



**Presidential Commission**  
*for the Study of Bioethical Issues*

TRANSCRIPT

**Retta Beery**

Mother of twins who benefitted from improved diagnosis gained by whole genome sequencing

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DR. WAGNER: I think we can move right into our first session.

We have the privilege of hearing from these three, who I promise to be very interesting speakers, going to talk not only about personal experiences with whole genome sequencing and its effect on families, but also, we are going to receive this morning, a brief update on the current state of human genome sequencing, and we hope all will discuss some of the ethical issues that are facing us.

Folks, what I'll do is introduce you one at a time, and as I do, I'll begin with you, Ms. Beery, and as I do, ask you to make your -- a few comments and then move down the line and then we will ask you to stick with us for a little while until about 10:30 a.m., so that all of the Commissioners can engage you in questions.

And so, our first speaker is Retta Beery and she is the mother of twins, Alexis and Noah, about whom we've read a little bit.

Their genomes were sequenced and analyzed, ultimately providing a necessary and what had been an invasive diagnosis of their medical condition, and provided the basis for improved treatment.

It was discovered through genome sequencing that the twins carry a rare mutation on a particular gene, SPR gene, and this discovery marked one of the first successful clinical applications of next generation sequencing technologies.

Ms. Beery is a patient advocate, also runs an online support group called the Beery's Dystonia Support Site, to help families with the challenges that come from dystonia and other kinds of movement disorders.

So, welcome. It's wonderful to have you here and we look forward to hearing more about your story.

MS. BEERY: Thank you so much.

DR. WAGNER: Okay, please, I think you'll need to push the button.

MS. BEERY: Oh, I'm in live volume, yes. Very good.

No, I appreciate the opportunity to be here and share my family's story and now, I want to make sure I understand. You're going to go down and introduce everyone, so I just have a few minutes?

DR. WAGNER: No, you should give your full presentation.

MS. BEERY: Okay, great. So, I am glad I asked that.

No, thank you, Dr. Gutmann and Dr. Wagner, for having me here, and Commission Members. I appreciate the opportunity to be here, and to share my family's story with whole genome sequencing and also, to be a voice for the voiceless, the patients that are out there, that don't have a diagnosis yet, that are mis-diagnosed. I feel that I am on - here, on behalf of them, as well.

So, I am going to start our with our story and take you back a little bit to 1996.

My husband Joe and I have three amazing children. They are pretty much the most incredible children -- excuse me?

(Off the record comments.)

MS. BEERY: As you can see, Zach is our oldest, in front. He was about three years old in this picture, and then our twins, Noah and Alexis. They were born August 16, 1996, came into this world in a vaginal birth delivery, went home two days later and we thought everything was fine.

We quickly found out that things were not as they seemed. Noah and Alexis were colicky for 15 months. They

cried non-stop. They had internal issues that were going on. They both threw up multiple times a day, and then they had developmental issues.

So, at nine months of age, we were sent to a pediatric neurologist, a pediatric gastroenterologist, an early intervention program.

And so, we quickly came into this world that was new to us, filled with medical doctors, testing, surgeries, and so, I have a list up here on this next slide, just kind of a snapshot of some of the things that we encountered with Noah and Alexis, and this was from 1996 to 2002. These were some of the specialists that we took them to.

So, in 1998, we actually had an MRI done on Noah, that showed brain damage in the ventricle area of his brain. So, there is a reason that I'm going down this path.

I want to, you know, just kind of describe what a lot of the patients go through.

We kind of go through a checklist, when you have a child with a neurologic disorder, when you have a medical ailment, the doctors normally go through a checklist and they start with metabolic testing, and they go down to MRI's, different blood tests, and after going through all of these

testings, we came up with a diagnosis of cerebral palsy in 1998, which we would discover later, was an incorrect diagnosis.

We also came up with a treatment that was centered around an incorrect diagnosis, and all of these tests and specialists that we went to, we incurred a lot of costs, financial costs for the insurance companies, for ourselves, and there was a high emotional and physical cost that was involved, as well.

This is a snapshot of Noah and Alexis, kind of showing a little bit about their -- where they were at, up until 2002.

You can see, Alexis is posturing in a lot of the pictures. Alexis' forearms would stay up to her chest. Her hands would point down. She would tremor for hours at a time. Her eyes would roll up into her head, and you couldn't reach her throughout the day.

By 10:30 or 11 o'clock in the morning, she could no longer sit up. She couldn't swallow. She certainly couldn't walk, and then in 2002, I was actually -- I had done research from the time they were nine months old, on, and I was in prayer about something completely different, when I

felt like God had led me to this article.

It was titled "Deft Diagnosis," Segawa's dystonia mimics cerebral palsy, but it's treatable, and one of the common threads in this article, this other disorder the mimics cerebral palsy, was how the patients functioned at a higher level in the morning and as the day went on, they became more debilitated.

So, I knew when I read this, this is what my daughter had. We contacted Dr. John Fink out of the University of Michigan.

Five days later, we were in his office, started Alexis on L-Dopa. She responded. She went from not being able to walk the day before, to being able to get out of a car on her own, being able to pull a seatbelt down on her own, walking and talking, and so, she responded to the medication.

A couple of months later, we found out that our son Noah had the same disorder. He responded to the medication.

So, life changed in the Beery household. We went from a house with two kids that were so impaired, that we weren't sure -- we didn't think Alexis would ever live

independently, to a house filled with kids that were playing sports.

Noah and Alexis were playing basketball. They were playing soccer. They were doing gymnastics. Things that we never dreamed possible, were happening.

Then, let me go back. So, then in 2008, my husband took a job -- he was the CIO at U.S. Airways, and he took a job at Life Technologies in Carlsbad, California, life science company, that was working on technology that would one day be able to diagnosis kids like Noah and Alexis at birth.

So, we moved the family out to San Diego, and then in 2009, Alexis had a chronic cough that she had been dealing with for years, that turned into a severe breathing problem.

We almost lost her on several different occasions. She would stop breathing. We had the paramedics rushing into our house. They were trying to revive her.

In a matter of a year, these tests and doctors on the left are -- we were thrown quickly back into that whole world of medical unknowns and medical tests and specialists, only to find no answers, once again.

The seven emergency room visits were in a matter of two months, because Alexis kept struggling for breath. I would take her, I would be driving her to the emergency room, while she was turning blue, and I was praying that she would hold on for life, until we could get her help.

So, again, from 2009 to 2010, on the left-hand side are some of the snapshots of the tests and the doctors and the specialists that we went to see, and on the right-hand side, were the results from those tests and those appointments.

We got no answers, no clues, as to what was going on with Alexis. There was, once again, a huge physical, emotional and financial cost that were involved, in the process, and it wasn't just -- the emotion cost wasn't just affecting our family of five. It was affecting our extended family and our friends, and watching Alexis struggling to stay alive, while we waited for answers.

Then in 2010, August 2010, we engaged in a project with Baylor College of Medicine in the Human Genome Center.

Dr. Gibbs, who is at my right-hand side, and Dr. Lupski decided to sequence Noah and Alexis' whole genome, and

we flew out to the Texas Medical Center. We met with Dr. Lupski and then we went over to the Human Genome Center, and you can see our family, minus my older son Zach, were standing next to the solid machines that my husband's company makes, and we actually -- Dr. Gibbs showed us Noah and Alexis' blood on the systems, while it was being sequenced, which was quite amazing.

So, we had their blood drawn in August. They went through the whole genome sequencing process, and then Dr. Gibbs' team called us in November, just a few months later, and told us that they had found answers for us.

So, we flew back out to Houston. We met with the team. Dr. Wisniewski, who is on the team, led a PowerPoint presentation in a room, not quite this big, but about this size.

We had a lot of doctors and scientists in the room with us, while Dr. Wisniewski went through the PowerPoint presentation, and in the presentation, he showed - - we did some targeted sequencing on Joe and I, and some of our extended family members, and it showed that there was a mutation that they had found in my husband, a mutation that was found in myself, and together, this is the slide that

they showed us for Noah and Alexis.

So, what they found, they found two hits, or mutations, in the DNA samples, in the sepiapterin reductase gene, which Dr. Wagner had mentioned, and on the left-hand side, you can see, the mutation showed that they were low in their Dopamine levels, which is what we had been treating, from the article that I had found.

However, on the right-hand side, you can see that they were also low in their serotonin levels, and so, we got the whole picture for the first time.

We weren't dealing with something that we were just dealing with as a response to a medication. We actually had black and white evidence of what was going on with Noah and Alexis, and we had a new path, if you will, to follow.

So, we took the evidence -- the information that we were given at Texas Medical Center, back to Noah and Alexis' neurologist in San Diego.

She used this information. She added an amino acid onto Noah and Alexis' therapy, called 5-HTP, something you can readily get over the counter, and after adding this new amino acid, Noah and Alexis -- Alexis started breathing normally. Noah started -- his function became higher.

And so, whole genome sequencing on the left-hand side, what we went through, we filled out consent forms. We had blood draws. We gathered information, and on the right-hand side, we got a definitive complete diagnosis for Noah and Alexis.

We added an additional therapy, resulting in breath for Alexis and higher function for Noah, and we got new life for our family, and could you play that video, please?

(Video played.)

MS. BEERY: And that was actually in a good state, and then, could you roll the next video, please, and this is Alexis after whole genome sequencing.

She took 18 months where she could not do any sports. No, I'm sorry, the video for the -- yes, thank you.

(Video played.)

MS. BEERY: This is after her after she had to sit out for 18 months, for doing anything.

The audio and the video are a little off, but you can hear how excited she was, for the long jump.

So, this is our family today, healthy, happy, vibrant, able to do all the things that we only dreamed

possible.

But, you know, this picture represents our story, but there is a picture of other families that don't look like this. They have wheelchairs. They have feeding tubes.

And so, again, I appreciate the opportunity to be here today, to share our story, but I'm also here on behalf of the families that stories don't turn out that way, that are waiting for whole genome sequencing, for answers.

So, thank you so much for --

DR. WAGNER: Ms. Beery, thank you.

MS. BEERY: Thank you.

DR. WAGNER: It certainly is a wonderful illustration of the potential of whole genome sequencing.

We want to turn now to Professor Gibbs, Dr. Gibbs, who was so integral in helping to solve the case.

Richard Gibbs is currently the Wofford Cain Distinguished Professor of Molecular and Human Genetics at Baylor University in Houston, Founder and Director of the Human Genome Sequencing Center there, and under his leadership, the Baylor Center was one of the five leading groups that was involved in the sequencing of the human genome project.

Since then, he has pioneered personal genome sequencing techniques and his work has been a major contributor to the development efforts to use genomics in clinical medicine.

He is a member of the IOM, the Institute of Medicine, and we are really very privileged to have you here today, Professor Gibbs, and look forward to your comments.

DR. GIBBS: Well, thank you. The privilege is mine, to join you, and thank you for having me here. But I want to thank you for tackling this vital and important issue.

I feel that there is something of a race going on here, I mean, there is some speed necessary, to come to resolution on how to properly and effectively and fruitfully distribute genetic information.

I should mention how pleased I am to be with Raju Kucherlapati, who is an intragal part of the genome project too, and we worked together in that area.

I hope you don't mind me reminding you how life changes so quickly and unpredictably with technology, and if we cast ourselves back to when cell phones were invented and people said, "Who would ever want one," and when we looked at

black and white television and never thought about internet commerce, and how those things are never predicted, with hindsight, of course, yes, but ahead of time, no.

And so, the simple linear extrapolations are where we are now, often fail to realize where we are going to go, and I think the same may be true for genome data and for genetics data.

So, I think we need to, while we tackle the issues that are obviously before us, we need to think a little out of the box.

Let me tell you just one or two things about history, that we should remember as we go ahead, when tackling this.

Here is my one slide history of all genetics and genomics. The roadmap looks like this, and it is a little simplistic, and I'm trying to convey that -- the simpleness of the notion too, that is, the idea that we sequence the human genome. There is it on the top right of the slide.

These three-billion bases, three-billion from your mother, three-billion from your father, that are in every single cell. With the order of letters known, then we can know many of the secrets of life.

With that reference sequence, we can do step two, which we did, to get a large scale genetic map of the major populations of the world, and then using that in disease studies, go in and look at groups, like for example, a group with diabetes, a group without, and then find the individual changes that are important in governing those disease phenotypes, and then with all the weight of biology and functional studies, go ahead and solve life. That is the vision of genomics.

Now, whether or not that has been fully realized, I think is in a way, another discussion.

But the model here, of the idea that the doctor will, indeed, look at your genome sequence and use the computer and other knowledge, to prescribe particular treatments, I think is in the front of all of our minds.

Those who have the faith, I think say that we have enough meaningful alleles to, indeed, justify this enterprise right now. Those who certainly do not, say that well, it's been something of a disappointment, that we can't, indeed, predict more about diabetes from genetics than you can from smoking or obesity.

So, that is another discussion to have. But I

wanted to tell you that along the way, we did something I think that was very important in the genome project, which was to create a paradigm of free and open data release.

The scientists, as we all know, are not immediately prone to give out their data ahead of publication, but as a group, we met way back in the 90's on Bermuda, a mutual territory, and established this principle of free and unrestricted release of human genome data to all.

I think in a way, we didn't realize the full significance at that time, because not that many people wanted to look at that data.

But in retrospect, I think it is the same as knowing that the internet is free and available to all. If, indeed, the internet hadn't been -- had to have been under some cloak of restriction and licensing, and that you'd have to pay a penny for every email, then you could never do internet commerce.

So, it's been profound in the way that it -- the release of these data has catalyzed other studies, and I list there, a number of projects, the Haplotype Mapping project, the genotype -- the mammalian gene collection and other acronyms many of you won't be familiar with, but these are

large generic projects, which have benefitted tremendously.

Probably the most significant of those right now, is the Cancer Genome Atlas Project, which is really transforming our view of cancer and the way cancer should be diagnosed and, indeed, treated and is fundamentally based on the idea that the data are made and put out there and shared, as soon as possible. This paradigm is extremely strong.

Now, of course, as researchers in the arcane field of human genomics 15 years ago, the tension between this and what really might happen to individuals was known at the academic level, but not truly felt at the level of practice.

So, we knew, only intellectually, that the benefits of disease risk and prediction and knowing your ancestry and all the prognostics would weigh against your insurability and your employment status and what this may do to you personally, but the pressure was really not there, because the technology was not there.

Of course, now, the difference is the technology is there and many, I think, of you have seen curves like this.

This is a kind of real-time cost of what a genome

-- what it takes to sequence a genome, starting at three-billion on the top of that log-scale, and going all the way down to somewhere around 2012, this is, I guess, a year or so old, somewhere less than \$10,000 for a complete first-class human genome, and you'll hear much lower numbers in the press. The press usually runs one or two years ahead of reality.

But not only that, we do have other technology and this one slide just shows you that there are methods for pulling out that one percent of the human genome, which is the genes which we actually know what they do and we can act on the information in them.

And so, the genes are distributed in these representations here, but we have methods now that can selectively sequence those, and it costs about a fifth then, of the whole genome sequencing, and it's even faster.

So, this accentuates the ability to get the critical genetic information from an individual.

And so, if you ask what is happening in practice then, you'll see that over this last several years, the few genomes that have been ached out, now, are exploding because of this lowering cost, and this number here may be

conservative. I think I saw a number closer to 300,000 from one study.

So, many of these are works in progress and are not fully released, but we've certainly gone from arcane science into large scale, but not ubiquitous production here.

Along the way in studies such as those with Mrs. Beery, we've done a number of what we call stunt sequencing projects, which are aimed to show this information off to the world, and we actually did the first one with Jim Watson, who was willing to put his data out there and have people look at it, a subsequent one with Dr. Tutu, which shows about the population variation.

Dr. Lupski, who is mentioned today, actually has a genetic disease. We solved that. We have not yet been able to do anything for him, but did find a molecular basis, and of course, Mrs. Beery's story, that you just heard, and these all showed us much along the way.

So, the question for us now is, what next? Do we have anymore stunt projects to do, or are we, indeed, in the mainstream, doing everybody, making this data clinically available?

Well, if that is true, we have a little bit of a

problem delivering the data, and I couldn't resist showing you this slide, which is Jim Lupski in this role, as a genetic counselor, telling Jim Watson about his genome, in particular.

Dr. Lupski is very used to genetic counseling with single locus, but all he had to say was, "Well, you have 10,500 non-so, yatta-yatta-yatta." So, nothing actionable for Dr. Watson, but still, you know, implementing for the field.

So, that is our question, I think, and the one that you are to bear on, which is who will interpret these genetic data?

There are many society activities and other, of course, commercial enterprises that are beginning to grow. American Society of Human Genetics is leading this in very many ways, because it's the aggregation of the clinical genetics community.

But I think we have to acknowledge that Mrs. Beery, who has been emblematic of the importance of these kind of work, is a very unusual person, in her degree of informativeness about this, her education and her connectivity, is the exception and not the rule.

So, what are we going to do about the 99 percent, who don't have genetic information and as somebody wise said to me once, "Most people don't wake up in the morning thinking about DNA and chromosomes."

So, how will those people get their first contact with genetic data and interpret that?

This is, I think, a reasonable summary of the what I call the armchair futurist view of how this will unfold, and I hark back to the first statement about cell phones being ubiquitous now, even though nobody thought everyone would have one, they didn't realize though, it only cost \$50 or whatever, and you could get them so freely.

Right now, we're in this state, moving into this state, where all of these genetic studies are contained within the academic framework, and we're beginning to see some of this information move over into the medical record.

We are part of that in Houston. I'll just finish by mentioning that activity.

At the same time, we're seeing some of these activities outside of our medical regulation, and I'm not really qualified to speak on, except for I do have a 23andMe account. I do have a Facebook page, etcetera, but this is

going to grow, as well, and but the next thing we'll see, I think, is very grand movement of these data into the medical record, and so, this is this golden arrow, here.

In Houston, we started a lab to do this, to consolidate all of our efforts, and this slide portrays the fact that the reports are complicated, but the information that comes from this is complicated, that's why it's been in the research arena so long.

But as this laboratory which started a few month ago, has been getting up and operational, it is doing a good job of simplifying that information and reporting back to the physicians, different tiers of information, that which is actionable for known alleles, that which is probably actionable to some uncertainty, for example, a known gene where there is a change that hasn't been seen before, and the things that are not known yet, to be important in more research categories.

So, that previous unreadable chart, then becomes a much simpler chart, in these categories, and I think we can look forward to that activity, driving that clinical representation of the data.

So, to summarize then, I'll just say that the

state of technology is that data acquisition is now simply, relatively inexpensive, and while the free access to genetic data has many positive benefits, we need to represent, of course, the tension of that with all of the other personal privacy issues, but the tide is rising.

This is happening as we speak, and we can predict that more of in the future, perhaps, through non-traditional paths.

So, thank you for hearing my comments.

DR. WAGNER: Dr. Gibbs, thank you very much.

The final speaker this morning is Dr. Daniel Masys, and we appreciate you being here.

He is -- currently serves as Affiliate Professor of Biomedical and Health Informatics at the Department of Medical Education and Biomedical Informatics at the University of Washington, and prior to this, he was Professor and Chair of the Department of Biomedical Informatics at Vanderbilt, in their School of Medicine.

He was Chief of the International Cancer Research Data Bank of the National Cancer Institute, Director of the Lister Hill National Center for Biomedical Communications at the NLM, National Library of Medicine.

Dr. Masys is a member of the Institute of Medicine, a Diplomat of the American Board of Internal Medicine in Medicine, Hematology and Medical Oncology. I'm beginning to wonder what I did with my life, and -- well, let me get to the end, and he's a Fellow, also, of the American College of Physicians, and we are really honored to have him here.

DR. MASYS: Well, thank you very much, Dr. Wagner, and I'm pleased to have the opportunity to seamlessly extend Dr. Gibbs' comments, particularly with respect to the information infrastructure for managing this data.

If the technology will abide by my attempts to use it, this slide, believe it or not, was published in the National Geographic in 1987, and it was this vision that if we understood all those A, C, T's and G's, we would know something about how those things were built, and so, this vision of what has become kind of a cultural expectation in our society was, I think, embodied in this Time Magazine cover on the event of the publication of the first draft sequence, that is now more than a decade ago.

But look what the words say on the Time Magazine.  
"A historic feat that changes medicine forever."

So, in essence, we've had this expectation of where we would be, when we had this completed, that included the notion that we have also sorts of molecular and clinical biomarkers for conditions you either have or might be susceptible.

It included all of traditional medicine, did not discard or replace that, but supplemented it with very large volumes of molecular data, including what I would call structural genomics, that is what you inherited from your parents, and of those 22 or 25,000 genes, only one or two percent are switched on at any point in time.

So, that is called functional genomics, and those genes give rise by means we simply do not understand, to about 400,000 different proteins that are actually machinery of cells and of life.

We also had this notion of it affecting healthcare, particularly the right dose of the right drug for the right person at the right time.

It's hard to believe this cartoon from The New Yorker is more than a decade old, where they -- a person hands the pharmacist her DNA sequence, and some of the strongest signals we've seen in genome wide association

studies are in the area of pharmacogenomics, and I'll pursue that a little more.

So, one might say, "All right, we have the genome sequence, so what," and this cartoon from the early 90's said the good news is, we have the human genome and the bad news is, the computer alphabetized it.

So, we have it and we've changed -- the cartoon is still relevant, but it has a new caption, and that is, the good news is, we have the human genome and the bad news is, it's mostly just a parts list, and not only that, we only understand even a putative assignment of function, perhaps, for about 30 percent of the parts.

So, to harken to earlier speakers, of course, it is playing in the media, as we speak, and Retta Beery's husband's company, you know, announced the \$1,000 personal genome equipment, that being one to two years ahead of the actual realization of that, was -- hit USA Today just two weeks ago.

So, that is what we're all expecting. Now, where are we -- the realities in 2012?

So, I am an informatics person, that is kind of working -- computing as applied to these problems, and I

think an important aspect of both the ethics and the functional operation of these and advancing the science is that electronic medical records, as Dr. Gibbs has already alluded to, have not only the expectation, but have actually already proven themselves to be a bi-directional channel for DNA-enabled healthcare.

So, look at -- let's look at the channel that actually guides care.

This is a project I helped in the launch of, when I was at Vanderbilt, called Predict, the pharmacogenomic resource for enhanced decisions in care and therapy, that used the guidance of both the published literature and things such as FDA black-box guidance on some drugs, for which it's already recommended you get genetic testing.

Vanderbilt has a very large DNA bio-bank associated with its electronic medical records, that allowed that institution uniquely to test whether the effect in the literature could be seen in their own patients, where those signals are found that goes to a pharmacy and therapeutic subcommittee, that decides whether the evidence is sufficiently mature for implementation.

That leads to prospective genotyping, that is an

alert that appears in the electronic medical record system as soon as a patient who has not yet been prescribed one of those drugs, but we know there is a high prior probability they will.

The institution actually pays for them to get broad-scale genotyping. It's several hundred markers now, but the infrastructure is actually designed to insert an entire personal genome in there, from which a small subset of data, that that's qualified for clinical decision making, goes back into the EMR, and then the loop is followed to say, do the clinicians follow the advice and are the outcomes affected by that input?

Now, what does this look like if you are a provider at Vanderbilt? It's not a paper that you have to read and it's not even a -- something you have to look at in the medical record.

What it is, is an alert that appears on the screen at the moment of attempting to prescribe a drug for which the genetics is relevant.

So, our view is that there is simply way too much data for anybody to read and remain current, even if they're specialists, so that the infrastructure for patient-specific

clinical decision support is the essential connector to the best evidence and the action of actually prescribing a drug for which genetics is relevant.

It also appears in the electronic medical record, as shown in this snapshot from the web view, but we also believe this is important for patients to have direct access to, so that in the 'My Health at Vanderbilt' patient portal, there are 135,000 users of this, the clinical record includes a bullet which is genes that affect my medicine for patients who had their genotyping done, and if they click on that, they will see a lay-language description of the gene and the medicine that has bearing for their own health.

Now, on the other way of the bi-directional resource, one may imagine that electronic medical records are, in essence, receptacles of a vast number of experiments of nature, as Ms. Beery has described, a very poignant one, where real things happen to real people, who have real genomes, and only a small fraction of that is currently understood.

The generation of genome-wide association studies that are -- have populated the literature, now more than 1,000 of them, have the general notion that you pick a

phenotype, you pick a disease, and then you try to look for genes that correlate with that.

Because electronic medical records are the real world experience, you can turn that on its head and do what we call PheWAS, phenome-wide scanning, where you take a genotype that has a known association to one disease and look for the co-occurrence of other diseases, and what comes up are some very provocative both expected signals of association of known diseases, but also, systems biology, that is underlying mechanisms diseases where people had not previously suspected they were related by a common mechanism.

There is an entire NIH network on electronic medical records and genomics called eMERGE. It includes seven members listed here, that are doing this bi-directional use of not only harvesting the genotype and phenotype relations, but then taking it back into the clinic.

The realities are, as Dr. Gibbs has just noted, that our ability to acquire a person specific DNA data far exceeds our understanding of it, and that the genetic data currently, exclusively -- conclusively explains only a tiny, tiny set of the more than 8,000 diseases and their human responses to therapy.

As a result, it's likely that this class of data, more than anything that has preceded it into the EMR, will need to be available for re-interpretation many times over, over the coming years and decades.

So, I think it is the case that genomics is really just the poster child for complexity in healthcare, because no practitioner can remember or absorb even a tiny fraction of this expanding knowledge based on human variation.

So, the only way to get it back and do the right thing, and only the right thing and do it every time is through computerized decision support.

So, how does that compare to where we are in America with electronic medical records?

Only about one out of five institutions in America even has the infrastructure for these alerts and reminders. So, we have a very widening gap of disparity between the needs and the volumes of data that are about to hit the EMR.

So, issues I think it is worthy to consider are, first of all, as we move into a 21<sup>st</sup> century that is -- has these classes of data available, is it even ethical to allow

our healthcare system to practice without a systems infrastructure for decision support?

The kind of Norman Rockwell model, or the Marcus Welby model, that your doctor knows and remembers everything and can do it all right, is hopelessly inadequate for this era of volume -- of data intensive healthcare.

This is shown by this curve that in essence, rather than using traditional clinical phenotypes, we now have a structural and functional proteomics that take the number of facts that bear on a medical decision way out of the range of human cognitive capacity.

Secondly, is it ethical to discard human -- person specific DNA data that has unknown significance?

So, this is how this data generally gets back into EMR, with either a piece of paper or a PDF that has a narrative description of two or three markers, the rest of them are discarded and then lastly, how this genomic consent differs from standard consent, and in that regard, as has already been alluded to, how does consent change when a person lacks genetic health literacy, when the health condition does not yet exist, but is a future probability and some of those may be non-treatable conditions.

When a health condition does not have implications for you, but it does for your offspring, what are the terms of consent there, especially if your offspring have different views about what they want to know about genetics, and then lastly, for these incidental findings versus disease specific testing, and with that, I'll just leave you with those questions, as the first of many that you will engage. Thank you.

DR. WAGNER: Thank you, Dr. Masys, in fact, thanks to all three of you.

Since I've got the microphone, I'm going to ask the first question, and you've taken us -- you've transitioned in your presentation to what I would like to ask about, and you have listed several barriers, and begun to list some cautions to going forward.

I'm wondering for each of you, if you could imagine what is sort of the most immediate challenge that needs to be faced, to move this?

You guys, you folks have talked about access, both in terms of cost and data management. At the end here, you started talking a little bit about the ethics, which is a lot of what we're interested in.

So, what would you -- could you identify sort of, the very next place we have to go with this?

DR. MASYS: Well, I think the technical --

DR. WAGNER: And the cautions associated with it.

DR. MASYS: So, the technical infrastructure to manage the data does need to be there, otherwise it will have no bearing on real decisions or on advancing the science.

But I think that is actually an engineering problem. It's not that we have to invent something or do research.

So, that brings us, I think, rather immediately to the questions being faced by the genome sequence, the clinical sequencing centers, and that is the maturity of the -- and the confidence of the inferences made from that data.

We have a small set of things for which they associate with Mendelian traits or we have very high odds ratios of associations that appear to be -- everybody believes they are actionable or the preponderance evidence.

Well, a lot of things in the middle and awful lot yet to be discovered, and how healthcare is going to manage those things that are not yet at kind of consensus level actionability, I think is front and center for us right now.

DR. GIBBS: Well, actually, I agree 100 percent. Today's pressure point is physician education and the tools to deal with these data and be able to make the expert decisions that are directed at these grey area discoveries, the things in the middle for which there is high probability, but you need expert attention.

Tomorrow's choice -- challenge though, is community genetics education, and wider dissemination of the tools and knowledge outside of the medical arena.

DR. WAGNER: (Inaudible)

DR. MASYS: I don't think you any of those people are patients, though, who want their data thrown away.

MS. BEERY: My thought is, the next step that needs to be addressed, and that is being addressed right now, is the bio-informatics piece of the information that we're getting, and if you look at, over the past 10 years, the advances over the last five years, the advances over the last year, and the data that has been identified, it's come very far, and I know that there are a lot of companies right now that are working on the bio-informatics piece of the equation and trying to figure out what all of this information means.

And so, that is where I think the -- where we

need to put a lot of focus right now.

DR. GUTMANN: Thank you, all. The sequence to -- wasn't a gene sequence, but the sequence of speakers was really marvelous.

If we didn't know as a Commission about the great potential here, then there would be no reason to worry about the ethical problems.

On the other hand, if there weren't any ethical problems, we would just say, "Let it -- let the science rip and let's not -- there is nothing to worry about."

So, I have just quick questions. First of all, there is a factual question.

Dr. Masys, I was really pleased to see your slide on the need for computerized patient specific decision support, and you quickly spoke about proteomics.

But I just think you should say a little bit about the way proteomics is an important, fairly new part of what genomic understanding now is, because at the base here, it means that people with the same genetic markers may have very different manifestations, depending on something else that we need a lot of knowledge of, which is the genetic environment itself.

So, I'd like you to say something about that.

DR. MASYS: So, we are -- we continue to be puzzled and amazed by how an instruction set, a primary instruction set, the alphabet of genes, of only roughly 20,000, gives rise to 400,000 effector molecules, which are the actual building blocks of cells.

That clearly means there is an amazing amount of knowledge we need to understand how that smaller instruction set gives rise in things that are -- may be encoded in the genome, but maybe not, that cause the creation of one protein, not another.

They have chemical names like post-translational modification, a variety of chemical steps beyond the genome, that are by and large, hidden to us now, but clearly have dramatic and important health effects.

DR. GUTMANN: Great.

DR. MASYS: And that is where we would expect proteomics will help supplement this molecular marker of health conditions.

DR. GUTMANN: Jim, I just want to quickly ask them one question.

Are you -- to what extent are you worried, given

the lack of information and understanding in the public, which is more than 99 percent, you know, there aren't one percent of the American public who understand this. So, it's probably more like 99.99 percent of the public.

There are snake-oil salesmen out there for everything, and if you go on the web, you can find all kinds of offers for what, you know, giving your -- allowing your genetic information to be, you know, used will be able to do for you.

I mean, maybe I'll ask this to Dr. Gibbs. We, as a President of a University, I believe in not only getting more knowledge, but getting it out there in the public, and it's all for -- that is really -- we've got to be for that and it's very good.

But to what extent, given that science takes time to develop, are you concerned and is there anything to be done, about the amount of mis-information out there?

DR. GIBBS: Well, I think life is full of sources of mis-information, and snake oil. I think these risks go far beyond our agenda in molecular genetics and the biology of disease.

But on the other hand, the slowing of the pace of

discovery that can transform lives, is dramatically affected by inhibiting the distribution and the access to these data.

To me, that is a vastly higher risk, than you know, what someone might foolishly sign on to, in the form of a snake oil offer, either in genetics or in used cars or you name your favorite source of mis-information. So, I come from the other school.

I'm going to sneak in an answer to the previous question.

DR. GUTMANN: Yes, although, there has to be -- you have to recognize both, right?

People, just as people get saved by doctors doing good things, people get harmed and sometimes killed by, you know, malpractice, not by, you know, good doctors. So, you can't just brush it away.

DR. GIBBS: Absolutely.

DR. GUTMANN: Okay.

DR. GIBBS: Absolutely, there's a tension here, but the danger of not knowing is as enormous as the risk of knowing.

DR. GUTMANN: Okay.

COLONEL MICHAEL: So, as research distills to

implementation, especially clinical implementation, I guess the first question is to Dr. Gibbs, which is, there are a number of platforms that are available, solid alumina and others, that can execute whole genome or whole exome sequencing.

So, as time goes on, there is going to need to be a need for cross-platform validation of these, especially if they're going to be used in the clinical sense.

And so, what -- and that, of course, has tensions between different manufacturers, who have vested interests in expanding their market shares.

So, how is that going to be guided by the research community, which I think is going to be important, and the question then to Dr. Masys is -- well, Bill is on the line, Dr. Gutmann asked, which is, this is really impressive. This was a great line up.

I agree, and I really appreciated the sequence of these discussions, but I've always been concerned about how eventually, when you distill from research to practice, how would you actually make it available for someone who sees patients?

And it looks like even though we've mentioned the

impact of looking at RNA expression and protein interactions, that it might initially be the best way forward to concentrate simply on the structure, on -- because otherwise, the complexity gets just enormous.

But I wanted to know what your view would be of how we actually handle that complexity?

DR. GIBBS: Yes, so, the deployment is a reality now. I think that is one answer. You know, we have -- in some places, at least, as a physician, you can order a genome test and get these data delivered with some level of interpretation back in your hands.

We lack standards. There needs to be much energy on those standards. I think this is a really relatively healthy area of interaction between the research community and the academic medical community, but we need to foster that without inhibiting the enterprise. I completely agree with your point there, and thank you for making that, and I think the next question asked is to Dr. Masys.

DR. MASYS: So, all of our laboratory methods have non-zero error rates. It's true in clinical chemistry and it's true in DNA sequencing, and so, from the perspective of the informatics infrastructure, what we have

to presume is, there is not a single truth about what your genome is.

There may be sort of multiple overlapping sets of observations that are concordant or discordant at a particular nucleotide location. Not only that, it appears your genome may evolve over age, and we know there are the somatic genetics of cancer.

And so, an EMR that has to be able to store multiple genomes and reason with them in this way that is not simple declared -- that there is a single declarative truth, and that is okay. We can actually do that, because reasoning in the face of uncertainty is what most of healthcare is about, anyway.

With respect to the other classes of data, certainly, the technologies are moving at different paces.

So, the way you get proteomics is either with these 2D gels or tandem mass spectroscopy and so, it tends to be a different sensor that brings a new class of data, that is either at the small peptide or the assembled peptide, as entire proteins that are mapped and found in say, the blood or tissue.

And so, that set of markers joins at the

vocabulary of biological objects, because the data doesn't actually merge, but what you can merge is the relationship between an enzyme and its parent gene, even though the observations came from different, fundamentally different classes of technology.

So, that is a fundamental problem of bio-informatics, and it is what we call data fusion of different classes of data coming together to reveal a pattern that is not present in either one, perhaps, or conclusively becomes evident, only when you join them.

The good news is that the research tools are evolving rapidly to do that. The clinical tools, I think, have not yet arrived because clinical proteomics is not even yet where clinical sequencing is.

DR. KUCHERLAPATI: I want to make a couple of comments and a question.

So, first of all, thank you all for coming and making a great presentation, and Retta talked about her -- the company that her husband works for, and for the record, this company provided all of the instruments for the entire community to do the initial human genome sequencing.

So, the company has made an enormous contribution

to our understanding about the human genome.

Richard was the very earliest persons who embraced genome sequencing technologies and, you know, he was the first one to be able to actually begin to sequence human disease genes, the HPRT gene sequence that he has done, and embraced, you know, the genomic approaches to look at that and involved in not only developing the technologies, but actually providing enormous amounts of knowledge that we all enjoy.

But also, Richard, Baylor has been a leader in human genetics and in not only identifying human disease genes, but also, caring for a large number of patients with the human diseases, and as you know, you know, sequencing genes to try to identify and diagnose human disease or really trying to determine the prognosis is not new.

You know, sequencing genes such as cystic fibrosis and trying to determine whether or not individuals are susceptible to or who actually have disease, and trying to define the mutations that would enable, as people, to determine how to take care of those patients has been known for a long time.

So, what is different? You know, we would

sequence say, one gene at a time. Now, instead of sequencing one gene, you sequence 42,000 genes.

So, tell us how it's different and what are the kinds of new problems, if any, that you sort of see, you know, going from sequencing one gene or a few genes, to all of the genes in the human genome?

DR. GIBBS: Thanks, Raju. I think the positive difference is -- was beautifully shown in Mrs. Beery's talk, how the physician no longer has to apply expert uncertain sources of knowledge to the problem, and can quickly come to a molecular diagnosis, at least in some scenarios, and so, avoid much of the pain and cost that would -- that we heard about.

Now, on the other side of the ledger is -- are the findings of which the patient is not expecting, which fall into the categories of things they weren't expecting, which are going to have a dramatic impact of known consequence to them, and then the set of things for which there is much less certain impact.

I think what is not new is the need to deal with those medical issues. That is not new to have -- accidentally find things of great importance to patients. It

is not new to find things which may be of great importance, to really not know what their ultimate significance will be.

But to do it so ubiquitously and as part of this other routine test, I think brings it to a new level of scale.

So, perhaps the short answer is, it's one of scale, and --

DR. GUTMANN: And accessibility.

DR. GIBBS: Yes, absolutely.

DR. GUTMANN: Accessibility and interpretability.

DR. MASYS: Yes, if I may speak to this issue of scale.

You know, the first 1,000 GWAS studies essentially were -- used a common minor allele frequency of five percent of the population as the threshold for assigning, you know, a probe that you were going to look at.

We didn't hit very many home runs doing that, and so, now, it has really transitioned this focus to rare variance, so, just as her children experienced.

And so, now, if you look at the combinatorics, that is the fundamental, mathematics of association of rare variance, now, we really, in order to advance the science

quickly, need access to hundreds, hundreds of thousands, if not millions of individuals, from which we can draw a virtual cohort to quickly do this genome/phenome correlation.

And the technology will exist to do that, because the classes of data will be there. The EMR observations will be there and so, I think the principle impediments is, this is a scale of science we've never seen before.

We're accustomed to FDA clinical trials, where you enroll a few hundred or a few thousand people, and not the idea that every one of us is a unique research resource for every other one of us, in the population, and that there is a kind of social obligation, if you will, for institutions to make that data available, instead of to hide it, as if it was a proprietary benefit for that institution.

DR. SULMASY: Thanks. I have two questions.

The first follows on some of the previous discussions, and when we hear, you know, the Beery family story, it's obviously a story of great suffering, but in the end, a story of great success and really scientific and medical and personal triumph.

But with some of the comments we've had about the complexity of the human genome and the complexity of its

phenotypic expression and disease, I was wondering if you might try to comment on, sort of -- would it be possible to give a really definitive numerical estimate, but you know, how many people out there can be expected to have an unexplained disease in which there is a single gene, and Mendelian inheritance and a single easy, orally administered, you know, medication that is going to produce the kinds of dramatic effects we had here?

It's a question that just sort of tries to make sure that we're not giving false hopes to people with, you know, a wonderful success story like this.

DR. GIBBS: Yes, no, thank you for asking that, because of course you know, the answer is not many, I mean, of the, I think it's one in 200 to one in 500 children will have some Mendelian issue, and the -- but the fraction of those for which there is a simple solutions is small.

But what is not being spoken of here is, I think the great hope that we have, that we can improve that number and bring drug treatments through a complete and full understanding of all the genetics architecture of all these disorders, as we just heard, you know, the appreciation of different classes of variation and how they interact to bring

us to disease is growing, and is growing with the rest of the enterprise.

As we can sequence for routine care, we can sequence for research, but these numbers are improving.

So, I think the hope is still great, that this will be a much happier situation in a few years.

DR. MASYS: And I would add that it's just anecdotally, no one -- so, I have a 23andMe account, as well, and no physician I've ever known, who had that done, did not get a piece of information they actually found personally useful.

And so, I didn't find any diseases I had, but I actually found that I had a couple of drug metabolism variants, one of which for a medicine I was already on, and another that there is a non-zero probability, I might be put on in the future, and my doctor may not know that, but I'll tell you, I'm going to keep that piece of information in my back pocket, so that if someone wants to prescribe that drug for me, I'll tell them, "You're going to have to choose a different dose than the standard one."

So, there is a large class of this information which bears on commonly administered drugs, and probably more

in the future, for very common diseases.

So, it's not a specific diagnosis, but it is -- it does very much modulate how you interact with the healthcare organization and whether they make mistakes, that could be avoided.

MS. BEERY: I would just like to add, of course, I don't know the number just like everyone else on the panel.

However, we have reached people through media opportunities. The reason our family continues to share this story in the media is because they're not getting answers in the medical community, and we've met a boy in Lake Elsinore, California, that was wheelchair confined at age 13, couldn't go to the restroom on his own, couldn't eat on his own.

He saw a show that was done on our twins and started on the medication and he is playing tennis on his high school tennis team at age 16.

And so, that is one of many stories. It's not one story in and of itself, but through our website and through media, we've been able to reach people that have been trapped in their wheelchairs, unable to communicate. The unthinkable is happening.

And so, we want more than just a response to

medication. We want more than someone having to watch some news program or media program. We want this to be a diagnostic tool that even if it only affects a half of a half of a half of a percentage of people that are afflicted, that have a good outcome, I believe it's valuable and it's worth it.

DR. SULMASY: The second question that I've totally got different topic, mostly for Professor Gibbs.

I very much appreciate your comments about the need to share data freely, and I was wondering if you or other members of the panel might want to comment somewhat on the implications of that for ideas about patenting of sequences and the restrictions that might have on science, and what sorts of technologies ought to be patented, and whether we ought to be patenting sequences, because we have to balance, don't we, getting the capital to make products available, because they're not all going to be food products.

DR. GIBBS: Thanks for asking that. I think we all endorse patenting and reward and protection of the execution of ideas and inventions that represent investment and hard work.

Most of us feel fairly negatively about land

grabs, the opposite of that, and this was played out in the history of the human genome project.

We didn't talk about it, but there was a moment there, that many of us know, where there was an attempt to sequence the human genome within a private organization, and that was a tension with the public enterprise.

The difference was, there would be some kind of intellectual property protection of the early sequence information, and that was preceded by other long stories, some of you know much about, the earlier patenting of sequences.

The response was, it's -- we love the patent system. We love invention. We love investment and we love reward, but we don't want anybody to simply blanketly protect space, for which they put in little effort or investment, in order to scoop the rewards inappropriately later.

So, I think that same principle should play out in the distribution of genetic information, and the point made just now, about the increased interest in rare variation, which will require many, many, many sequences to be accumulated, will indeed, result in the aggregate of a body of genetic information, coupled with the disease

phenotype information, which will have great value, and that is perhaps, another area for attention, how we can protect the principle of not grabbing that, not doing a land-grab on that data, but allowing it only to be -- allowing it to be freely used in areas of high investment and high effort.

DR. GRADY: Thank you. Thank you all, for very excellent presentations.

I wanted to ask a question about cost, because each of you alluded to the fact that the technology is cheaper and there is lots of attention to the \$1,000 genome and all of that.

But as I understand it, there is -- there are a lot of hidden costs, in terms of what you do, once you run the sequence, what you follow up on, how you interpret what you see, whether you decide to follow up on certain unknown variants or uncertain variants, that kind of thing.

And so, I wonder if you could say a little bit about those hidden costs, but even maybe more importantly, the extent to which you think cost might end up being a driver in answering some of the questions you raised, like what will we do with unknown -- you know, DNA with unknown meaning?

Will we keep it? Will cost be a reason that we decide, one way or another, what to do with that?

Cost is a factor in determining what we return -- what results we return to people, and not. Cost is a factor in determining what -- you know, how much interpretation of the data we do. That kind of thing.

So, any of you who can speak to issues around cost and how that might factor into those decisions.

DR. MASYS: So, I think the most non-sustainable path of cost that we're currently on, is the cost of the intellectual horsepower that it's taking for every single institution to decide whether this data is going to be used in their institution.

So, clearly, I think the pathway here is to have a national library of clinical decision support rules, that represent best evidence, and not have very high paid people sitting around, trying to decide on their own, whether we're going to do it in Omaha or Kansas City, and so, that has to change.

Right now, it is not the cost of acquiring the primary data, as we've alluded to in today's presentations. But this cost of assembling the best evidence of what is

implementable is currently -- that is a show-stopper. That would keep us from using this data, especially if every hospital thinks they have to do it on their own.

MS. ALI: First, Dr. Masys, first, thank you so much. This is so fascinating.

You implemented this, or it has been implemented at Vanderbilt into patient care, which is phenomenal, that they could actually access it.

But let me ask you, because one of the things that we will grapple with at this Commission is privacy issues, and when you're talking about putting this on the internet and making it available through your electronic records, and people can access this information, what kind of consent forms are you using, to actually acquire this information, this data for DNA collection, and how are you telling them that it is being used?

Is it something that is flagged separately from regular consent forms? Is it explained to them, and how does it differ?

DR. MASYS: Excellent question, and as a result of focus groups with Vanderbilt's patients, they determined that DNA data actually did have a different set of public

perception associated with it, and it wasn't the same as standard clinical laboratory testing that your doctor would just order a liver test or an x-ray, and that was considered ordinary.

And so, in the standard consent for treatment form, which was revised with the predict project, patients have an explanation that Vanderbilt will use this information to help in choosing the proper drug for your condition, and if you do not wish to have DNA data used, you can opt out of that.

If they choose to opt out, then care proceeds as if that data was not available, because it won't be. If they don't opt out, then at institutional expense, Vanderbilt is actually acquiring that genotyping because insurers are not paying for it.

MS. ALI: Right.

DR. MASYS: But the institution essentially is looking at the economics of avoiding adverse events, and I'll stop there.

MS. ALI: That's okay. The other thing I wanted to ask you is that when the patient accesses that on their website, or however they are able to access it, are you

providing other information just aside from drug interactions?

Is it like personal health of what they may be susceptible to, what they may have a genetic pre-disposition to, or is it just with regards to drug applications and usage?

DR. MASYS: Just drugs.

MS. ALI: Just drugs?

DR. MASYS: Yes.

MS. ALI: That's okay. I also have another question, if you don't mind. I'll give you a minute there, for Mrs. Beery, because I understand, you know, how this must have weighed on you, as a mother, having two children that you didn't have answers for.

But how concerned are you, with regards to these issues of privacy re-occurring in the future, as these children grow up and try to seek coverage?

I don't know how it has affected your personal medical coverage insurance, but you know, insurance companies are going to try to want this information, for whatever reasons, but how has that affected your family, and how do you perceive it affecting your children?

MS. BEERY: So, I feel like I should say up front that when Dr. Gibbs and his team was going to write the paper, they were going to do it anonymously, and I was the first one to say, "Include our name," because when you put a person to the data, it brings it to life and it brings it -- and it pushes, I believe, the advancement to treatment in a broader way and in a faster way.

So, I just wanted to preface the answer with that.

We talked about that, when we started this project, we spoke about that, and honestly, we -- the answers -- we believed that this saved Alexis' life.

So, the matter of privacy versus life saving treatment, it didn't have any equal balance at all. Her life far out-weighed the privacy issues.

The other thing that I didn't mention, that I also feel led to share is, something that we found out, that I don't know that we really thought about, but because they wanted to sequence our family members as well, to see if there was a link, a connection, we did find out that our oldest son Zach, who is 18, does not have the genetic mutation, and this particular disorder, the onset can come at

any time.

So, whenever I would have him with me at doctors' appointments, they would always look at him, and not everyone responds to the medication. We didn't know what kind of -- you know, we -- we made an assumption, because they responded to the medication.

So, that was another discovery in this process that was huge for us, because we no longer have to worry or wonder if Zach is going to be affected at some point.

MS. ALI: Has it affected your medical insurance coverage?

MS. BEERY: It has not.

MS. ALI: All right.

DR. HAUSER: Thank you. I wanted to ask about the sequencing experiment, which was just so inspiring to all of us.

One of the lessons in the deep sequencing era, is the un-nerving realization that we all have many, perhaps 100 or several hundred variants that predictively disrupt the protein coded by the DNA.

And in your children's situation, there was the good fortune that the compound heterozygote mutation was

found in a candidate gene, that we had previously known was responsible for this condition.

More often, I would think, we would find things that would be new genetic clinical disease correlations, and in the absence of lots of data that we don't yet have, we would have to make a guess, as to cause and effect, and this is particularly important if the -- this is potentially actionable at the bedside, perhaps with a treatment that could have some risk.

So, I know there are no easy answers to this, but wondered how Dr. Gibbs and Dr. Masys was thinking about this problem at University of Washington and at Baylor.

DR. GIBBS: Thank you for beautifully articulating what we dismissively said is the second tier of discoveries, the things that look suggestive, for which there is some weight of evidence for a conclusion, but not a full weight of evidence, and indeed, there are many.

And this is why we, I think as an institution, subscribe to the notion that it will be the expert clinical geneticist physician, the expert in the particular specialty, who uses yet one more piece of evidence to draw their conclusions upon which they base the next phase of treatment

or patient interaction, in many, many cases, ahead of the era when we have a complete database of all consequences for all genotypes.

So, I think this is an important issue, because as we see a proliferation of groups and of activities that are looking for simple algorithmic solutions to the interpretation of these data, they will not achieve the right result in many cases. They will have to go back to the experts.

DR. MASYS: Steve, my voice is back. It's good.

Russ Altman at Stanford has argued, particularly in the area of pharmacogenomics, for a standard of non-inferiority, and that is where healthcare is based, you know, a lot of healthcare is on average, everybody is average.

So, we guess and we know we're going to be wrong, and we're comfortable being wrong.

So, if you could only do better than that, you know, then whatever the standard of guessing is, then even inconclusive data may have value in clinical decision making, and I think that is a new kind of thought, a new space for clinically informative data, because we're so used to having a conclusive FDA approval for a clinical trial, as opposed to

suggestive data that is not beyond a reasonable doubt evidence of the proper path to take.

But I think we could get comfortable with that space of things that help inform the -- they give you a nudge, in a direction, rather than saying definitively, "This is the answer."

DR. FARAHANY: Thank you, all. This is incredibly informative, and quite helpful.

I too, have a 23andMe profile and have learned a tremendous amount from it, you know, just even downloading the raw data, being able to use it in other areas, was able to develop a much more targeted therapy for migraines with my neurologist, as a result of that, which I think is phenomenal.

The Vanderbilt systems concerns me in the following way, as opposed to 23andMe, which is, I voluntarily chose to be part of the 23andMe system opting in, as opposed to the Vanderbilt system, which deliberately made the choice to make it opt out, rather than opt in.

And having also been at Vanderbilt and been through the Vanderbilt system, I've experienced what that looks like, which is you receive an electronic form, perhaps,

where the person simply reads it through to you. There is no print-out, because we're trying to be more green.

And there is just a little more -- you know, there is a little check mark that they say, "Do you want to opt out?" If not, you go through and it is just read to you.

What concerns me about that is that there is a lot of DNA data-banking that is happening independent of just the drug profiles, at Vanderbilt and other systems that are doing it.

And I know that Vanderbilt went through a very deliberate system of considering opt out versus opt in, and the data shows that people are much more likely to actually contribute data if it's opt out, as opposed to opt in.

But you know, one of the things that we are going to struggle with is the issues of privacy and the implications of having information and your medical record, which potentially, insurance companies, notwithstanding GINA, could make determinations about, and data that impacts not just you, but also family members and other people who are related to you.

So, I was hoping that you could all talk a little bit about your perceptions of this opt out versus opt in

system, in your own experience, with the Vanderbilt system, about that.

DR. MASYS: So, before Vanderbilt went operational with this quality improvement project, they had begun a bio-bank for discovery called bio-view, that was built from discarded leftover blood that would otherwise have been destroyed, linked to de-identified data from the electronic medical record system.

So, it was working in a space of de-identified data for genome-phenome correlation and was fully -- in that regard, is fully compliant with federal and human subjects protections in that regard.

The decision to do that was predicated on about four years of work, of looking at the acceptability of that model for not the world, but for Vanderbilt's own patient populations.

And they found in doing a survey of 5,000 patients and having a variety of focus groups, that there is what I would call a gap of volition, and that is, in the -- the attitudes among the patients that were surveyed, were about 30 percent passively favorable to science. They think bio-medical science is good.

Those that are affirmatively altruistic, they really want to help the next person that has the same disease, and then people that have no strong feeling one way or the other about it, and then about 20 percent of concerned, five percent who believe that is -- they don't want any part of that.

It turns out that across one-million consent events, five percent opt out. So, it was predicted.

DR. GUTMANN: Daniel, can you just do the percentages again, because you went, there is 30 percent who are passively favorable to science and --

DR. MASYS: Sorry, what I can do is get you the actual pie-chart.

DR. GUTMANN: That would be great.

DR. MASYS: Yes, and it's been published.

DR. GUTMANN: It would be very helpful to have the results of that.

DR. MASYS: Yes, I'll provide that to you.

The point, I think, however, is that what we discovered in doing that, is what I would call a gap of volition, and that is, people who trust in the institution, want the science to go forward, believe there should be

genomics.

But when you put, you know, an eight-page consent form in front of them, now, they have -- now, it's, "Oh, wait a minute. These are written by lawyers and if I sign this, I think I'm giving something. I don't want to sign something, because I don't know what I am -- I don't understand it enough to know what I'm giving up."

So, there is this kind of paranoia about the requiring of a consent signature in a full -- you know, in the full blown OHRP kind of model of research consent, and so, I only leave that as an observation, that the -- the bio-bank, which began really, as -- you know, in an IRB model of risk and benefit, it was all risk, right, because nobody even knew if you could get good DNA data out of discarded blood samples.

And now, there is a deepening trail of genomic science that shows that those phenotypes really are quite valuable and they have clinically meaningful results.

And so, the risk and the benefit are coming into balance in that opt out model, and so, I just offer that it is -- it does appear to be a functional model that works well in a sustained fashion over a number of years, and not the

only model for that.

But I do believe that both the concerns about genomic privacy, just like the privacy of electronic medical records, have been informed in the HIPAA regulations, and the dialog that led to those, by a sort of polar-anchored irreconcilable, you know, fundamentalist, you know, privacy fundamentalists who say nothing about me, without me, and that the reality of most people's sense of balance of value returned for trading off privacy, is not found in those polar extreme arguments.

And so, that is the space I think that I --

DR. WAGNER: Just let me ask real quickly, though, is it possible -- how much of the scientific value of such a bank, a bio-bank, is compromised by efforts to anonymize the data, to make -- to -- do you see what I am saying?

DR. MASYS: Yes.

DR. WAGNER: Can you do something in the middle technologically?

DR. MASYS: Yes, so, as part of the eMERGE network, the requirement of NIH funding is that both the genotypes and the phenotypes have to be uploaded to DB-GAP,

to a public database.

And so, what we found is that if you look at electronic medical records data, you only need about three ICD-9 codes, maybe four at the most, and each one of us becomes unique, all right.

So, the gospel of re-identification requires two elements. One is, you have to -- in a large population of records, you have to establish a single unique record, then you have to link it to a naming source, so that is name, address, some kind of demographic that causes it to be associated with the real person.

It is possible to do this data mining that reconstitutes identities out of de-identified data.

So, that was a long winded way of saying that when we upload data to DB-GAP, we have to down sample, pretty severely that, and we upload the phenotypic attributes that correlated with the genotypes, but there is an awful lot of much richer electronic medical record data that has to be kept within the institution, so it is not all published, and I think that will continue to be the case.

The clinical data is so inherently rich in attributes that the full publication, in an open --

completely unconstrained fashion, will not be available without some kind of policy that governs its acceptable use.

DR. KUCHERLAPATI: Dan, you talked about the large amount of data and the difficulties in analysis in providing clinical decision supports. Maybe you and Richard can talk about that.

How big of a problem is that, number one, and number two, where are the solutions coming from, and are there any difficulties in obtaining the right kinds of solutions?

If you take the analogy of just sequencing, for example, in a relatively short period of time, in 10 years, you know, we've been able to reduce the cost of sequencing from, you know, \$3 billion to \$1,000, and that is done all by industry.

So, I want to understand what the concern is.

DR. MASYS: In principle, none, because the actionable items are a tiny subset and we expect will continue to be a small subset of the total volume of genomic data.

There is no reason to compute across your entire genome, every time a drug is prescribed.

But what you would do, for example, is at the time that a full genome is acquired is, look for the patterns that are clinically relevant, re-look for them again over time, as -- and the deposit that as a small set of sort of key words in the clinical record that can be fired on by decision support rules.

So, I think all of the technology pieces are in place, but the interpretation and the advance of the science still awaits us.

DR. WAGNER: We could keep going, but I think the better thing to do is to ask the three of you to accept a very genuine thanks for being with us today.