issues. So they're giving you things where your risk may vary by 20 percent or 30 percent or 50 percent from normal. But it's important to remember the difference between relative and absolute risk.

As a male, if I have a mutated BRCA2 gene, a breast cancer gene, my risk of getting male breast cancer goes up about a hundredfold compared to the rest of the male population. About 4,000 American men a year get breast cancer. But my lifetime risk is still only about 1 percent. So I'm a hundred times more at risk, but I'm not very much at risk.

For many of these companies, they'll do things like tell you that your diabetes risk is elevated 20 percent or 30 percent or 40 percent, but that's from a population-wide risk of 8

percent, roughly. So a 40-percent increase is 3.2 percentage points; your risk is 11.2 percent instead of 8 percent. How much does that change your life? Or one of the strongest ones they've got is on Crohn's disease. They can tell you that your risk is quadrupled from 0.7 to 2.8 percent lifetime risk – not very powerful. You're not getting very much.

And, in a sense, you're getting even less than that. Let's take the diabetes example. They might say, average risk: 8 percent. Based on the genes, your risk is 10 percent. Or maybe, for me, my risk is 6 percent. But that's only based on those genes without taking into account anything else. A doctor looks at my age and my size and my weight and says, whoa, your risk isn't 6 percent. Your risk is substantially higher for reasons that have nothing, directly at least, to do with genes. The genetic risk doesn't necessarily relate very strongly to your real risk. It's a piece of the risk; but your diet, your lifestyle, habits, your age, all those things factor into it as well.

Finally, these companies, obviously, need customers. They decide what tests go onto their panels, and how much evidence there has to be that this test is accurate, works well, and tells you something useful, before they put it on their panels. They need customers. I think there is over time a strong pressure to include more and more things, because you need more and more stuff to sell.

Now, none of these are ever approved by the FDA. These tests do not go through the FDA to see whether they're safe and effective. And so, as a result, the companies – without any regulatory authority – decide what's good enough, how many studies they have to have; how many times it has to be replicated; how widely accepted it has to be – in a context where their commercial pressure says always add more.

Third issue is the lack of context. Now, one of the companies, Navigenics, is a little different on this. But most of them provide no professional intermediation. You get the information through the website, through email. And you're left to deal with it as you want. You can check their website for further information on it. The lack of a professional intermediary worries me.

Let's say you're a woman and you're told your breast-cancer risk is low, because some of these companies do breast cancer risk, though not with the BRCA1 and BRCA2 genes. And let's say, as a result of that, you decide not to get mammograms. That could be a fatal decision, because although your risk may be lower than average, it may go from the population 12 percent lifetime to 10 percent or 11 percent or 11.8 percent. And not getting mammograms could kill you. If you talk to a genetic counselor or a physician about it, they'll tell you that. If you get that information over the Web, I'm not so confident that you will hear and understand it.

The last issue is kids. There's very little that is almost unanimously agreed upon among the group of us who study ethical, legal, and social issues among genomics. But one of them is you shouldn't do genetic tests on kids unless the results are going to be important in their medical treatment or their other treatment while they're still kids. Let them wait until they're adults and make up their own minds.

Navigenics says it won't take kids; deCODE and 23andMe take kids. And kids are actually kind of a selling point to get this wonderful family information and figure out whether your daughter really does have her mother's nose, et cetera, et cetera. Well, you're getting a large amount of information about those kids without their consent, whether they like it or not. And that bell, once rung for each individual kid, can't be un-rung.

So what's the future of this? It's complicated. I think soon – I hope as soon as George thinks, although we'll see – we will move to full sequence rather than just these SNP chips. And then, all the genes will be on the table for companies like this. And we'll face very different regulatory challenges.

I think in the long run, regulation is needed but can't do very much here. What we really need is consumers who are well educated, who understand what the limits and what the risks are of the information they're getting. And in order to do that, we need consumers. We need educated journalists to help educate consumers. So thank you.

(Applause.)

COLLEEN MCBRIDE: Good afternoon. I was asked to speak today about genetic susceptibility testing and what we're hearing about from these new companies, and to comment on whether there is any evidence for benefit for health behavior change. I think you're hearing the tension already in the sense that we have this very rapidly moving technology and lots of questions often framed as concerns about where this is all going to lead us.

In terms of the data that we have around the question of whether this kind of information can influence behavior change, we really have a lot of optimism that is being circulated and presented, sometimes even to the extent of hyperbole, but very little data to support most of those assertions. So from 30,000 feet in my allocated seven minutes, I'm just going to highlight some of the data that is out there and then talk very briefly about some of the efforts that we're taking in our social and behavioral research branch to learn more about and answer some of these questions.

So first off, there are very few studies out there that are involving actual genetic testing and feedback to individuals and then evaluating the impact on their health habits. Much of the science that is out there is based on hypothetical vignettes where individuals are asked to imagine what they would do under certain circumstances. And I think we all know that there is often a gap between what we think we'd do and what we'd actually do.

So far, these kinds of tests that are being offered tend to attract the highly motivated. And among the highly motivated, most of these studies have been in the area of smoking cessation, and have shown no evidence of lifestyle changes in these, again, very few studies. But on the good side, there's actually been no evidence of fatalism either, no evidence that individuals are walking away from these test results falsely reassured or unduly reassured about their health habits. Now, again, if you look at the individuals who are showing up at the door and the fact that they're highly motivated, that may be in fact the reason why we're not seeing changes in lifestyle or changes in how people are thinking about the results.

We also have, I think, a good sense that feedback on single-genotype test results can be understood. And in the few studies that have tried to do this without the help of a genetic counselor, using telephone counseling, printed materials and so forth, we've actually seen that folks can walk away with a reasonably good understanding of what the test result means and that this doesn't necessarily require a health professional to do that. But keep in mind that that is just a single genotype. And what we're hearing about today and what these tests that are being directly marketed to consumers include multiple genes in which we don't know how those genes interact; we don't know a lot about many of the other genes that influence these health habits or these outcomes. So we are basing our research now on a fairly simple scenario.

I think we also have a good sense that test context and the risk result also probably plays a role in how people understand their test results. So when testing is offered in the context of a family member's diagnosis, we see some evidence that individuals that are told they're not at risk have a little bit of a hard time accepting that information. And that may be well understood given that their family member has just been diagnosed with a health condition that they're concerned about.

Likewise, we see when individuals are given high-risk results in a context that is rather frightening, those individuals may have some motivation to distance themselves from that information and not find it as believable. So I think we clearly need to explore more in terms of understanding how context plays a role in receiving test results. But I think, really, the safest thing to say is that the data is so thin, so few studies and so few studies involving actual testing, that the reality is most of what we're hearing about how this is going to influence health habits is all assertion, and that we really don't have an evidence base to support any sense yet of where this is going.

With that in mind, and with our anticipation that these kinds of tests that are being offered were coming, about three years ago my colleagues and I at NHGRI set about trying to fill that hyperbole gap with some real data. And we took on what we're calling the Multiplex Initiative to address really three very basic, very early questions: who might be interested in this kind of testing, would the individuals who sought testing be able to understand the meaning of the test results, and how might this test result, the test results they receive, influence things like their seeking other risk information, family history information, getting behavior risk factor assessments. All of these are quite antecedent to the things like do they quit smoking, do they eat better, do they exercise more because, really, we feel first we have to understand how best to communicate this information before we can even begin to test whether this has benefits for health behavior change.

This is a study that is ongoing right now, so unfortunately I have very little data to share with you. But I just wanted to give you what I think are the real strengths that this information will bring to these questions. This is a study that's being done in collaboration with Henry Ford Health System in Detroit. We chose that because they are all insured patients who have access to preventive services should they need them.

This is a population-based sample, meaning that we are going to know a whole lot about the denominator, that is, the individuals who we approach, are offered testing, but who choose not to get tested, which is something that we really don't know very much about right now. We anticipated that we would have to touch about 5,000 individuals and that might attract as many as 500 to get tested. And we targeted primary prevention, which has been touted as one of the real advantages of genetic susceptibility testing, is that we can tell healthy people that they are at risk for things before they get those health outcomes, and perhaps influence them to take steps to live healthier. So we targeted those who are ages 25 to 40, and they could not have any of the health conditions that were on the test battery.

This is like the tests that are now being offered, being done completely through the Web. Individuals make a decision about whether or not they want to be tested, fill out some questionnaires along the way, and then at the end are guided through a decision about whether or not testing is right for them, told a lot about the pros and cons. All of the things that Hank was telling us were not on the other sites, are indeed on our site. And then, if they do choose to be tested, they need to come into a clinic and have their blood drawn, and they go through a more intensive consent process as well.

Right now, we have just completed recruitment and these numbers are hot off the press. We approached about 4,000 individuals and were able to complete telephone surveys with just over 2,000 Henry Ford Health System patients. Of those, just over 600 went to our website to consider testing; we still have a few more weeks that they can opt for testing, but 362 have been tested so far, 260 so far have had their blood drawn, and we have given test results now actually to closer to 200 individuals. But the bottom line is that about 11 percent of those that we approached actually sought testing.

Now, that strikes me as a fairly low number; 89 percent didn't seek testing. But when you aggregate that to the population level, that's actually a large number of individuals who might be approaching a physician with test results in a system that's really not prepared to handle it.

In terms of the denominator against which we will compare the characteristics of those who got tested, who we sampled were fairly representative of the Henry Ford Health System: half are female, half are married, half are African American. We had fully a third who were under a high-school education. And most of these were research naïve, had never participated in a clinical research study, but were quite savvy and sophisticated with the Web. In fact, we ruled out no one because of not having access to the Web. So clearly, the Web is an avenue for trying to do some of these services.

I'll close with a tantalizing little bit of data. There've been a lot of concerns raised about the fact that the public is quite deterministic when it comes to genetics, and that they will be disinclined to see the complexity of this kind of circumstance when they're presented with this information. What I present here are the eight health conditions that are on the test. The red bars are the level to which these individuals think the health condition is caused by their own health habits, their own behavior; the blue is the belief they have for the genetic contributions. And what you see across the board is that, regardless of the health condition, these individuals believe

that their health habits have a lot to do with determining these outcomes and, across the board, more so than genetics.

However, they also have a sort of nuanced understanding that that varies by disease, and that for diseases like lung cancer, where cigarette smoking is clearly the major cause of lung cancer, they appreciate that there's a significant difference there in terms of genetic contributions.

So with that I will close and thank you.

(Applause.)

ROBERT GREEN: Well, thank you. And I hope that for the wrap-up I don't actually have to disrobe, but I will be sharing some personal information with you in conjunction with today's theme.

My research has been on genetic susceptibility testing for Alzheimer's disease, and I'm supported primarily by NIH, NHGRI, and the ELSI branch. I believe we have the longest running ELSI branch grant in the history of ELSI, which has been very gratifying. In conjunction with the ethical flavor of today, I want to point out my disclosures, including uncompensated advisory positions to several of the companies we're discussing. However, the Myriad Association is actually around their Alzheimer drug, not around anything to do with their BRCA work.

The gene that sparked my interest in this is APOE. And approximately 25 percent of the people sitting in this room have at least one E-4 allele of the APOE gene, which means you're at increased risk for Alzheimer's disease. Not just a couple of percentages as in the examples that Hank was mentioning, but you're three times as likely to get Alzheimer's disease if you have one copy of the E-4, and about 15 times as likely if you have two copies of the E-4. So we're not talking about 20 percent increased risk; for a quarter of you we're talking about 300 percent increased risk. It's a significant risk marker. It's probably the most robust risk marker for Alzheimer's disease.

And it's been known for a long time, but no one's used it for predictive purposes because of all the ethical concerns that you've heard discussed. We set about 10 years ago exploring how to utilize this in disclosure. And by good luck, we picked a gene that not only had this robust risk profile but was analytically valid, clinically valid in the sense that I just mentioned, and what we decided to explore was its clinical utility. What did people do with the information? How did they understand it? What was the impact? How many people even wanted it? So it had all these excellent features for studying this and, in addition, it had no market pressures. None of you has ever received an advertisement for getting your APOE done because there's no treatment for Alzheimer's disease, and the world had decided it wasn't a good idea to market it.

And yet, it's a terrifying disease. So if there were ethical implications, or if people were going to threaten to jump off of roofs when they got this information then, indeed, we would be in a position to safely examine this. So we did a series of randomized clinical trials, just a like

drug trial, except the drug was the information. And in the first of these we actually gave people their genotype, versus an arm in which they didn't get their genotype, and we put 162 people through that.

But we're now in our third randomized trial and we've completed this one; we've completed this one in which we compared a very brief protocol, like you'd get online or in a brochure, to an extended protocol, and we looked at those results. And we're in the midst of completing this one, where we're actually giving people their Alzheimer risk as well as incidental findings of another disease that you're at risk for with APOE, so it's a surprise. And this, we feel, mimics some of what happens when people might go online, for example, to get their risk for condition A, and then they end up finding out their risk for conditions B, C, and D. So in all, we have put close to 600 or 700 individuals through these randomized trials, of whom about 500 have received their APOE genotype. So we've got quite a bit of experience now accrued, and quite a number of papers that I'd love to share with you on another occasion.

But let me just share with you one slide that tells you about our key findings. First of all, as you heard from Colleen, a lot of people want this information. We went to a series of individuals with Alzheimer's disease in their family, and 24 percent of them not only said they were interested, not only came to the informational meeting, but stuck out their arms and had their blood drawn, which was remarkable to us.

In our hands, with a great deal of careful screening beforehand and a great deal of genetic counselor support afterwards, the psychological impact of receiving this risk information was modest. Individuals got upset but, knock on wood, no one has had any catastrophic reactions and, overall, in following very careful, validated indices of anxiety and depression, we found that if they got bad news, people returned to their baseline level in a few weeks. And if they got good news, they got relief that was sustained for years. Whether they got good news or bad news, they were extremely satisfied with the experience. We'd like to think that was partly our protocol, but they knew what they were getting into because we educated them well, and they were very happy with the results.

We tested them on whether they understood what we gave them and whether they remembered it, and both understanding and recall were quite good. We actually demonstrated, for one of the first times in history, that people change their health behaviors depending on their genotype. This is quite remarkable because we went out of our way to explain to people you couldn't really change your future risk of Alzheimer's disease no matter what you did, and yet people tried things.

Some of the things they tried were, I think, dangerous, that we've documented – for example, we haven't published this yet, but we've documented a substantially higher use of non-medical supplements in people who found out they were E-4 positive. We also were the first study to document that people had five times the likelihood of purchasing long-term care insurance if they found out they had one of the E-4 alleles, versus if they found out that they did not. And, as you can imagine, this rocked the long-term insurance industry a bit because it suggests that the possibility of adverse selection is now real, and that they have to deal with it.

We found an interesting phenomenon, that people come into our study with a kind of worldview, magical thinking if you will, about what their risk is. They were extremely resistant to changing that. So they walked in with a sense of their risk being here, and we would tell them their risk was here or their risk was here, and their own perception would drift slightly toward what we told them but then kind of settled back somewhere in between what we told them and what they walked in believing. So there was a natural resistance to actually even believing what we told them. It was fascinating, and we have a lot of interesting details about that we could share with you on another occasion.

As you heard, there are quite a number of commercial entities and, although I was not compensated with funds from any of these, I was asked to speak to several of them. And I was actually given the opportunity to be a beta tester for two of the ones that you've heard about, 23andMe and Navigenics. There was one prominent geneticist who wrote in a front-page story that if he received a report from one of them, he'd ball it up and throw it in the trash. I am extremely impressed with the sensitivity and with the commitment of the scientists and individuals running these companies. I disagree with one item that Hank said. I do believe that their consent forms actually are quite thorough, and I believe that they are relatively explicit about the kinds of issues that Hank was appropriately telling.

Now, I have to go back and check if they actually mention parenting, but my recollection when I've reviewed some of their consent forms is that they're pretty darn explicit that you could find out some things you don't want to find out, and they warn you; now, whether people will read them or not, of course, is quite a different question.

I had some beta testing for this and the first thing I was interested in was APOE. Now, look, I've been studying it for 10 years and I actually didn't want to know. I didn't want to know because I just didn't want to worry about it. I deal with Alzheimer patients, and it was too scary. But you know what? It was different. It was different when all I had to do was check a little box of 10 things and I went ahead and checked that box. So the first thing that told me is that it's different getting a panel than it is going after that one thing.

And here are my results from Navigenics in which I have, fortunately, a lower than average risk of Alzheimer's disease and, therefore, using the SNPs that are in linkage disequilibrium with APOE, they've told me that I probably do not have an E-4 allele. Now, I think there are some technical questions about this, but you can also look at my other results here. You can see that, as Hank I think beautifully pointed out, my diabetes type II risk on average is – in the population they say is 25 percent, but mine's 19 percent. My multiple sclerosis risk is in orange, meaning I should pay attention to it, but whereas the average risk is .3 percent, my risk is .5 percent. Now, that's kind of interesting but there's a real question about whether that degree of change is helpful to me in making my own health decisions.

So being a guy, I thought – I mean, there's a great amount of information on this; there are 70 items on the 23andMe. I thought, okay, what about heart disease? I'm a runner; I have no cholesterol problems, no history of heart disease in my entire family, so let's just focus in on heart disease. Navigenics says my risk of heart attack is actually 44 percent, whereas the average is 42 percent. Well, I'm feeling pretty good about that, you know; I've got this environmental

stuff under control. I don't smoke. They give me a nice little graphic with the two genes that they – two of the four genes that they pick that I actually have a signal from, so this one's increasing with an odds ratio of about 1.28 and this one about 1.25, each one increasing my risk by about 25 percent.

23andMe, again, gives me this beautiful layout of 70 different things, I believe we're up to, with 23andMe, including some things it's easy to make fun of like earwax, but also some things that are fun to look at like whether you have a gene for height and have a gene for muscle speed. However, let's focus on heart disease; they say that on average, 2.5 out of 100 men of European ethnicity will get a heart attack between the age of 45 and 54, which is where I am. And they give you this helpful little graphic which helps kind of put it in context and perspective; I like that. They tell me that my risk is about average, maybe 2.4 percent. Well, and then they give me one of those genes that you saw before, and they actually tell me that it's lower than average, whereas the – if I understood correctly, Navigenics told me it was higher than average on that same gene.

So there's a couple of points to take home here. I'm not actually sure these match up in terms of the actual indication that they're telling me on the exact same gene, number one. Number two, they're both telling me my risk is pretty close to average. Here's the comparison, the 9p21 is up here and the 9p21 is down there, so there seems to be, frankly, a contradiction. And does it track with my health?

Well, here's the Full Monty part: After all of that good living that I told you about, I was running in Central Park and had a little bit of chest pain, and actually found myself on a cath table with three-vessel disease and a week later, had a coronary artery bypass graft. So if anybody was a genetic risk for heart disease, it was me because there are no environmental factors here; it's got to be genetic. So I'm quite okay, thank you very much – (laughter) – but in the one instance, at least in my life, where this could have alerted me, it did not.

Now, do I think this is a worthless industry and ought to be outlawed? Absolutely not. But do I think that there are real reservations about the degree to which people can interpret this information? Absolutely, and I think all of us have emphasized that.

So my last slide is this: Many consumers want this information, but they do so with a high potential for misunderstanding its current value to their health. The currently available genetic information on health is of limited or, in some cases, no medical value and it may actually falsely frighten or falsely reassure consumers. Data are needed on the risks and benefits, and while I truly believe that these companies are ethical and committed to improving people's health, I believe that market forces may push them in the direction of exaggerating the benefits of their product.

Genetic information coupled with health information, however, could have a public health benefit. If 100,000 people learned that they are at slightly increased risk for diabetes type II, might they each lose one pound each? And on a population basis, could that improve our health? That's a real possibility and it has nothing to do with individual risk. On the other hand, if 100,000 people are falsely reassured that they don't have a risk for type II diabetes despite

their big tummies, then that could do a real public health harm. So there are elements to this that have nothing to do with individual risks that could be beneficial or harmful.

But let's keep in mind that additional genetic discoveries could completely redefine this risk information and truly provide health benefits. So I think we need to help this industry, not just shoot it down, and we need to help them through you and your voices. Thank you very much.

(Applause.)

HUDSON: I'd like to open up the discussion now for all of you. We have floor mikes that are going to be handed around, Juli over here and Shawna up behind her. When you ask a question, if you could let us know who you are and from what organization you come from. We are taping today's proceedings and those will be available on our website probably in several weeks, www.dnapolicy.org. You can also sign up there for our newsletter.

So while we're waiting for people to wave for a microphone, I'd like to start off with a couple of questions. We have some old precepts in genetics that are being challenged by what we now can do and are doing in consumer genetics and in genetics in general. We used to think that genetics was special and, Colleen, I really liked your slide about the public's awareness that genetics isn't so special; it mixes in with an environment and lifestyle and other contributors. So we can sort of throw that old precept out.

We had the belief that information was toxic and that having information where there was a disease with no intervention, that was the highest-risk kind of information. At an old advisory committee the secretary, in fact, put that as the highest-risk kind of information and it seems to me, Bob, you've sort of thrown that one out the window, that people aren't going to jump off a bridge.

Another one was that we need pre- and post-test counseling for every genetic test that we have, and that healthcare providers need to be involved in genetic testing. And I sort of wanted to get people's reaction because I wasn't clear where you stood. The American Society of Human Genetics two years ago put out a position statement in which it said all tests are not created equal; some are appropriate for direct-to-consumer availability without a healthcare provider, even a healthcare provider employed by the company. And then, this year, the American College of Medical Genetics came out with a very different position saying no, no, no, all genetic tests require the steady hand and wise counsel of a healthcare provider. And so I'd be interested in -- you know, genetic tests are across a continuum and maybe you want to divide it up -- but in general, the panel's reaction to do we really need docs involved and if so, when.

GREELY: You don't need them on the earwax test.

HUDSON: (Chuckles.) Okay, we don't need them for earwax. Bob? Or Colleen, go ahead.

MCBRIDE: I was just going to say that I think I would agree that it's a continuum, and that for some things we do need healthcare-provider involvement. I think probably more important is that – I think if patients consider genetics as part of a fuller picture of their health, that it would only be natural that they would take that information to their healthcare provider. So it may be that it's the opposite direction and healthcare providers need to be ready and prepared, but not necessarily involved in actually giving the test results.

GREEN: Yeah, I would agree with that. I think that there's not going to be one size fitting all, although I think there's a real distinction to be made between deterministic testing in which learning the result means, with nearly 100 percent certainty, that you're going to develop the condition, versus susceptibility testing or risk testing that most of us have been talking about today. So I think that there is a clear distinction there and what our data suggest is that people, once they understand that it's risk testing, the psychological impact isn't quite as devastating, even when they find out the results are positive.

GREELY: And the earwax example was intended to be humorous, anyway, but I do agree there's certainly a continuum of the seriousness of the test, and what kinds of serious implications might follow from the patients or the consumer's interpretation of it. I don't imagine that everyone needs to have, needs to come through a trained professional, but I think a lot of them do and I think it would be good to have trained professionals available. Again, the three companies involved differ on this. Navigenics does have genetic counselors – they're employees or they're independent contractors – but available to talk by phone with anyone about their test results. The other two companies don't.

I think, of course, it depends, but I would rather err on the side of safety and have a professional who can put it in context, particularly in a world and in a country where people still think genes are magic and tend to overestimate their power.

HUDSON: George, for Knome, which kind of advice or guidance is provided to folks who have big chunks of their genome sequenced?

CHURCH: Well, many of these individuals have their own concierge level of medical advice to start out with, but in addition they are given as much as they are willing to accept, basically. There's a lot of value that's intended to be added and part of that's to find out what it is that people would want if they could afford it.

HUDSON: We have a question over here.

Q: Hi, my name's Stephanie Demani (ph). I'm from Children's National Medical Center. My question is for Dr. Green. I noticed when you said some of the participants who got the results that they had a mutation for APOE were changing health decisions and also were resistant to the results. And my instinct was that maybe that was a sign of more anxiety than they were reporting back, and I was wondering if you guys had thought about that.

GREEN: Yeah, that's a great question. In our first look at what they did with their results, we just had some simple questions that were lumped together about: did you change

exercise, take vitamins, or do any kind of different medications? And as a lumped-together variable, people who were E-4 positive did more changes than the people who were E-4 negative.

We are currently analyzing that, breaking it down, and it looks like most of that is happening through supplements. And that's both reassuring because at least they weren't going out and completely getting inappropriate medical care for the risk of Alzheimer's disease, since there isn't a preventative treatment that's known to work, but it's also scary because it just highlights the way that this information could be used with the nutraceutical industry, for example. I mean, you could just imagine in unscrupulous hands, and I think there are already websites that do this – here's your genetic profile and, by the way, here are all the vitamins and supplements we'll sell you to counter the things our genetic profile just told you. So I think that highlights a fairly scary aspect of this.

Q: I have a question pretty much along the same vein as that for Dr. Green. My name is Scott Douglas with Health and Human Services.

You mentioned in your revealed data that the preexisting risk perceptions were resistant to change among the population in your clinical trial, and I wonder if this is because the patients in the trial at least had some association, some prior association to Alzheimer's. And how generalizable do you think this resistance to change in the risk perception will be with the broader generalizable population that maybe haven't had the exposure to Alzheimer's and those types of things?

GREEN: Well, I think you're exactly right. People would walk in the door and say, I look like my mother and I identify with my mother, and my mother got Alzheimer's disease so I'm going to get Alzheimer's disease. They walked in with these perceptions.

So I think it is, in effect, powerfully due to their personal experience and that's very different. And I'd like to hear what other people think about the panel concept because that's very different than the way I think these companies are presenting their product, which is sort of, don't come to us necessarily because you're interested in one gene or another. Come to us and just kind of get a panel and get a whole flavor. What do you think, Colleen?

MCBRIDE: I think that that's the point of this being offered as a single gene in the case of Alzheimer's or BRCA or whatever makes more sense, but in these, for common health conditions, that's not the way it's going to be presented. And I think folks may come in. We, actually, in our study will be able to ask some of these questions, the beliefs that you come in with, the reasons that you think that diseases are caused, what you know about your family history.

Does that influence what you may track on in terms of these panels of tests? So if you have a family history for heart disease, do you pay a lot more attention to the heart disease genes, and likewise for cancer? So I think we can disentangle some of that but right now we don't know, but getting more information should be a bit more distracting from sort of hanging on to one belief, would be my guess.

GREELY: I do think that it's unclear at this point whether the customers for these companies actually are people who are interested in a general genetic overview or whether they are intrigued because they're worried about breast cancer or Alzheimer's disease or diabetes, all of which the websites say they'll give them some information about. I'm sure some of them are general, eager early adopters, a lot from Silicon Valley out where I am, but some of them, I think, may be people who buy the whole package but are really interested mainly in one thing. And we just don't know what proportion that is at this point.

HUDSON: But it's knowable, which is very nice. I mean, Colleen made the point of trying to find the facts between reality and hyperbole, but I also think we need to find the facts between reality and sort of the doom and gloom of everything bad that could possibly happen. We've found that the companies are very happy to collaborate in collecting that information about who their consumers are, why they're coming, and what they're going to do with that information. So hopefully, that data will come.

Q: I'm Greg Lennon. I'm from a group that runs SNPedia, which is the largest website with single nucleotide polymorphism information. And I want to point out we're not beholden in any way to the direct-to-consumer testing companies like 23andMe, but we have many of their customers come to us. And I'd like to make both a comment about that and then ask a question related to it.

The comment is really twofold, sparked by both what Dr. Church said and Dr. Green. The folks who come to our website do so because as customers, they have gotten their information on a one-time basis. But of course, as Dr. Church pointed out and Dr. Green, this information is changing daily. I mean, our website grows by three to five single nucleotide polymorphisms per day that are newly reported. And the person that's getting one report gets it one time, and then, of course, not surprisingly, they are learning that could change and their risk estimates can change over time just in general because we find out more things, but also because it's a little naïve to think one nucleotide in a sea of 3 billion is changing risk in a way that we understand today. We are clearly learning a lot more about how the other 2.999 billion affect that risk, but we're learning it slowly and it's going to take time.

The thing I want to ask about, though, is related to how, even though we're in the National Press Club, this is actually an international phenomenon. And in particular, genetic testing is something that is international. These companies are international. The information is on the Internet, yet some of the regulation is actually at the national level. And I'm curious, in each of the areas that you've spoken about, how do you see the play between national – in this case U.S. – and extra-national European or other concerns, especially in light of things like genomes that have been sequenced include already a Chinese genome, including the fact that the incentives, in particular the healthcare incentives, outside the U.S. to get genetic testing done are quite, quite different than the incentives or perhaps disincentives to have testing done within the U.S. So I'm just curious, in each of the legal or Alzheimer or technological areas, how do you balance and what do you see coming within the U.S. versus outside the U.S. for each of the panelists?

CHURCH: I could say there's a considerable amount of interest internationally, both in the Personal Genome Project and some of the specific technologies that I've described, and it's clearly a case-by-case basis. We have two pro bono lawyers, legal firms that are working with us to try to make contact with the international equivalents and find out what the local legislation is. Obviously, the United States just moved forward a little bit in terms of Genetic Information Non-Discrimination Act, but then there's still all sorts of things that fall outside of that in our country and in other ones, some of which are not legislatable.

GREELY: It's a good question and I've been trying to figure out my answer to it. I don't have a really good one other than I think we're still in the early days of this. It's not just different national jurisdictions; different states have different regulations that have some significant effect with respect to the ordering of tests, with respect to the role of doctors and the doctor-patient relationship.

As far as I know, I don't think any country yet has really come to grips with how, if at all, it's going to regulate these kinds of issues. So I predict that we're in for an interesting 10 years or so while governments try to regulate based on what the science was five years before. And by the time it finally comes into effect, it's likely to be moved. So we probably won't reach a stable state for 10 to 20 years, would be my guess, and there'll be some significant confusion between now and then, is a safe prediction.

MCBRIDE: I just came back from a meeting in Barcelona, Spain, the European Society of Human Genetics and a sister meeting on psycho-social implications. And it was clear in presenting the multiplex initiative that the kinds of concerns that get raised and the questions and the challenges that get raised about why the project isn't a good idea or is a good idea are very different. In the consumer-driven kind of health market, there's a set of concerns in socialized medicine that is completely different, where this is not likely to be directly marketed to individuals but it has to stand up to a high bar of being clinically useful early on.

But what I think isn't different in either of those settings is the importance of data and bringing data to these questions so that we're not simply sort of stabbing around trying to figure out or having lots of attitudes about it but no data behind it. So that – but, yes, you're right.

GREEN: I would agree with all that's been said, particularly Colleen. I haven't noticed very many other countries or scientists in other countries really jumping to do APOE, for example, even though it's been well recognized and accepted as a risk factor to the degree that I mentioned, sort of internationally, for about 10 years. So I think we are a bit more on the leading edge here. And it sort of all leads into this concept of Americans looking for what's now being called pre-disease and treating pre-disease, which is when you're talking about probabilistic risk, is rather strange and has sort of a nightmare scenario of expanding the population of diseased persons. I mean, as I say, a quarter of you are at elevated risk for Alzheimer's disease. Do you have it or do you not have it?

Q: My name is Anne Reed. I'm with the Board on Life Sciences of the National Academy of Sciences. And teeing off of a couple of things people said, first that these companies don't offer tests for the linkages that are most firmly established for Huntington's, for

breast cancer, for the BRCA genes. And then, the very last thing Dr. Green said, which is, right now, these direct-to-consumer tests don't offer anything terribly concerning, but down the road they could really provide a great deal of service. They could be really helpful.

So are we in some sort of bizarre situation where the instant something gets a really strong link, they don't offer it anymore because it's clearly a medical issue that needs to go through medical professionals? And who makes the call when that information shouldn't any longer be provided by these services? And it's such a rapidly moving target. As the last questioner said, that clearly someone is going to have to be drawing that line of when it can be offered directly to the consumer and when it has to go through a medical professional, and who's going to do that?

CHURCH: I just want to point out that there's a technical component to this which hasn't been addressed. So there is a direct-to-consumer company, DNA Direct, that actually does do some of these actionable – and the many ways of getting up to 1200 tests that are recorded in gene tests. But the technical component and the reason some of the more prominent and recent companies don't do it is because it doesn't fit on a SNP chip. Huntington's is direct tandem repeat that requires a very specific electrophoretic test and BRCA1 and BRCA2 require sequencing, neither of which really fit on a SNP chip as they're currently cost-effective. So I think doing the combination of all alleles – a real whole genome test -- is still in the future.

HUDSON: George, IP probably plays a role here too, but I'm wondering whether or not the businesses are looking at what the market is out there and that there's a stronger market for these incremental risk alleles and not for the more certain information. I mean, some of the more high-penetrant alleles must be susceptible to be put on an array.

CHURCH: Yeah, I think some of them could be. I think that it's really – these arrays haven't been around that long. And I don't think they're excluding things for that reason alone. I think it's more complicated than that, certainly for the two examples I just mentioned. It's a technical problem.

GREEN: But I think also, this is an area where we probably wouldn't want to lump all the companies together. I think that the philosophy of at least one of the companies is truly, it's your genome and everything on it you have access to. And as soon as they can sequence it, they'll give you that too. And I think the philosophy of at least one of the other companies is much more measured in terms of what they feel is appropriate to give out and has much more medical intervention tied into it. So I think there are meaningful differences in the philosophy of companies that have been jokingly referred to in print as targeting the older generation and targeting the younger Facebook generation, but I think it remains to be seen how these play out. But I agree, it's mostly technical at this point and philosophical, not I think the distinction that perhaps you were alluding to.

MCBRIDE: I would expand a bit on the philosophical. I know in our thinking around putting together a multiplex test, we were looking for common health conditions. We were looking at what are the public health priorities right now and what are the major burdens of health conditions that are laboring our healthcare system, and that there was something that we

could do about it. And then perhaps having that information earlier that affected a large population, we might – that might really be the promise of personalized medicine; might not work, might not have any benefit. But it was worth asking the question. So if from that standpoint, genes like BRCA and so forth wouldn't have the same impact as, say, type II diabetes, so philosophical.

HUDSON: We have a question over here.

Q: Yeah, both a question and a comment. My name is Mike Spear. I'm with Genome Alberta, which is a not-for-profit research organization in Canada. I've had my sequence done by 23andMe, deCODE, and the DNA Ancestry Project. And I do a series of radio interviews and blogs and whatnot and talk to people about it. And the comment is kind of, though I don't have anything like a heart attack, it showed me of average risk for asthma, but I have asthma. So I really point out to everybody that it's a roll of the dice. Somebody has to have it based on those odds; I have, so if that's the way you want to do things and run your life, based on that roll of the dice, that's up to you.

But my question is, have you noticed any difference in age demographic, how they respond. Because I find when I talk to high school, university students, their response is, why? Why would I do this? Why do I want to know? Why do I care? People more my age, it's, where do I find it? What's the Web address? How do I sign up and where's your blog so I can find out how the process works? And I can't really tell from the downloads because I've used SNPedia to post my file, so I can't really tell from the downloads what the demographic is, but I suspect based on comments, again, it's the older ones downloading it. Young people just shrug and say, why, I just don't care.

GREELY: That last point's really interesting to me because I give a lot of talks about this to both: students, high school, college, professional school, various alumni and other groups at Stanford. And I find exactly the opposite. Now, it's not dealing with this kind of SNP-based, very limited, probabilistic information. It's usually a hypothetical, it's either Huntington's disease specifically or a hypothetical based on Huntington's disease. But I find the kids, when I present it, do you want to know about this possibility that you'll have this terrible disease at such and such an age and so on? Eighty to 90 percent of the kids say yes. When we get up to the higher-value development groups, the people in their 80s and up, almost nobody wants to get it.

Now, I'm a lawyer. This isn't data. This is a couple of anecdotes, but it's been strong. It's really struck me over the years, how there's almost a perfect inverse correlation between age and interest and at least learning about these highly determinative, non-intervenable diseases, maybe that the nature of the disease makes a big difference.

HUDSON: So the answer to those questions is infinitely knowable, but I don't think we know it yet. I think the other interesting question, which I would love to know the answer to, is on 23andMe's site, you can do the sort of genomic equivalent of "friend-ing" people, so I'll show you my genome if you'll show me yours. And I would love to know sort of who those people are and if they're our age or our kids' age.

SPEAR: I did get a request from somebody entirely out of the blue. I have no idea who he is. He must have seen my name off of the blog. He won't respond to any emails asking why did you ask me, what use is it for. (Off mike.)

HUDSON: Oh, interesting, yeah, that's interesting.

GREEN: I would just say our data on age is that young versus old were no more or less eager to learn their APOE genotype, I think, because ours was really driven by interest in Alzheimer's disease per se. However, there was one important difference. When we measured how well people remembered the risk information that we gave them, the older people did significantly worse. (Laughter.)

HUDSON: I knew that. We have a question in the back. David?

GREEN: David Mongillo, American Clinical Lab Association. Primarily for Mr. Greely, but anyone can answer. It has – I think there was a question earlier that it sort of follows up on. It's this distinction, if there's a clear legal distinction between pre-disease and screening and practice of medicine. And if there is a clear distinction, what role would the states have, the state medical boards, for some of these issues that we've talked about?

GREELY: As far as I know, there's not a nice, clear distinction. The state of New York pinged 23andMe, Navigenics, and deCODE over whether they were in compliance with New York's requirements for clinical testing and caused some significant stir in the industry with respect to that. It's all going to be a matter of state law and how the states interpret their laws with laws that were not written with this in mind. So I think that's going to be messy for a while. As far as I know, there is no real nice, clear answer, and even if there were, it would only apply to any one state.

GREEN: I'm not usually the only M.D. on a panel, but I am today, and I think for those of you in the audience who are clinicians, you know that everything we do is in essence some kind of risk assessment. If someone comes to the emergency room with chest pain, you're doing a risk assessment based on your experience and the echocardiogram as to whether that's indigestion or angio-neural or something else. And so this doesn't fall that far from the model. We've gone to cholesterol and blood pressure. We know how critical it is to manage those to prevent future disease.

So I don't see it as inherently different. In fact, I think part of the problem is that the universe of consumers sees genetic risk information as inherently different from other types of risk information, whereas it is not inherently different. It is a risk factor, not in most cases a deterministic factor.

Q: I'm Scott Boyle. I'm a AAAS fellow at the Department of Health and Human Services. And I had – it seemed like a commonality among a lot of presentations in this area is a need for consumer information and education. And so I was curious what ideas you guys had about increasing consumer understanding of risk and what the genetic basis of disease and these things are that you just mentioned.

MCBRIDE: I would say that actually empowering consumers is probably the biggest thing that we could do in terms of reducing all of these concerns that we're talking about, but that probably doesn't just extend to genetic testing. That's probably across a lot of different things that are marketed to individuals. So I think that we can – I mean, part of our effort and the reason that we did the population-based approach that we did was, we knew that all of those that went away, whether they chose to be tested or not, would know a whole lot more about these tests in ways that would be critical, would enable them to be critical of the tests.

So I think there are lots and lots of good approaches out there that have been used over and over again to raise public awareness about important issues. I don't think there's anything magical, frankly, about this that we couldn't use some of the same things that we've done over and over again. So whether there's enough pressure or will to do that yet, I don't know.

GREEN: I stayed at the Sherry-Netherland Hotel in New York the other day and a white-gloved gentleman pressed the elevator buttons for me. There was a time when no one would actually press their own elevator buttons because that was too technical and no one would pump their own gas because that was too technical. And now it's almost unthinkable that we wouldn't do that for ourselves. So I see the diffusion of understanding your genome along these same lines as almost inevitable. And I think it's going to be a kind of – I think actually the consumer genetics companies, the legitimate ones such as we are discussing, are going to major positive forces in doing that.

GREELY: But I would like to see more good journalism on this, pointing out the limitations on some of the tests. I'd like to see something on a website, maybe in an NHGRI website, spelling out in very clear language what some of the limitations on these probabilistic tests are. And I continue to think there's an important role for professionals as intermediaries, whether it's geneticist, primary care physicians, genetic counselors, or others, to help people make sense of this information. Over time, the ability to make sense of it will diffuse throughout the population. But the faster we can make that diffusion happen, the fewer tragedies or even misunderstandings and mistakes there will be.

Q: Yeah, I'm John Compton. I'm with a company called GeneDx. We do rare hereditary genetic testing in completely predictable disease, if you have a mutation. My question goes to the reliability of this, the technical side of the information. A colleague of mine has a Chihuahua, which is rather a large for its breed, it looks just like a Chihuahua, but it was quite large. There are companies that you can send out and get your dog genotyped and it will tell you what the mixture of breeds are. So she thought she'd find out why her Chihuahua was a giant for his breed.

The results came back; according to the results, the dog was a Beagle, no Chihuahua whatsoever. This was clearly an error in the analysis. It was actually a limitation in the database they were using because she pursued it. Here we have companies that are relying in some cases on studies that have been published in reputable places, maybe they've been replicated. But I'm thinking, it may be a good thing that most of the results are of little consequence because I think knowing from my own company's work, getting the data right is not quite as easy as we'd all

like it to be made out to be. And I don't know who's watching the farm here when you get your results. I'd like some comments along those lines.

HUDSON: That was our last question, so I'll let the panel respond to that question as well as share any final thoughts you have.

CHURCH: Well, so this also relates to the previous question about education. I mean, we need quality-control software and testing mechanisms, as we have in many of the other genomics and other fields where you're delivering very information-rich resources. So you'll take standard samples and give it to multiple companies and see whether they get the same answer. And that's standard in the microarray field and it will hopefully be standard here. And we need to, I think, have a way that people can then find that information, kind of a Consumer Reports on the Web.

You already see that in some of these companies, like 23andMe has a ranking for what they consider the quality of the test that they're getting from the literature. So they say that when you read something in the press today, then you can go to their website and see whether they give it one star or four stars. So I think that these are two sides of a multifaceted field where we need quality control and easy access to the results of the quality assessments.

GREELY: Well, I think the issue about the limitations on data and the limitations on how much we know is very, very important. With respect to the disease-related traits, particularly though with respect to one of the hottest areas we haven't really talked about with these companies, and that's the ancestry side, where people are so eager to learn something they think is concrete about their history that they don't push for and the companies don't volunteer just how limited the information is that they're able to get, like your Chihuahua-Beagle.

The databases aren't very big. The mitochondrial DNA and the Y-chromosomes which they usually use aren't that informative. So I think there needs to be a real concern about this and the more health related it is, the greater the worry has to be. The ancestry stuff is fun but it's not a matter of life and death. Some of these issues can be matters of life and death. In general, I guess I've been cast as the gloom-and-doom guy here. (Laughter.) I'm not opposed to these companies. I'm not opposed to – I'm certainly not opposed to the science. I have friends at both Navigenics and 23andMe. And I have talked to both companies. They are, I think, very well-meaning, enthusiastic people, who are enthusiastic and optimistic. And the world couldn't move forward without enthusiastic, optimistic people.

But it also needs a few curmudgeonly people at the same time saying, yeah, well, what happens if it doesn't turn out quite as well as you think? And I think I am also not anti-capitalist. I think living in a capitalist society has a lot of benefits. But it also has some cons. I was struck by Colleen's comment about how different these things look, if on one hand you are thinking about a company pushing it on consumers, and on the other, you are thinking about a national health system serving as a gatekeeper. We are in the first of those models. And I think we need to pay a little more attention to making sure that –to try to prevent the kind of commercial hype that goes on throughout our society from spilling over into areas with significant medical

implications more than it already has. So that, to me, is the challenge here – not to say this stuff is all bad, but to try to minimize its harms, maximize its benefits.

MCBRIDE: The specific issue around the reliability of the – at least, I can comment on our testing. We do have our tests done in two different labs. We have found a very small number of inconsistencies. And then we rerun the tests, but really do hold it to a very high standard. I can't speak for the commercial companies. Clearly, there does, I think, need to be some kind of oversight of this if this is going to be done in the way that it looks like it is unfolding. I would echo the suggestions that were made around educating the consumer population.

And I would just like to put a pitch in that I think NHGRI is developing a website and a communication strategy around personalized genetic testing.

GREEN: Well, I think NHGRI has led the way in terms of not only the human genome, but in terms of being forward-thinking about funding and encouraging this sort of research and really ought to be credited for that. I think in terms of reliability, there are a couple of points that have been brought out. Is it scientifically reliable? Are the numbers and studies reliable? And do people have the numeracy skills to understand well-established risk data, which is not easy.

But I just want to leave you with the thought that as we attain the ability, thanks to people like George, to rapidly sequence the genome, we have got a whole new reliability problem. And as I have had the privilege of talking about with George lately, we have got a situation emerging where you can actually look at your sequence, your individual sequence variations in a very important gene and see that they are different than the norm, but not know anything about what that means. There will be no statistics informing that because your personal genome will truly be your private, personal sequence. So we are going into a new era with sequencing. And all these companies are saying that sequencing is the next step, where we don't even have the comfort of statistics and the limited ability to talk about and communicate statistics. We are going into truly uncharted territory. Thank you.

HUDSON: And with that, I would like you all to join me in thanking our fabulous panel today. And thank you all for coming.

(Applause.)

(END)