

10-16-2013

## Panel 1: Personalized Medicine: Possibilities, Hurdles, and Practical Solutions

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### Recommended Citation

Shore, Justin, Corrine Parver, Julie DeLoia, Gail Javitt, Sheila Walcoff, and Jeff Gibbs. "Panel 1: Personalized Medicine: Possibilities, Hurdles, and Practical Solutions." *Health Law & Policy Brief* 5, no. 2 (2011): 3-14.

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# PANEL I: PERSONALIZED MEDICINE: POSSIBILITIES, HURDLES, AND PRACTICAL SOLUTIONS

## INTRODUCTORY REMARKS

### Justin Shore\*

Good morning, everyone. Thank you for coming. It is a pleasure to have you here. My name is Justin Shore. I am the president of the Health Law and Justice Initiative, and along with the Health Law & Policy Brief and the Health Law and Policy Project, we are pleased to present our Founders Day event, *Drugs, DNA and You—Personalized*

\* Justin Shore, JD Candidate 2012, *American University Washington College of Law*. Justin Shore is a third-year law student at the American University Washington College of Law. Originally from Prescott, Arizona, Justin graduated from the University of Arizona with a Bachelor of Arts in economics. Prior to law school, Justin was a project coordinator and research assistant at the Brookings Institution's Engelberg Center for Health Care Reform. While in law school, Justin has interned at the War Crimes Research Office, the United States Attorney's Office for the District of Columbia, and is currently interning within the DOJ's National Security Division, Counterterrorism Section. In addition to his past work as president of the Health Law and Justice Initiative, he is currently editor-in-chief of the National Security Law Brief, and has been an editorial board member of the Human Rights Brief and a founding member of WCL's Project LEAD.

\*\* Corrine Parver, JD, *Founder, Health Law and Policy Project, Program on Law and Government; Consultant, Program on Law and Government; Former Practitioner in Residence and Executive Director, Health Law and Policy Project, Program on Law and Government American University Washington College of Law*.

Corrine Parver designed and implemented Washington College of Law's health law specialization as part of the LLM Program on Law and Government's Administrative and Regulatory Law concentration. She was the faculty advisor to the Health Law and Justice Initiative, a student organization, and the Health Law & Policy Brief. Prior to joining WCL, Professor Parver was a partner in the Washington, DC, office of Dickstein Shapiro Morin & Oshinsky LLP (Dickstein Shapiro), where she headed the firm's Health Law Services Practice, focusing on fraud and abuse prevention and counseling; health care compliance; reimbursement, coding and coverage of services and devices; privacy; mediation and litigation strategy; legislative and regulatory advocacy; and general health law. Previously, Ms. Parver was the president of Parver & Associates, a legal and consulting firm, and the president & CEO, National Association for Medical Equipment Services (now American Association for Homecare). She received her Juris Doctor cum laude from the American University Washington College of Law, where she was an assistant editor of *The American University Law Review*, and her Bachelor of Physical Therapy degree and PT diploma from McGill University.

*Medicine in the 21st Century*. We have three amazing panels before you today. Our first panel will be moderated by Professor Corrine Parver, practitioner-in-residence and executive director of our Health Law and Policy Project.

### Corrine Parver\*\*

Good morning, everyone. We have a great panel this morning that I would like to introduce. Our first speaker is Julie DeLoia, interim dean of Georgetown University School of Nursing & Health Studies. She joined the University in August of 2007 as the associate dean of academic affairs and associate professor in the Department of Human Sciences in the School of Nursing and Health Studies. Prior to that commitment, she was instrumental in founding the University of Pittsburgh's Ovarian Cancer Center and served as the center's director of research. She has published more than forty-five peer reviewed articles, has served as the principal investigator on two R01 grants of the National Institutes of Health, and is a co-inventor of a patent for gene copy number profiling. She holds a PhD in human genetics from Johns Hopkins University and completed a postdoctoral fellowship at the University of Pennsylvania in developmental genetics.

To Julie's right is Gail Javitt, who is counsel in Sidley and Austin's Food and Drug Regulatory Practice. She joined Sidley after seven years at the Genetics and Public Policy Center in Washington, DC as the law and policy director. In that position, Gail was responsible for developing policy options to guide the development and use of reproductive technologies and also led an initiative to provide oversight of genetic testing quality. She was a Greenwall Fellow in Bioethics and Health Policy at both Johns Hopkins and Georgetown Law Center and has worked as a research scholar and adjunct professor at both institutions. In addition to her work accomplishments, she has written on a variety of science, regulatory, and legal topics, including direct-to-consumer marketing of genetic testing and Food and Drug Administration (FDA) regulation of biotechnology. She also is on the editorial advisory committee of the Food and Drug Law Institute. She holds a bachelor of arts

magna cum laude from Columbia College, a JD cum laude from Harvard Law School, and an MPH from Johns Hopkins University.

To Gail's right is Sheila Walcoff, who is the founding principal and health and science attorney of Goldbug Strategies, LLC. She offers business strategy, federal legislative and regulatory advocacy, and legal counsel related to personalized medicine and FDA-regulated medical products. Previously, she was a partner in the international law firm of McDermott Will & Emery. Her senior executive government service includes counselor for science and public health policy to the United States Department of Health and Human Service and, particularly, to the secretary, Michael O. Leavitt. She was the associate commissioner for external affairs at the Food and Drug Administration. As well, she was the health policy team leader and senior health policy advisor on a 2007 presidential campaign. She has worked on Capitol Hill as majority counsel to the U.S. House of Representatives Armed Services Committee and has held legal and policy positions at two trade associations. She graduated from Georgetown University's Law Center.

Our final speaker this morning is Jeff Gibbs, counsel at Hyman, Phelps & McNamara, a firm serving clients regulated primarily by the Food and Drug Administration. He has represented health care companies on FDA-related matters since 1984, advising them on a wide variety of issues, including product approvals, marketing clinical studies, and enforcement. Prior to working at Hyman, Phelps served in the Chief Counsel's Office of the U.S. Food and Drug Administration as an associate chief counsel for enforcement. He is currently on the editorial advisory board of IVD Technology and Good Clinical Practices and is a member of the Human Subjects Research Board for George Mason University. He serves as secretary and general counsel of the board of directors of the Food and Drug Law Institute. He graduated from Princeton University summa cum laude and the New York University School of Law with honors.

We are indeed privileged to have such a wonderful panel of experts with us this morning. Personalized, or patient-tailored, medicine uses new methods in molecular analysis to help manage a person's disease or a predisposition towards a disease. The goal here is to achieve optimal medical outcomes by helping physicians and their patients select patient-specific disease management approaches based on a person's genetic profile. Such approaches may include genetic screening programs that more precisely diagnose diseases and their subtypes or that help physicians select the type and dose of medication best tailored for a certain group of patients. Data on human genetic variation helps scientists to understand human origins, susceptibility to illness, and genetic causes of disease.

But one of the more controversial elements of advancing technology is the use of race and genetics to help create more specific types of medicines that will help combat diseases and conditions that appear to be more prevalent within certain races or ethnic groups than in others. There is concern that race- or gender-based treatments could be used to legitimate discrimination. Our speakers today will address the relevance of genetic information and will touch on the

issue of how race and genetics have affected the development of medicines, pharmacogenomics, and personalized medicine in the United States. They will address legal and ethical issues relating to research that relies on the use of genetic information and also will examine significant issues facing the future of personalized medicine that tailors patient clinical therapies based on the results of genetic testing. With that very brief introduction, I would like to call upon Julie DeLoia to present her remarks.

#### **Remarks from Julie DeLoia\*\*\***

Welcome everybody. Thank you for the invitation. It is always fun to talk about personalized medicine. By way of background, I am not a lawyer. I have been a lab rat for many years, and now I am a passionate educator and administrator. So when I was in school at Johns Hopkins working on my PhD, people started talking about this concept of sequencing the entire human genome. You have to understand, at the time, I was required to do sequencing and it would take months, literally, working seven days a week to generate about three hundred base pairs of sequence. People thought this concept of sequencing three billion nucleotides in humans was anathema. It was crazy. It was very much a stretch. A lot of my professors, a couple of them with Nobel prizes, were worried that this was going to trash all of funding for science as we know it. You might get the opportunity later in life to look back at your professors and say, "Hey, you were wrong about something." They were wrong. The Human Genome Project got kicked off in 1990. The technology to actually complete the project did not exist. The informatics systems did not exist to hold the data, to look at the data, to analyze the data, to retrieve the data. But lo and behold, although it had a fifteen year timeline, this project was completed ahead of schedule and under budget, like all federal projects generally are [*laughs*]. As a result of the Genome Project, not only do we know exactly how many genes we have in our genomes as humans, which was actually much smaller than what my professors told me, but we also got to the next step of being able to analyze very quickly and, now pretty cost-effectively, the differences between any two individuals at the genetic level. Again, we did this at a relatively small cost and a very short turnaround.

\*\*\* Julie DeLoia, PhD, Associate Dean for Academic Affairs; George Washington University, School of Public Health and Health Services. Dr. Julia DeLoia is the associate dean for academic affairs, George Washington University, School of Public Health and Health Services. Previously, Dr. DeLoia served as the interim dean of Georgetown University School of Nursing & Health Studies, where she also served as the associate dean of academic affairs and an associate professor in the Department of Human Sciences in the School of Nursing & Health Studies. A committed educator, she has taught undergraduate, graduate and continuing professional courses on human genetics and genomics. Before Georgetown, Dr. DeLoia was a tenured associate professor at the University of Pittsburgh School of Medicine in the Department of Obstetric and Gynecology. She was instrumental in founding the University of Pittsburgh's Ovarian Cancer Center and served as the center's director of research. She has published more than forty-five peer-reviewed articles, served as principal investigator on two R01 grants of the National Institutes of Health, and is a co-inventor on a patent for "Gene copy number profiling." Dr. DeLoia holds a PhD in human genetics from Johns Hopkins University and completed a post-doctoral fellowship at the University of Pennsylvania in developmental genetics.

Why do we care, except for folks like me who just sort of dig on this stuff? Well, we know that we vary biologically. If I had a bad cold and I were to sneeze on this group of folks, some of you would get a worse cold, some of you would get the same cold that I had, some of you would get sniffles, and some of you would just be irritated that I was rude. The underlying mechanism for that sort of biologic variation is genetic variation. If we look at the old (Mendelian) genetics—the classical stuff that I was taught—those diseases had a lot of impact on the families that actually had that burden in the family. But from a public health perspective, it wasn't a great impact. Strokes, heart disease, cancer, and adverse drug reactions are the diseases and health concerns that we really want to be able to approach to figure out who is at risk for what.

So if we lived in Lake Wobegon, where all the health care providers were perfectly knowledgeable and all the patients were completely compliant, we still wouldn't have perfect health. There are reasons for that. One is that we don't know who is at risk for what disease. So we do sort of a population approach. I turned forty; I got a prescription to go get a mammogram. I turned fifty; I got a prescription to get a colonoscopy. Did I need those? Probably not. Did I do them? Probably not [*laughs*].

One of the barriers to better health is that we don't know who is at risk for what. A second barrier is we don't have great tools to diagnose diseases early. The earlier you can find a disease or a disorder, the better you are at preventing the consequent progression and morbidity or death. We are not the best at diagnosis. If you know any pathologists, I apologize. But a lot of current technology is used in the following diagnosis process: we get a chunk of tissue, slice it up, stain it with a two-cent dye, and pass it on to some folks who work in labs that smell really funny, who look at it and give you an idea of what that is. We know for sure that when you treat those patients, they don't all respond the same way. Undoubtedly, there are different diseases that look alike under a microscope.

We talked a little bit, and we will talk a little bit more, about pharmacogenomics, which is sort of the poster child of personalized medicine. A layperson may say, "Golly, what is my prescription for, if it is not the right drug and the right dose for me? I kind of thought you knew what you were doing."

The last part of this is prognosis. We still have a hard time predicting the outcome of any individual disease. So now we go back to the Human Genome Project and what it has done for us. Well, it has allowed us to look at genetic variation between groups and people. So we can use genetic variation now to look at who is at risk for what disease. Something that bothers every woman once she reaches a certain age is that niggling fear, "Will I get breast cancer?" One in ten women ultimately will get breast cancer. The reality is most of those women are postmenopausal. But once you get to a certain age, you start thinking about that. How do we determine risk? Well, it used to be by looking at family history, which is still a great tool for geneticists. You can't beat family history.

But now there is a test called *OncoVue*<sup>®</sup> that combines a person's own history and adds in some genetic markers to come up with a

personal risk for breast cancer. Again, do I still need a mammogram at age forty? Well, maybe I can get this test and say, "No, you can wait until forty-five or so." But one of the problems that you have with a predictive test, is that it is based on archived samples. So researchers have thousands of samples, with the patient's history and the women's breast cancer history. They know who got cancer and who didn't. It is all looking backwards. The next step is difficult. It requires taking this information and using it to manage patients who don't yet have cancer and trying to guess who needs to be screened and who does not. That is where the trickiness comes in because care providers are nervous to change how they manage patients based on a test that is not yet validated. Insurance companies aren't going to want to pay for it. For example, imagine someone who is forty-three and there is not a strong family history of disease, but the genetic markers put that woman at a higher risk. Is the insurance company going to pay for more aggressive screening for you? Are they going to pay for an MRI? Are they going to pay for prophylactic Tamoxifen? They are not willing to do that without the data that says this is worth changing patient management.

With many of these new genetic tests, you eventually get to at that point. As of today, there are dozens of diseases and disorders that are undergoing genetic analysis. They are the common diseases that all of us will interact with either personally or through our families. So that is coming down the pike. We are not ready to take the next step, I don't think, to say, "We are going to put this into clinical practice."

Early detection of disease is another thing that really could improve health significantly. I have been working in the cancer field with ovarian cancer, a disease where the mortality is very high because there is no good screening test. There is no good diagnostic test other than surgery. And generally, women come in because they have symptoms—either GI symptoms or reproductive symptoms. This is a common scenario with many cancers. You don't know it is there until it has progressed far enough to cause physical symptoms and, consequently, is difficult to treat. The cancer is very far along, and their life expectancy is quite short.

There is a test out from Exact Sciences to find one of those cancers that often remain silent until it is far along: colon cancer. Out of disclosure, I have stock in that company because I think they have a cool idea. Basically, the concept of the test is simple. Your feces coming through the canal pulls cells and DNA with it as it travels through. The DNA is indicative of what is in the colon and the rectum. So, by collecting feces that contains DNA, you can use this test and have a way to look at genetic changes happening in the colon. It is a test that looks pretty good. It will detect about 85 percent of cancers and about 65 percent of precancerous lesions. Now that is not as good as getting a colonoscopy, but the reality is, the vast majority of people at age fifty who get that prescription never use it. If everybody who should get a colonoscopy did get one, I think there would be something like a ten-year backlog. So, is this genetic test as good as colonoscopy? No. But is it better than nothing? You bet. And it is something that people may be more apt to use. In 2008, the American Cancer Society advised that people

use stool DNA to do colon cancer screening. The test is not yet FDA-approved. They are hoping in 2012 it will be approved and launched in 2013. That is a five-year lag time, which is significant.

Obviously, more accurate diagnosis is a big thing. We know that for many cancers, the response rate is highly variable; some will respond to therapy and some won't. Yet, the cancers look alike on the slides. If we could analyze the gene expression profiles, which again, are part of personalized medicine, and be able to separate what looks like the same cancer into different groups, you can now either treat people more specifically or say something much more difficult: "I don't have anything to offer you." That is something that most health care professionals really have a tough time saying. So most health care professionals generally try with first line therapy, second line therapy, third line therapy, and then palliative care. The reality is we probably put many patients through expensive therapy, with many co-morbidities, unnecessarily. Perhaps these patients would be better served by treatment with palliative care earlier because we simply have nothing that is going to help them. Hopefully, not only will we be able to spare some people from useless treatments, but by having the genetic profile from their diseased tissues, we can start designing therapies that are specific for the genetic alterations that are happening more specifically in that disorder.

Pharmacogenomics is a big, big area. Some drugs are great. With a beta-blocker, odds are it is going to work pretty well for you. There is probably no need to do high-end genetic analysis of the disease. But in my field, cancer, we are pretty bad at predicting who is going to respond to what drugs. If you can now start looking at those tumors specifically, you can use more tailored therapy. And I would say living in DC, we are lucky. We are in an academic medical center corridor. We have the NIH. People who get sick here will get the best care in the country. Most academic centers now do some sort of genetic profiling for most cancers. Those people who live in areas removed from academic medical centers will not always have that level of access. That is an inequity that is built into the system that is going to be there for a while.

Another use of genetic information is in determining drug dosage. One great example is in determining the dose for a drug called Coumadin, which is a blood thinner. About a million people go onto Coumadin every year. Coumadin is tricky because it has a very small therapeutic window. Too much Coumadin, you could bleed out. Too little Coumadin, you could clot up. A lot of folks end up in the ER after they go onto Coumadin because the dose was not quite right. Many people who are on Coumadin are elderly and so returning to the health facility to get their blood clotting time checked every week is difficult. It is a stress. Lo and behold, there is great data out there to say if I weigh you, get your BMI, and do simple genetic testing on just two single genes, I can account for about half of all the variation in response to this blood thinner. With this information in hand, a person's specific dose can be narrowed and negative outcomes reduced. This day is coming; people are excited. It seems so rational to have this be the first test approved to determine drug dosage. But unfortunately, more studies have been requested from the Center for Medicare & Medicaid Services

(CMS) before reimbursement for the FDA-approved genetic test for Coumadin dosing is approved. The question now becomes, Is the bar for using genomic information higher than what it is for actually prescribing drugs?

The last topic I want to touch is prognosis. It would be very useful to identify which patients have a higher likelihood of recurrence for a disease. The first, and only FDA-approved kit for predicting recurrence for breast cancer, MammaPrint, is now commonly used. About 250,000 women a year will be diagnosed with stage 1 breast cancer. A vast majority of them are not at high risk for disease recurrence. Without this information about who is going to have a recurrence, you are going to treat everybody aggressively because you want to be safe. So if you can now identify those women who are going to have a higher chance of recurrence, you can treat them aggressively. Alternatively, you no longer have to treat those women at a low risk for recurrence. This could save money for the health system. And it could save co-morbidities for the women.

That was a quick overview from the science side, which is obviously very exciting for me having been in genetics for a few decades now. Our ultimate goal is to improve the health of the population. Tremendous questions remain. Who is going to pay for these tests? Who gets the data? Who gets to use the data? Does the entire population have access to these tools? What is the psychological impact? What is the counseling that goes along with genetic testing? My hunch is that I will spend a good deal of my remaining time educating both providers and patients on what this information means and how you can use it. Thank you for your time.

#### **Remarks from Gail Javitt\*\*\*\***

Good morning, everybody, and thank you. Dr. DeLoia was actually a great background and segue to my topic for this panel, direct-to-consumer (DTC) genetic testing. When we think about personalized medicine, there is the personalized nature of genetics that is individual to us, but there is also a personalized aspect to access. You brought up very well that issue of access. The traditional model of getting genetic testing, or any testing, is through your doctor. But why is that? A new model has come up in about the

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Gail Javitt is counsel in Sidley Austin's Food and Drug regulatory practice. She joined Sidley Austin after seven years at the Genetics and Public Policy Center in Washington, DC as the law and policy director. In this position, Ms. Javitt was responsible for developing policy options to guide the development and use of reproductive technologies and also led an initiative to improve oversight of genetic testing quality. Ms. Javitt is also a research scholar in the Berman Institute of Bioethics at Johns Hopkins University and has served an adjunct professor at the Georgetown University Law Center, University of Maryland School of Law, and Washington College of Law. Ms. Javitt was a Greenwall Fellow in Bioethics and Health Policy at Johns Hopkins and Georgetown. In addition to her work accomplishments, Ms. Javitt has written on a variety of science regulatory and legal topics including direct-to-consumer marketing of genetic testing and FDA regulation of biotechnology. She is a member of the advisory board of the Victor Center for Jewish Genetic Diseases and previously served as editorial advisory committee member of the Food and Drug Law Institute. Ms. Javitt holds a BA magna cum laude, Phi Beta Kappa, from Columbia College, a JD cum laude from Harvard Law School, and a MPH from Johns Hopkins University.

last ten years, trying to offer genetic testing directly to consumers, bypassing the health care provider. This model has caused a lot of consternation; adulation; and all sorts of other adjectives, both positive and negative. I want to give you a bit of a history about this debate because, while DTC genetic testing is just a way of getting a genetic test to consumers, it is also a good lens to look at some of the larger issues around genetic testing, including issues of law, ethics, and policy.

So you know it is big when Google gets involved, right? Because ain't nothin' more personal than Google. So a couple of years ago, Google announced that it was taking a small stake in a genetic testing company, 23andMe, which promised to help consumers understand and browse their own genetic information. And there probably even could be an app for that—whatever that means. At the time, there was already a growing interest and concern about genetic testing, but certainly having Google involved and focused on how we get your genome raised the profile. Indeed, in 2008, *Time* voted the retail DNA test, meaning over-the-counter, as one of the best inventions of 2008.

How did we get here? Well, certainly as a result of the Human Genome Project and all the data that it allowed access to, there has been a sharp rise over the last ten to twenty years in the availability of genetic testing. There are more than two thousand diseases for which you can get a genetic test. Now the tests may tell you different things. They may be very definitive: “You will get this.” Or they may be less definitive: “You may be at increased risk for this.” But certainly what we can mine out of our genome—although a small fraction of what is in our genome—is steadily growing. And genetic tests run a wide spectrum. If you are thinking about having a child or perhaps you are already pregnant, you can find out what genes you might be carrying and, therefore, find out what your future child might be at risk for. If you do it when you are already pregnant, it is called prenatal testing. You can even test embryos as part of in vitro fertilization to try to select embryos that are free from certain genetic defects.

In Texas, there has been a big controversy regarding what to do with bloodspots left over from newborn screening. Every newborn in the United States gets between five and forty tests when they are born to detect genetic diseases. The genetic disorders of interest are those where early intervention could both increase survival and prevent bad health outcomes. There are several types of genetic tests: 1) diagnostic testing, which uses DNA to diagnose or identify what kind of disease you currently have—newborn screening is limited to these diseases in this category; 2) predictive testing, which as discussed by Dr. DeLoia, tests for your risk of diseases such as cancer; and 3) pharmacogenetic testing, which tests for what drug will work or will not work for a person and in what dose. And then outside the health care environment, there is paternity testing, ancestry testing, and forensic testing, as we all know about from CSI.

What is DTC genetic testing? What is the gloss? Well, it is three components. First, there is the “testing.” We talked about all the things you can get tested for. Second, it is “genetic,” meaning it

uses some sort of DNA or DNA derivative. Third, it is “direct-to-consumer,” meaning you don't need to go to your doctor to get it. So what is a genetic? There is no single definition, but basically you are looking at DNA/RNA, chromosomes, or proteins that are coded for by your DNA either to detect things that you might have inherited or problems you might have acquired: for example, through environment exposure (e.g., chemicals, radiation) that mutates (causes changes in) your DNA.

Under the traditional model of genetic testing, you go to your doctor, who does a thorough screen and might order a genetic test. You might get referred to a genetic counselor or geneticist, who decides what test you get and what information you receive. And the results go back to your doctor. So there is somebody standing between you and your genome.

How did we get to this DTC environment? We have now a much better understanding of the role of genes in disease, the ability to sequence the genome or perform genetic testing. The cost of performing the tests has come way down, and there has been little regulation. All of these factors have enabled companies to offer genetic testing directly to consumers.

In some cases, there has just been direct advertising of the availability of tests. But most frequently when we talk about DTC, we mean direct access. How does it work? A customer will go to a website and order a test. You will get a sample collection kit, usually something you spit in or rub on your cheek, like kind of a toothbrush, or a dry bloodspot. You send that to a company, which will conduct certain analyses on it and send you a report. What tests can be offered? All sorts of tests. The rate limiting step in terms of offering a test DTC is that you have to be able to test saliva or blood. So, for example, you couldn't have a DTC amniocentesis (which is an invasive procedure), which is a good thing, I'm sure. But there has been a huge growth of companies that offer DTC testing on everything from what kind of earwax do you have to serious diseases or serious disease risks. In addition to discrete tests, there are a couple of companies that offer to look broadly across your genome for risks based on certain variations.

Why have some people touted this test as the greatest thing since sliced bread? Well, it is about access. It is about deciding what test you want, and what concerns you may have about going through a health care provider intermediary. And the results can motivate you to make lifestyle changes. So, for example, Francis Collins, the Director of NIH, tried this test and apparently said that after he received his results, he got off his motorcycle and started exercising. And others have claimed that the test motivated them to take that next step to make improvements to their health.

Why are we worried? Well, because of the limited oversight thus far. Some people also have raised concerns about whether these tests are accurate. Other questions are also troubling: Are consumers getting what they think they are getting? How do we know the companies offering the services know what they are doing? How do we know that consumers understand the information and are appropriately using it? And who else will get access to the information?

The Government Accountability Office (GAO) has been looking into these questions since 2006. A much more recent hearing raised concerns about the claims that are being made and the accuracy of the results, and a number of government entities have recommended improvements in oversight. GAO raised concerns about the results being misleading, medically unproven, ambiguous, and thus, providing no medical information.

A number of publications in the scientific literature state that many of the tests currently offered DTC may have potential, but are not ready for primetime. The evidence for many of the gene-disease associations and many of the claims that are being made are just not there yet, according to these articles. At the same time, some of the tests that the health care providers think aren't ready for primetime are already being offered. So there is a concern about the science lagging behind the access or the access preceding the science. And studies comparing some of the different companies have discovered that the results from different companies don't agree with each other, depending on how the companies report the results and on unknown factors—because a lot of the laboratory methods used to perform the testing are proprietary. One article recommended that there needs to be more data, given that there was 50 percent or less agreement in the predictions between two different companies. Additionally, although there are many assertions about what the public may do and what mistakes may be made, we don't know a lot about how those people who are accessing these tests are using the information, what they understand, whether they are satisfied, and whether any harms have occurred because of the testing. There is a need for more empirical data to answer those questions. Overall, the message from the scientific community has been that the test is not quite ready for primetime.

Another level of concern is that not only might you access your DNA, but others may seek to access it as well. Very little law is in the way preventing your professors or others from testing your DNA without your permission. So isn't there a law to prevent all of this? It is a law school; it is a good question to ask. When you break that down, what would you want to regulate? What entities would you want to provide the regulation, and for what purpose? Do you want to stop it entirely because this is a terrible idea or regulate it to make sure there is truth in labeling? There are a whole variety of policy objectives you might want to reach. There are a number of players who could potentially help us reach them, but it has been very much a regulatory work in progress. FDA has very kindly issued a notice last week that they are having a meeting next month to talk about how FDA should regulate DTC genetic tests. They have said, "We want to regulate them; we are concerned about them; we think they are under our jurisdiction"—which is a whole topic in and of itself—"but we are really not sure how to think about the risks here." Is the risk of something that tells you how to lose weight better or the same as the risk of something that tells you, you might get cancer or you need to change your medication? They have asked for expert help in thinking through those issues because while the abstract "We should regulate it" has some merit, when you get down to the nitty-gritty, it gets much more complicated, as I am sure you have learned in all your law school classes.

And what can the states do? The states are a bit of a patchwork—got to love Federalism. Where some states say, "Look, if you want to order any kind of lab test, except something really simple like a pregnancy test, you've got to go through your doctor." Period. End of story. Some states say, "Yes, consumers can order tests on their own." And some states just haven't addressed it. In the era of the Internet, what does it really mean to have states regulating this? It may mean less than one would like.

As I said, some government entities have recommended increasing oversight not only of DTC, but of genetic testing more broadly. Many of the concerns I have raised aren't really about the DTC-ness, they are about underlying quality issues in genetic testing. As I mentioned, DTC is just a way of getting a genetic test. Whether it is DTC or through a provider, you want to have certain quality measures met. As I mentioned, there are a number of policy approaches one could take with pros and cons. So let me leave you with this: they could range from "buyer beware"; to "you get what you pay for or don't pay for"; to "take it with a grain of salt"; to "let's stop this—this is just not something we think that should be going directly. Just like prescription drugs can be gotten only through a doctor because we think that consumers need to go through a doctor to use them safely, DTC is just not a good model for genetic testing." All those options really are still on the table. As I said, FDA was kind enough to announce a meeting. They have said they want to regulate. They haven't said really how they intend to. It is part of FDA's broader initiative to regulate laboratory testing. FDA has said that it expects companies offering DTC genetic tests to comply with FDA's rules, but the Agency has not actually said what those rules are. So we are in a bit of a murky situation, I guess, is the best way to say it.

So we are still left with this question, and I am curious to hear what you all think: Is direct-to-consumer genetic testing the best thing since sliced bread or very scary?

Thank you very much.

#### **Remarks from Sheila Walcott\*\*\*\*\***

It is kind of hard to follow Gail. I would also have to say the murky situation that we all tend to work in right now results in a great employment opportunity for lawyers. The murkier it is, the more

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opportunities we have to tell the FDA what we think they should or should not do and to get people to agree with us or not agree with us.

I thought I would start out by turning it back a little bit, not on direct-to-consumer testing, but on those diagnostic tests that are physician-ordered, those that you would have to go through your physician to get. I thought I would start by just asking how many of you know somebody or are related to somebody that has had breast cancer? It is usually a lot. And of those folks, how many know somebody who has gone through chemotherapy? As you probably are aware from those relationships, it is a pretty tough thing to go through. Something that really surprised me when I started working in this area is for some early-stage breast cancers, only four in one hundred women actually benefit from chemotherapy. But right now, it is the standard of care. Genomics is really changing that whole paradigm. Imagine that you, or your mother, or your sister, or your aunt has early-stage breast cancer. She can go to her doctor, and her doctor could order a test that can take a look at the genetics of her actual tumor and then let her know and advise her, as part of her decisions on treatment and how she is going to go forward, what her risk of recurrence would be. Meaning, how likely is it that that breast cancer is going to come back? Previously, this was determined primarily on family history, age, and the size of the tumor. But if you could actually look at the genomics of the tumor to determine recurrence, then you could make a better-informed decision on whether to have chemotherapy. In fact, genomics might even identify women who would benefit the most from chemotherapy and make sure that they get it. Perhaps they wouldn't have gotten it because their tumor was very small or they are elderly. If we could reserve the use of chemotherapy only for those at high risk for recurrence, we could then enable those who are not at greatest risk for recurrence to avoid the really toxic side effects of chemotherapy.

There are several such genomic tests. One of them has already been mentioned this morning. There is sort of a burgeoning industry in innovative diagnostics. Some tests use more complicated algorithms that involve a lot more research and development, which are more like producing a drug than a standard cholesterol test or other more straightforward type of test that you would get in a lab. The rise in the availability of such tests has developed a great area for lawyers to determine how these tests are going to be regulated. It is not just the direct-to-consumer tests that FDA is struggling with, as Gail mentioned, it is all of these tests that are either developed and performed within a lab, which are called laboratory developed tests. These tests are not shipped anywhere in interstate commerce, which, I'm sure, is something you have learned about because I spent all kinds of time on interstate commerce when I was in law school. And there are kits that are produced for testing that are sold in interstate commerce that are sent to these labs. Part of the challenge right now for FDA is trying to determine where it uses its regulatory authority, what is its regulatory authority, and how it uses its resources to ensure that physicians and patients obtaining these tests are using this information in a way that they can be confident in. At that point also, there is concern over whether an insurance company would actually pay for the test, which is the whole reimbursement issue. The key hurdles in my view for personalized medicine is how

physician-ordered diagnostic tests will be regulated, how they will be reimbursed, and how payers will pay for them so that they will be available to you, your mother, your sister, and others who may develop these types of very serious and life-threatening diseases.

What are the options for the FDA? What are the options for industry in figuring out what regulations it needs to follow to actually get their tests on the market? Folks invest a lot of money in these tests and, of course, they want a return on their investment. Right now, it is really a patchwork quilt. Laboratory-developed tests are regulated by one agency under the Clinical Laboratory Improvement Amendments under the Center for Medicare & Medicaid Services and those tests that are kits sold in interstate commerce are regulated by FDA under the Food, Drug and Cosmetic Act (FDCA). Of course, FDA believes it has authority to regulate all of these tests, an assumption that could be a subject for a legal challenge. It hasn't been challenged at this point. That issue has been largely parked by a lot of stakeholders to try to figure this out. What are the policy options going forward that are reasonable, efficient, and do not completely stall all of the innovation in this area (either because FDA is overwhelmed by its work, or the rules are so unclear, or the bar is so high that companies won't invest in making these more innovative tests)?

You can develop policy through a regulatory pathway, which means looking at the current existing law and regulation to figure out how you might fit the regulation of innovative diagnostic tests into that law. Right now, FDA regulates diagnostic tests as medical devices. A large group of stakeholders—a lot of them that I work with—believe that diagnostic tests which produce information that is used in treatment management are very different from your understanding of a medical device like a knee implant or something that actually touches or impacts your body. How does FDA figure that out? Should there be the same level of evidence required to demonstrate that a medical device is safe and effective for its intended use as there should be for diagnostic information that a physician uses along with his or her training to determine what your treatment might be? Is it different if that diagnostic test says, "You have gene marker X, and you absolutely will not benefit from this particular drug"—that's pharmacogenomics—or, "You have gene marker Y, and that means you absolutely would get a great benefit so you should definitely use that." Some of the questions that the FDA is constantly asking in these debates are, what if the test is wrong? What if you have a false positive or a false negative? And, how often can that be the case and you still view those tests as reliable?

While the FDA and a lot of great people are struggling with those questions, there is another option, not just a regulatory approach you could take. We are here in Washington. You could take a legislative approach. You can march up to Capitol Hill, bringing all of your stakeholders and explain to Congress why we should have a new law that regulates diagnostic tests differently than medical devices. This law perhaps sets up a new framework based on the risk of information rather than the risk of a thing itself that might touch your body. But if you take the legislative approach, you have to create new definitions. What is a diagnostic test? What does this include? What doesn't it include? What are the factors for

determining risk? Is it that it is a one-to-one relationship—if you have this marker you get this drug? That is the most risky versus a test that provides information about whether you might be at a higher risk for recurrence of breast cancer, or you may not. It is more of an adjunctive use that the doctor would use along with other information. What if people think it is really no risk at all? We have been doing this test for ten years, and we really understand how it works and what the results mean. Maybe FDA shouldn't step into that because whenever a regulatory agency steps in, that usually means increased cost and increased time to market, which factor into how fast personalized medicine will develop.

What are the answers? I think there really aren't any right now. It has really proven to be one of the most fascinating areas in which I have ever practiced. It is why I actually left my law firm and formed this company called Goldbug. I am sure you have all been wondering what is Goldbug while you have been sitting there. Why would I leave a great three-name law firm to do that? It really is because of my love for personalized medicine. It doesn't refer to a virus. I had somebody ask me that once, "Is Goldbug like a unique virus?" It is really based on a children's book where you find the gold bug. You all are probably either too old or too young to know this book, if you don't have little kids. But there is a book by Richard Scarry called, "Cars and Trucks and Things That Go," which has crammed onto page illustrations of all these different vehicles, like the toothpaste car and the mustard car. And there is a storyline through it. On every page, there is a gold bug. I was actually reading the book to my son one night. I looked at a page depicting a massive crazy car crash and thought, "That is just like Washington. That is our policymaking process, our legislative-making process." There are all of these crazy ideas and things going in different directions, but at some point it makes sense, and at some point there is an answer. That is really how I feel about personalized medicine. I hope you all continue on with this and help me. We'll all need associates—sooner rather than later, probably—as we are going forward.

#### Remarks from Jeff Gibbs\*\*\*\*\*

My focus is on FDA regulation, which is a little bit different from, but complementary to, the other three perspectives. What I want to do, in the somewhat limited time that we have, is just quickly talk about ten different points. It is kind of a "Dave Letterman Top

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Ten List," although not necessarily in ranked order. But here are ten points that I think are worth considering.

First, it is clear that diagnostics are fundamental to the advancement in medicine, such as towards what we heard about with breast cancer medicine. It is perhaps a 4 percent response rate. I just read a book that talked about leeches. Two hundred years ago leeches were the thing. They had been the thing for centuries, and sometimes leeches worked. In fact, FDA has cleared leeches for marketing for medical purposes. They have cleared leeches for use, proving that they really do work in certain conditions. However, most of the time they don't work. The problem with leeches was that they were applied in inappropriate conditions, so most people did not get better. It is not that different now from chemotherapy. So, as we sit here looking back smugly at the doctors and physicians who used leeches two hundred years ago, people fifty years from now are going to be looking at us and saying, "We can't believe that doctors in 2011 subjected patients to the rigor of chemotherapy with all the pain and discomfort and risk when it was completely inappropriate for 95 percent of patients." Thus, personalized medicine is going to be essential.

Second, there are many factors that influence the availability of personalized medicine. We have heard of some of them: technology, reimbursement, science, and patents. But there are huge intellectual property issues. Those of you who are on the patent side, it is a burgeoning field. There is a case going up now about accountability of genes. But there are also regulatory concerns. Gail and Sheila talked quite eloquently about some of the regulatory challenges, particularly on the FDA side. The regulatory issue has to be addressed. It is a major stumbling block right now. What will the regulatory regime look like? We need greater clarity. People need better predictability.

Third, the basic FDA regulatory framework does not work terribly well for diagnostics, particularly the new diagnostics. And there are a lot of reasons for that. But the basic problem is that the law was written in 1976, and it was constructed for different kinds of products and at a different time to address different issues. One of the major pathways to getting products on the market through FDA is called the 510(k), referring to section 510(k) of the [Federal Food, Drug, and Cosmetic] Act. In order to get a 510(k) you need to show substantial equivalence to what is called a predicate device. The new products that are coming out in personalized medicine and diagnostics don't have predicates. That is what makes them valuable. They are different. Yet if you are tied to predicates, you have a bump in the system. The other approach or the other route to market is called a premarket approval application, which is very costly and very time-consuming. There are a lot of reasons why those would be barriers to innovation, and yet the statute does not really handle the situation well.

Another category is called *de novo* reclassification, which allows companies to reclassify products if there is no predicate device. It is on the books. It has been used about four times a year since it was adopted—about two diagnostic devices a year. So it exists, but it is

not really viable. That is just one of the reasons why a legislative fix is needed to address what is really a fundamental structural flaw in the law.

Fourth, in addition to the law itself, there are problems with FDA's regulations. FDA developed regulations without thinking about diagnostics. For example, if you get your product cleared by a 510(k) and you make a change, you have to submit a new 510(k) if that change could significantly affect the product. With these new diagnostics, they are always making changes. There are always new markers and better algorithms that are being developed. You think about what you want with these diagnostics, and what you want is something that keeps up with knowledge, evolves with the state of the art and is flexible. You don't want something that is cast in stone and has to stay the way it is based on the knowledge at the time when it was cleared or approved by FDA. But that is the way it works under the current system. Unless there is a way to handle new knowledge, new markers, and new algorithms, and better ways to use the diagnostics, we are going to get products that are cleared that are going to be obsolete almost instantly. That is another major flaw with the regulatory structure right now.

Fifth, companies need to do a better job. There are problems with the law, FDA's regulations, and with the way companies handle their diagnostics. And by companies, here, I am talking specifically about diagnostic companies. If a company has got a novel product and it can go in to meet with FDA and ask, "What should we do? How do you like our protocol? How do you like our claims?" And companies have these meetings, and then they get FDA's feedback, and then they ignore it. Or they will get the study design drafted, get it reviewed by FDA, and not follow FDA's advice. Or they will submit an application to FDA which is poorly crafted, and FDA has a hard time making sense of it. Some of the burden lies on industry. And industry is going to have to do a better job in presenting data and doing good science. When you are talking about cutting-edge products that are going to be the basis for making decisions on whether you have surgery or administer chemotherapy, companies have to do a much more rigorous job. We are not talking about cholesterol tests anymore, and the standards that applied for cholesterol and other basic blood chemistry don't work.

Sixth, drug companies have to do a better job understanding diagnostics. Some of the most important applications that we have relate to drugs. If the drug companies don't know how to use diagnostics, then they are going to find that their way to FDA approval is going to be hampered. There is a new report about how the percentage of drugs getting through the process and succeeding has dropped even more, and part of the problem is that they are not taking advantage of the diagnostic tools that would improve the success of drug companies.

Seventh, one of the things that is abundantly clear to me having worked both with diagnostic companies and drug companies is that drug companies don't understand diagnostics at all. It is just astonishing how they will be far along in their process and then start thinking, maybe we ought to have a diagnostic. They have already

spent \$100 million dollars, and then they start thinking about, maybe we should find some way to identify the patients who are going to respond. Some of these cancer drugs have a ten percent response rate. It is not random. There are factors that lead to people responding. Why aren't the companies doing a better job analyzing and trying to figure out who are those 10 percent and developing a companion diagnostic to go along with it? That is an area that needs a lot of improvement.

Part of the problem there on number seven, it is not just the drug company's fault. FDA has been working on a guideline for companion diagnostics for years. It is still not out.<sup>1</sup> Everybody is in the dark. We have heard the word "murky" here. This is murky. It is another murky situation, and it would be much easier for diagnostic companies and drug companies if there were clear guidelines on how to handle these companion diagnostics.

Eighth, FDA needs to take a different way at how it looks at risk for diagnostics. These are not the implants; they are not cardiovascular products; they are not defibrillators. Risk needs to be assessed differently. It is a separate topic. You could have a whole seminar—a two-day seminar—on risk in diagnostics and how do you calculate it, how do you assess it. But a fundamental problem with the whole process right now is how FDA evaluates risk with diagnostics, and is the level being set too high, and what does that do for accessibility and availability?

Ninth, I think it is useful to have a presumption in favor of more information rather than less. That notion permeates the U.S. system from the First Amendment onward, and yet FDA in general takes a much more restrictive view. And if you think about diagnostic tests, perhaps they don't tell you the answer, but they may be additive. The appropriate question, I think, is not to ask, "Do they answer all questions?" But the question should be, "Compared to the standard of care right now, do they provide useful information that will help make better decision-making?" If doctors are going to have a better idea of whether this is a patient who responds to leeches or chemotherapy, then it is a useful tool. It may not tell everybody who is going to respond and not respond, but if you can double the success rate, that is certainly an improvement. So the role of information and incremental benefits in information, I think, needs to be assessed better.

And then tenth, FDA has to use its resources more efficiently. We have heard about FDA looking at lab-developed tests. We could debate whether FDA has the legal authority, but I don't think there is much debate that FDA has put a lot of time, effort, and money into it. Given the president's budget and given what Congress is doing with the budget, the idea that FDA should expand its jurisdiction to take on huge new endeavors is something that is highly debatable. But even aside from that, FDA needs to be efficient with its existing resources. FDA, when it has these meetings with companies and develops guidelines, has to be prepared, has to give good guidance, has to come out with guidelines to provide meaningful information that will help guide the regulatory process. There are a lot of things that could be done right now so that FDA gets more with existing

resources. I think the FDA has to think long and hard about taking on any more responsibilities given the contraction or limits in funding that will be available.

I could easily have expanded this to twenty or fifty or one hundred points, but these are ten points that help, from my perspective, frame some of the key issues involving FDA regulation of diagnostic devices.

## QUESTIONS AND ANSWERS

**QUESTION:** For the panel overall, in terms of “it is a murky situation,” how do we actually push this regulation forward? Is this where you see, for instance, public-private partnerships coming in, FDA’s critical path, those sorts of situations? Is that where you see maybe the best chance for regulation, or do we actually think that there is a legislative fix that could be coming soon? Where do you see this actually going in the next few years?

**SHEILA WALCOFF:** As Jeff and others have mentioned, there has been a lot of work at the FDA. This has been going on for a long time. In fact, I was actually at FDA and at HHS when this started four or five years ago in earnest with respect to these more innovative diagnostic tests and how they might expand to laboratory-developed tests. As I said, there are two pathways, regulatory and legislative. I think there is emerging a more realistic and viable legislative fix. It is a complicated effort to go for a legislative fix. I was skeptical at first, years ago, because I thought, “Well, we can continue to work with the agency.” And they certainly are open—and I think even more open now than they have been in previous years—to getting stakeholder input because it is difficult. It is hard. They are stuck with a law, a statute and regulations, that, as others have said, doesn’t really fit for what these new innovated products are. And they are trying to make it fit, and it is ill-suited, and we are trying to figure out how do we establish appropriate standards for regulation so that companies know what they need to do and that the agency knows how it needs to respond.

Because there is this kind of stalemate and continued murkiness and inability to get an answer really out that is going to work for the industry and work for the agency, there has been a pretty significant effort to get legislation—one member and a couple members, in particular, with Senator Hatch from Utah emerging as a leader in personalized medicine. He has been very interested in this area for a number of years, and he is working on a draft bill that is fairly substantial. It is very technical. It creates a separate medical product that is regulated by FDA called in vitro diagnostic product. It intends to be technology neutral and business model neutral, meaning it wouldn’t matter if it was a kit in interstate commerce versus a laboratory-developed test, trying to bring that regulation together in a more unified fashion. Some people like to say, “Level the playing field,” but it is definitely more complicated than that. It is great, and there has been a lot of work from a lot of stakeholders that have gone into this proposed legislation. But it is one member, and it is a bi-partisan issue certainly, bicameral issue, and there is a lot of work going into that right now, but there is still a big road.

As I like to describe it to my clients, it is really a marathon. It is not a sprint. Otherwise, you sprint and you become exhausted. Actually, you become manic-depressive over it because one day you think everybody is in the same lane, and all the stakeholders are going in the same direction. But the next day you find out that this major group has just peeled off, and now they are talking to some other member and doing something completely different. So getting all that to work together, I think there is a great opportunity in the next two years. With the FDA, there is a structure in place for approval of medical products that utilizes user fees and that has to be re-authorized every so many years. I think it is every four years. And that is coming up in 2012. So what we say is that provides a viable legislative vehicle, a way to actually get this through. There are a lot of steps in that process. I think we are closer than we have been in the past because we are really starting to understand what does personalized medicine mean, what do we really need in this industry? Legislation previously has called for an IOM study. Well that is very good; it is something you can get through; it sounds great. The IOM is very distinguished, but then what do you do? Then you are still stuck with this statute that doesn’t really work. So I guess the short answer is, “Yes there is a lot of work going on in the legislative side.” It is very exciting for a lot of people, but it is also very frustrating. I think it is not something that is going to be resolved quickly.

**GAIL JAVITT:** And, actually, just an historical note to add on; Professor Grossman will correct me if I am wrong. If you look at almost every legislative change, including the creation of the FDC Act itself, was driven by crisis, disaster, and death. So—Thalidomide, strengthening of the act, the Dalkon Shield, food safety. You don’t have that here, which is a good thing. So you need people to coalesce around other big ticket things, like improvement of health and impeding of business development, but it is harder to get legislation through when you don’t have that. I think the history of the FD&C Act bears that out.

**JEFF GIBBS:** That is absolutely true. Historically, it has been largely driven by significant problems. But this could rise to a level soon, not of a health care crisis like Thalidomide or Dalkon Shield, but of a major issue. I don’t know about the legislative prospects. I defer to Sheila on that, but I do know that we really can’t wait for legislation to be adopted for companies that are dealing with FDA right now. There is an ongoing problem. I work with a lot of companies that are struggling right now. If legislation is enacted, say in 2012 when the user fees come up, there are going to be a lot of issues in the meantime. But also once it is done, every piece of legislation runs into implementation questions, rule-making, enforcement, guidance. And so legislation might be a great start. It could address some of the major issues that we have, some of the flaws that are structural, but it is not going to be the whole solution. I think that to your question, there really does need to be involvement with stakeholders of all sorts—probably a fundamental rethinking of how to handle this.

To use the tired phrase of “paradigm shift,” the way that FDA and companies are working right now is just not terribly efficient. Some

fixes can be done by just rethinking, What is the role of diagnostics? What do we expect from them? How do we want to view them? What should the criteria be? And some of that could be done right now without legislation, but there are very different perspectives on it as well, and that is going to require input from a lot of different people to think what should we do with diagnostics. What standards do we want to apply? Those are very important kinds of questions that need to be addressed very rapidly.

**CORRINE PARVER:** Perhaps cost, though, can push the envelope a little bit. I was astonished to learn the statistic that you quoted that only 4 percent of patients actually improve with chemotherapy when it is the standard of care for all patients who have breast cancer to have chemotherapy or radiation. With a focus on cost containment and both houses of Congress looking to ways to try to decrease spending, if you look just to the Medicare population and the incidence of breast cancer in people of sixty-five years of age or older, there is a tremendous amount of costs savings there. Isn't something like that a rationale?

**JEFF GIBBS:** It is a real paradox because right now you think of some of the expensive drugs—the chemotherapy drugs that cost \$50,000 to \$100,000 a year and yet benefit a relatively small set of patients. If you could come up with a diagnostic test that would identify people who are much more likely, you could save a lot of money. But when it comes to reimbursement of diagnostic tests, there are very poor payment procedures. You talked about Coumadin as an example. We thought that the Coumadin diagnostic was going to be a great role model—better titration, better outcomes. But Coumadin genetic testing has been very poorly adopted for a variety of reasons including the lack of reimbursement. So yes, you would think that people would be looking at this and saying it is cost-effective, but so far that really hasn't happened to the extent that one would have expected.

**JULIE DELOIA:** This is also through the medical provider's psychological view. It is really tough if you have a forty-year old woman with a couple kids who wants chemotherapy and you say, "You have a pretty good chance of not getting recurrence," and she wants the chemo just because she has a lot of life ahead of her. That is a tough call for a provider to say, "I am not going to recommend that this gets reimbursed." I don't see that happening for a long time unless the validation studies are much cleaner.

**SHEILA WALCOFF:** I would just add what is interesting is the standard of care in some instances is really moving beyond this whole regulatory conundrum. You have medical societies recommending certain tests that have been on the market for awhile that may or may not have been subject to FDA approval—not because they have avoided it, but because they believe it is not required of them to be legally marketed. You have a situation where the cancer societies are telling physicians, "This test is recommended in these instances" and then you will hear about it because of course it is the Internet age and you go to your doctor and you say, "I would like this test. I want to know if I am at risk for recurrence and if I really can have some more information to make my decision about chemotherapy—one

that is not easier but will give me greater confidence—some amount of greater confidence. It may not be 100 percent, but it is something more than nothing or where we are now.

And then the reimbursement challenge of that is some payers are not paying for it. What that means is you could ask for that test and your doctor could order a test and you can get the test, but you would have to pay for it yourself because your insurance company will not pay for it. That is also a struggle because that is not consistent across third-party payers. Medicare might pay for it, but if you are in the military and you are serving our country, TRICARE may not pay for it. They have different standards to evaluate whether they are going to pay for something or not and not even mentioning the private insurance industry. So all of these things are forming together to make this more of a crisis of a different market situation—a crisis of a different kind.

**JEFF GIBBS:** I'm glad you mentioned TRICARE. It is a really interesting case study. A few years ago FDA approved a Pfizer drug for HIV. And in the label it said that there should be a certain kind of test that was done in a laboratory, and so it is in the label of the FDA-approved drug, and TRICARE won't cover the test. So here on the one hand you have FDA saying you have to do this testing in order to identify the appropriate patient population, and TRICARE saying we're not going to cover it.

**JULIE DELOIA:** One other comment—will we get to a point where if the insurance companies reimburse for diagnostic tests, then you as a patient are obligated to go down that path? So, the insurance company pays \$3,000 for aunkatype, and the patient says I am low risk for recurrence but I still want the chemo because I am worried. And the insurance company says, "Okay, we'll pay for the diagnostic—the \$3,000 test but we are not paying you \$50,000 for the chemo." That is another caveat.

**QUESTION:** My question deals with the government's 180 in Myriad deciding now that the Justice Department doesn't want to support this idea of patenting human genome therapies, how does that muddy the waters in terms of scaring off investors and making it harder for these diagnostic companies to succeed?

**SHEILA WALCOFF:** I think for those of us in the audience who don't know what Myriad is. Myriad is a company that does genetic testing for markers in breast cancer. It actually is a very complicated, very emotional issue with anyone you talk about in terms of patenting because what are you really patenting. I'm not an IP (intellectual property) expert, but with respect to the broader question of how does that impact investment and innovation, it absolutely does. I think most companies are waiting to see how that ultimately resolves itself, most likely at the Supreme Court level. But if you are not able to protect your investment in your product, in your intellectual property, you are not going to make that investment. I think that does stifle innovation. There is a lot of debate about whether you need this particular type of patent or whether the other kinds of patents will be able to protect your investment. As we move more into these more advanced diagnostic tests, it does require a greater level of investment. Some of these

breast cancer tests we have talked about today have been upwards of \$50 million in the investment in the data to demonstrate that the tests actually are supported by actual clinical data.

**JEFF GIBBS:** I think that the government's position might have been more of 120 degrees because they didn't completely flip but they took an intermediate approach, confusing everybody. That was completely unexpected. But I think the bigger point and a key aspect here is this uncertainty. Whether it is the Myriad decision or the patent thicket, as it is called, where there are lots of patents, and someone who wants to do a multiple sequence test has to try to negotiate twenty, thirty, forty patents or whether it is FDA uncertainty over a laboratory-developed test or the reimbursement, all of those have an effect on innovation.

I have talked to venture capitalists and people in companies. Every time that there is a change like this, it does have a chilling effect in that the lack of certainty as to what is going to happen is a negative.

Now everybody investigating this knows that you can't have complete certainty. That is not going to happen. That is unattainable. But the high level of uncertainty that we have is having a deterrent effect—whether it is the Myriad decision or the FDA regulation of laboratory-developed tests or reimbursement debates.

**SHEILA WALCOFF:** I would just add—we talk about patent thickets. There are ways to get through patent thickets and everybody probably is holding one. There are definitely legal mechanisms to get to a place of greater certainty, if we can just move past this frustrating point we are in now.

**CORRINE PARVER:** Please join me in thanking our first panel.

<sup>1</sup> Since the symposium on personalized medicine, the FDA has released draft guidelines for companion diagnostics. See *Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices* (July 14, 2011), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.