

## **Personalized Medicine Coalition's Fifth Annual Keynote Luncheon**

Tuesday, March 3, 2009 from 12:00 p.m. to 2:00 p.m.

National Press Club in Washington, D.C.

Edward Abrahams:

Good afternoon everybody. Good, good... good afternoon. Welcome to the Personalized Medicine Coalition's 5<sup>th</sup> Annual Keynote Luncheon on the State of Personalized Medicine. My name is Edward Abrahams. I'm the executive director of the PMC. This luncheon has become a signature event for the PMC. In many ways, it has marked our evolution from an idea in 2005 that there should be an educational and advocacy organization to promote a new paradigm we call personalized medicine, to where we are today, a coalition of over 160 stakeholders in healthcare who believe that our current healthcare system will be vastly improved if it incorporates the principles of personalized medicine. Those principles are basically that science, efficiency, and what's best for patients should drive decision-making in healthcare. Whether it is what drug to prescribe, what therapy to avoid, or how to prevent chronic disease. Our growth as an organization, and ability to deliver this message would not have been possible without the support of the PMC's Board of Directors. Because they have all underlined their support for our mission, especially at this critical and difficult moment, I want to take a moment with your indulgence to recognize the diverse institutions they represent. They are Abbott, Aetna, Critical Path Institute, Duke University, Endo Pharmaceuticals, Genomis, Genzyme, Health Futures, IBM, Lab Corps, Moore Davidal Ventures, Medco, Pfizer, PhRMA, Sytec Strategies, Millennium and XDX. They include the PMC's elected officers: Wayne Rosencrantz; Brian Monroe, past president; Jeff Cossman, new secretary; Denny Van Liew; and Robert Wells. I would like to ask them all to stand, from all the institutions, and accept our thanks, especially my thanks, for their participation. So please stand.

(Applause)

I'm also especially delighted to recognize the sponsor of today's luncheon, Johnson & Johnson Pharmaceutical Research and Development. I'm particularly pleased, because the pharmaceutical industry's commitment to personalized medicine is unfortunately not well known. Indeed, it really should be, because the future of medicine depends in large part on its ability to produce new cures to dreaded diseases. The pharmaceutical industry will play a big part in executing on that goal. Today, there is hardly a compound in development anywhere for which there's not also a bio-marker discovery program,

to find out for whom the drug works and for whom it does not, in an effort to develop safer and more efficacious drugs that meet patient needs. The pharmaceutical industry is committed to being able to payers, to providers, and especially to patients, in the words of one of the industry CEOs, "This drug is not for everyone, but it is for you."

This is especially true at J&J. The company is devoted to using the latest science and technology to improve patient care, as it moves away from one-size-fits-all, to one based on targeted and personalized therapies. It is my honor in this context, therefore, to introduce Doctor Paul Stoffels, Company Group Chairman, Global Research and Development, Pharmaceuticals, at J&J. He in turn will describe that vision that is transforming J&J, and also introduce our keynote speaker, Doctor Denis Cortese. Paul.  
(Applause)

Paul Stoffels:

Thank you, Ed. As a physician, scientist, and on behalf of Johnson & Johnson, I am honored to be here today with the leadership of the Personalized Medicine Coalition and the Mayo Clinic to discuss the state of personalized medicine. At Johnson & Johnson, we believe personalized medicine is in essence the aspiration that we can provide the right treatment for the right patient at the right time and the right dose. This vision to apply personalized medicine approach to patient treatment is aligned with Johnson & Johnson's mission to care for the world one patient at a time. It represents a paradigm shift from the traditional blockbuster model that focused on understanding and crafting treatments for specific diseases, not specific patients. And in its days, it was not without value. The gains of the last two decades in reducing deaths from diseases such as HIV/AIDS, heart disease, and cancer are testaments to the power of past innovations in medicine. But recent advances in science, genomics technologies, biomarkers, and drug development provide an opportunity to take an approach that is more personalized to specific patients.

Personalized medicine is not a concept far off in the future. It is happening now in our laboratories, and it lies in large part on our ability to combine diagnostic tools with therapeutic solutions. Let me give you three specific examples. First, in the area of HIV drug development, a field I worked in for a long time, today HIV/AIDS has become a chronic and manageable condition. But when I first entered the field,

being diagnosed with HIV meant a death sentence. However focused scientific research, innovative drug development, and extraordinary collaboration and commitment among scientists, physicians, industry, patient advocates, and regulators changed that. And it took all of these people working together very intensively to change this area.

One of the key factors that accelerated HIV drug development was the use of viral load as a surrogate biomarker for HIV disease progression. When I entered the field in '96, the market for HIV drugs was about \$1 billion. Today it's going to \$12 billion. The main reason for that was the development of biomarkers allowing better and faster drug development. It's not about the market, but it's about today, in those days, HIV was a disease with a life expectancy of two years. Today, people will survive 30, 40 years, and probably won't die anymore from it. So, that evolution was completely based on biomarker research and genetic analysis.

At Johnson & Johnson combining diagnostic technology and therapeutic technologies is allowing us to take a personalized approach to HIV development. Johnson & Johnson's companies, Virco Diagnostics expertise leads to the development of resistant diagnostic test to better predict how any patient's virus will respond to any drug. This information helped another Johnson & Johnson company, Tibotec develop new drugs to outwit HIV, including Prezista, a second generation protease inhibitor, and Intelence, a second generation NNRTI. And other drugs in our pipeline. The development on those new drugs based on those new technologies was astonishing. It was focused on smaller populations. It was much simpler to do the clinical trials, much faster. The FDA response to those types of data, because they were so much better, was so good that we got faster approvals. In the end, reimbursement was obtained for 90% of the patient in the U.S. within two-to-three months. So after all, a lot of people think that going for personalized medicine is limiting the possibilities of drug development. I think it is the opposite. It is the future on how new drugs should be developed, and much more targeted patient to combining drugs and diagnostics.

So, this knowledge now has also translated beyond drug development to areas of the world where medicines are barely affordable for patients and no resistant testing exists. But the way we can use these technologies now is by providing first analyzing patients' evolutions, and also now providing guidelines on how to better target therapies for larger groups of patients. Similarly in oncology, our biotech company

Ortho Biotech and our diagnostic company Veridex are collaborating to educate physicians about our cell search circulating tumor cell tests. This simple test captures, identifies, and counts circulating tumor cells in patients with certain type of metastatic cancer. When used in combination with other tests, the cell search test allows the doctor to detect changes in a patient's status, and provides information about patient's prognosis to allow physician to choose the right therapy for the right patient at the right time. In CNS today, we use Genomics biomarkers, molecular and cell-based diagnostics and bioinformatics routinely as part of our R&D efforts, to develop personalized approach in medicine. We have the largest database on DNA samples in psychiatry to help future efforts to identify subsets of population who will respond to drugs, and a large-scale effort to identify markers for efficacy and side effects of central nervous system, or CNS drugs. The pharmacogenetic approach is used for almost every compound we develop now. For example, we have collected and stored approximately 10,000 DNA samples for patients participating in clinical trials of two of our new CNS drugs. We are now looking for markers for response and for adverse events to better understand our current compounds, and to improve effectiveness of future compounds. Again, in this field, to develop new drugs for schizophrenia or for depression, the only way will be identify those patients who will not respond to the current drugs, identify those and figure out how we can make drugs for those patients. That is the future again for a very large field of schizophrenia and depression. So again, a field where a lot of work will need to be done to get to next generation compounds.

At Johnson & Johnson, we're also partnering externally to improve the odds for patients. An example is a partnership with Tianjin Cancer Hospital in China. With five medical oncology wards, Tianjin treats more than 300,000 outpatients, making it one of the premier treatment cancer centers in China. Under our partnership the center has collected and cataloged approximately 14,000 fresh tumor specimens that are proving extremely helpful in our efforts to identify biomarkers which will help advance in our vision to take a personalized approach to cancer treatment. Additionally, we are part of the public-private biomarker consortium, and we have established partnerships with industry groups like the Serious Adverse Events Consortium, of which we are a founding member. The consortium is executing projects to identify and validate genetic variance, useful in predicting the risk of drug-induced SAEs, including a bioinformatics project to share information freely with researchers.

In closing, the sequencing of the human genome and the explosion advances in science have given us reams of data and powerful new tools to tackle the major diseases that continue to afflict human life. But they also reveal how much more remains to be done and the extraordinary new skill of collaboration that it will take to get there. We have much work to do, to realize the full vision of personalized medicine. The science is challenging and the business model is still being defined. To give you one example, in HIV, we developed a diagnostic test. When you do that, you get a reimbursement of \$150, which really predicts a response in a patient. When you develop a drug in HIV, you get reimbursed \$5,000-8,000. The difference is information or drugs. The result for the patient, good information could be as important as giving a new drug. And today, our society doesn't recognize the value of information, and we absolutely need to work on that before it will ever take off. You can't do a full drug-like development for a diagnostic, and then end up with a market of \$2-to-3 million. It's not possible. So we need to work with politicians and with the leaders in society to make them understand that information is very, very valuable.

For personalized medicines, benefit to be realized all of us, scientists, the regulators, policy makers, and pharmaceutical company leadership must embrace a new mindset and take a more network open innovation approach, one in which we can successfully share pre-competitive information in common platforms such as biomarker, genomic data, predictive toxicology, and serious adverse event information. By working across companies, universities, and research institutes, we can tap into a wider range of expertise, capabilities, and resources. Together we can share in both the benefits and cost of innovation that will yield more useful technologies and solutions that will contribute to new advances in healthcare. Today's information empowered flat world makes a ripe landscape for us to use this approach, and we must do this soon because the patients are waiting. The age of personalized medicine is here. But it's up to each of us to decide how quickly its benefit can be made to patients, and how willing we are to embrace and advance it. As we continue to evolve our business models, engage in new collaboration, invent technologies and innovate new medicines, we must all put the patient first as we work together to architect a healthcare strategy to benefit patients and shape the future of healthcare.

I will now turn our discussion over to a keynote speaker, Doctor Denis Cortese, of the Mayo Clinic, to provide a view-point of personalized medicine from his position as the CEO of a leading healthcare provider. Doctor Cortese has a long-standing interest in both health policy and healthcare delivery that

has truly allowed him to stand as a leader within the healthcare industry. He has been appointed to the Institute of Medicine of the National Academy of Science, and is currently the chair of the Institute's roundtable on evidence-based medicine. He also serves on the healthcare leadership council and the Harvard Kennedy healthcare policy group, among others. Please join me in welcoming Dr. Cortese.

(Applause)

Denis Cortese:

Good afternoon. Real pleasure to be here and talk to you about the area of personalized medicine. At Mayo Clinic, we call this field individualized medicine. So if I use the term interchangeably, just make sure I'm talking about the same thing that you're all interested in. Going to move this away. I think I'm on with this microphone here.

Couple of comments. I'm going to spend a little time about the idea of value. But to do that, I'm also going to emphasize the idea of teamwork and how you might look at individualized medicine or personalized medicine as part of a scheme that would be a vision for healthcare in the United States, a mindset for healthcare in the United States. You're all relatively sophisticated with regard to personalized medicine. But I'll just make a few comments as I move forward. First, 1911, Will Mayo gave a speech at the Rush Medical School graduation class, almost 100 years ago, where he said, "At the best interest of the patient is the only interest to be considered." Then there's a comma after that, and the rest of the sentence is, "In order to bring advancing knowledge to the benefit of the patient, a union of forces is necessary." So the concepts in that one sentence of focusing on the patient, translated into the Mayo Clinic's core value, which is the needs of the patient come first, period. That's been our core value for 100 years. And the second concept is the concept of teamwork. People coming together, working together collaboratively to get something accomplished. That was 102 years ago. That is still true today. And it's important -- no, 98 years ago. (Laughter) I knew my math was wrong, and I'm going through it. I was stuck on that little calculator up there. So I had to get that. So we're clear, it's 98 years ago that he said that. But it's been an embedded process within the Mayo Clinic environment. I think it needs to be an embedded process just like you just heard in healthcare thinking and designing for the United States, particularly for this century. We got away with it last century, because frankly in the first half there wasn't

much you can do for people anyway. The second half, there was a lot more we could do that was a little more designed around people. But this century, it's coming at us very fast. And indeed, we have an obligation to look for it, to look for specific treatments for patients.

So when you think about the concept of personalized medicine, we really view it as the entire scope of the science and medicine of human variation and individual medical need. So that's how we approach that from sort of a macro level at the Mayo Clinic perspective. There are lots of different definitions for individualized medicine. You can make up your own. But we do capture the idea of using science, using medicine, when we use the word medicine, we mean the delivery system, and I'll break this out to you in a minute. And then when we talk about concepts of individual variation, that brings in all the new science that we're talking about. And then the concept of the medical need for the patient designing what is really best for them, given all the medical information you might have about that patient.

And now I'm going to talk to you from the standpoint as a provider, as a physician who interacts with patients. You say, OK, what value is all this? What does this really mean for people? I'll give you a couple of examples. Let's just take the example of the promise of personalized medicine in the area of serious adverse drug reactions. Just take that box of problems. If you believe the Institute of Medicine's report, came out a couple years ago, there are probably two million people per year that have a serious adverse medical drug reaction. What I mean by serious, I'm talking about a disability or requires an intervention or there's a death. So serious reaction. About two million of those people a year. That leads to about 100,000 deaths per year in this country. A lot of people argue it's more. Some people say it's less. The point is it's more than zero. If it is 100,000 a year, that's about one 747 crashing every day-and-a-half in the United States. If it's half of that 100,000, that's a 747 every three days. See where I'm going with this. It's at least a 747 a year. I'm not here to argue with politicians and others about is this a serious problem. We wouldn't tolerate one 747 crashing a year without putting a serious effort to understand what led to that cause, systematically analyze it, and systematically using engineers, try to improve it and prevent it from happening in the future, right? We don't do that in the United States. Where's the agency that does that? That's an outrage in this country, that there's no safe place for errors to be reported. So if you just say let's just tackle that problem right there, we have about 6% of hospitalized patients will be affected by what I just talked about. And out of that, somewhere between

0.1% to 0.3%, one in a thousand to three in a thousand people will actually, are people who are admitted to the hospital will die because of an adverse drug reaction.

Well, it would be nice if we had these markers that could predict the risks, can identify some of those risks. We do have some of those markers, as you well know. In our institution, Dick Weinschelbaum (sp?), 1980 identified the marker with methyltransferase deficiency, and being able to predict that an increased thiopurine sensitivity to children who were being treated for leukemias. That was 1980 when he identified that marker. We've been using it in our practice ever since. And I think it was actually approved by the FDA to be folded in to the use of that drug around 2002. So it took a little while to come on through. But since then, there've been at least three others that have come through this sort of a process. And you know them: warfarin and the statins. And then you have the one for tamoxifen, that also came out of our laboratories about a few years ago. That was approved about two years ago or three, around 2006. That was around the genetic variation for cytochrome P50. And if there was that defect in a person might be not as, they don't metabolize tamoxifen appropriately, so they're not as sensitive to it, so it's not as effective.

Well, everything I've just described produces high value to that patient. Reduces risks for a population that fit into those categories, which also then, if we apply it right, produces value. It reduces the spending, reduces waste, and it theoretically and measurably raises the outcomes and gives better safety. Now, that's, I'll go into the definition of value in a minute, but I want to focus on value because it is the thing that's missing in the United States healthcare is the focus on value. That's what I'm building up with my discussion as my slide indicates there.

Also recently the cytochrome P50 as you know has about 200-some alleles that have been identified and that are published on the website, and then one of those alleles being identified as, when it's low, there's an increase, poor metabolism, meaning an increased sensitivity to beta blockers for instance. And that's been published more recently too. Could have very much applicability. Some of us, like myself, I'm on a beta blocker. So many of you might be also. It's an interesting thing to know about.

OK, so when we look at the breast cancer example for instance, we've had a story, one of our patients who had a breast cancer removed elsewhere, and had been told that it was positive for estrogen receptor, was appropriately started on some tamoxifen. Then she read a report about this defect possibly

existing. She came to our institution, had a test, and indeed was low on that. We changed her over to the aromatase inhibitors for her, which we think would be more effective given her particular situation. And then when you look of all of the gene signature studies, the gene studies that are now being done that are being used to identify sensitivities to drugs, particularly in the cancer area right now, with regard to all the tumor markers that might exist, when you start looking at the potential of what that will all bring in a systematic fashion, everything I've just described has a significant potential to improve the value of what we deliver to patients.

So enough on some of the examples. Let's talk about value now, because I think that's the thrust that we all need to be focusing on yourselves especially as you think into the future. If we define value as the quality, divided by the cost to get that outcome, when I talk to politicians and I talk to former presidents, and I say, "What is the number one problem that you see for healthcare in the United States?" They don't use the word value, but they all say, "You know, we're spending an awful lot and we're not getting much for it. We're not getting what we should be getting, when it's measured particularly to other countries, et cetera." And I say two things. First of all, in the United States, there are several examples of where you're getting better value than you're getting in Europe. There are examples of that in the United States. There are five states in the United States that perform better than all the European systems. But you would never know that. The commonwealth data I'm talking about now, but commonwealth doesn't tell you that either. This is, we have great examples in the United States of how healthcare can be delivered. That's the first observation. But the second observation that I make, which is the key one, is that if you don't think we're getting what you're paying for, then what you're really describing is that value equation. And the really bad news for the politicians is, we are actually getting exactly what we pay for. We're paying the most amount of money to the regions of the country that have the worst outcomes, the worst safety, and the worst service. And it's being done systematically, by the federal government, through Medicare. And the Board of Directors of Medicare are our politicians. Congress. They are systematically running an insurance company that is paying the most money for the worst outcomes. So they've got to come to grips with that themselves. Because if you really are going to complain that we're not getting value, then you ought to doggone well pay for it. That would be a first step in the right direction.

So that's the kind of emphasis that we put on the value part. Now, let's take value and break it down into its component parts. I say quality over the cost. It should be, we define it as in the numerator, the measurable outcomes, measurable safety, which is pretty easy. It should be zeros. And service, to measure that from the patients. Divided by the amount of dollars you spend over time to get those outcomes. That's our definition of quality. A lot of people accept that, and the politicians actually add maybe one other in the numerator, they call it access. Tom Daschle used to always put access up there when I would talk with him about it. And it's a good point. Access should be part of it. But once you get everybody insured, that disappears. You're just dealing with the value equation as I've talked about.

So what I just show you now is a little bit of a vision. I'm going to use just a couple of slides to just give you some visuals. But if you start looking at saying, if we really want to design a healthcare system that's going to generate value, there might be some concepts to build into the thinking around that effort. So let's talk about the components of a healthcare delivery system. The major goal on all of that is that the whole delivery system should be organized in a way that we're generating information. We're generating knowledge. And we basically have a learning organization structure. Won't go into detail what that is, but that's sort of the background. Everything we should be doing is in a way that we're all learning together what is of value in the delivery system. And the purpose of this model is to produce one thing: that's value for the patient. I've already defined value for you, but the purpose, top of the pyramid, is to produce value.

Now, what are some of the little things underneath that that will get you towards value? One, is integrated coordinated care. The concept of, we talked about talking care of more people, they're going to live longer, have multiple complex illnesses. Want to be taken care of out of the hospital. I didn't ask my favorite questions. Going to stop here and just ask you, if you really want to design the system, we need to design it with some picture in mind. And I'm going to ask you, I'm just curious to see how you answer my questions. Who in this room would like to be hospitalized tomorrow, even if it's the best hospital in the world? OK, so you all chuckle. So far, in that room over there, about a year-and-a-half ago, in the national press club, I had three hands go up. The only place I've had any hands go up after asking this for thousands of people. But it went up. We stopped right there and I said, explain to me. "Well, if I'm really sick, I want to go to the best hospital." I said, "Of course. It's what you want." But

what's the second question, who wants to be sick tomorrow? And the third question is, who actually ever wants to be a patient? Because a patient is defined as a person who long suffers or has to endure something. So, if you now are going to design individualized medicine for the future, we need to answer, be able to let people answer those questions, no, they don't want to go to the hospital. They don't want to be sick. How do we keep them as well as we can? To do that, we have to organize a structure, learning organization, producing value for the patient, to make sure that they are being cared for in non-traditional settings, wherever they are in the world, whenever they need it, by whatever doctors or non-physicians that you need, non-traditional providers. That becomes a mindset that we should be aiming towards.

There's a gap in between. What fills in those gaps? These are our Mayo Clinic strategic priorities that I'm listing for you. Here's how we fill in those gaps. Individualized medicine. This is the personalized approach that you're all talking about. We're going to talk more about that concept of course. But the role of individualized medicine, where you have that coordinated care, but you're focusing on producing value for the patient is huge. The ability to specifically tailor what is best for that patient is what we should be focusing on. Now, in Mayo Clinic's culture, this is a no-brainer. Because we've always had the needs of the patient come first as a culture. In the United States delivery system, especially when you get into public health, you got to change the culture. Public health is measuring averages. You want to improve the health of a population, you've got to do it one-on-one and you've got to take care of each person. This is hard for some folks to accept. I could be wrong, but I can't see how you could improve a population of diabetics without tailoring the treatment for each one of them, like they do in Inner Mountain and they get the best results at the lowest cost in the country. They individually tailor the treatment for 25,000 diabetics. They have four endocrinologists. They don't see patients. They conduct the orchestra of care that gets down to each patient designed for them. And that orchestrated primary care doctor, could be a nurse, could be somebody going into the children's school to see if they're getting the right food. It's that sort of thing. You got to tailor for the individual. And that then links over to what we call the science of healthcare delivery, which is what I just described for Inner Mountain. They engineered the approach to caring for each person, systematically using system engineering approaches to deliver the care to each individual person, making use of the knowledge generated through individualized medicine,

integrated care, and producing value. And they can measurably demonstrate it. This is happening in pockets in the country.

So that becomes the overarching vision. That's it. There's two components where the government has to buy this and help us get there. And the two components are at the bottom. The first is, if we're going to be generating value as the main output of the system, we ought to dog-gone well pay for it. We got to begin to define value nationally, and recognize it, and pay for it, so you can move the system along. And then the second is, everybody should have insurance. And I'm not here to debate that issue. We got to get it behind us. Once that's behind us, we can really get to what needs to be done: change the delivery system. Because you won't solve anything when everybody's insured. An awful lot of people get bad results, have lots of insurance. So insurance is just the thing that needs to be done. And fortunately, the administration is moving in that direction. I wish they'd move a little faster and get that behind us.

OK, now let's talk a little bit about that individualized medicine piece, which is your personalized medicine. And there are some requirements. I've already alluded to the fact that we have to have a culture change. There's another requirement about IT infrastructure. I'm going to show you some diagram on that. And then the concept of comparative effectiveness, I want to spend just a little time urging you to get engaged and become proponents for it. I'll make my case and you can decide whether you accept it or not. And then I'll close up with the pay-for-value point one more time.

Culture change. Already talked a little bit about that. It really goes all the way back into the medical schools. I go to our medical school, Mayo Clinic, and I continue to ask the question, I'm getting better answers, but they're not quite where I want them to be yet. When is the last time a medical school class took a clinical exam, a patient exam, so that collectively, every person in the class got it 100% right for that patient? (Pause) That's called cheating in today's healthcare system. But when you leave medical school, you got to cheat the whole rest of your life, if you're going to do a good job. You got to find whoever or wherever the knowledge is that you need to take care of that patient at that moment. So why don't we think teams to begin with? Why don't we train people to think teams? Why don't we train people on how to solve problems, not how to memorize the current diagrams? It's a total different mindset, and it brings really system engineering approaches, to be thinking about how do we train people. And the idea of working afterwards collaboratively with other groups is a key component of it, of this new culture that

we're talking about. And we have to be able to work within and among organizations, like you all are doing. The different sectors need to come together and work collaboratively to advance the science and the medicine practice for the benefit of patients. It will be hard for some people, because it will challenge their business models for a while. J&J has been on the cutting edge of this in some of the work they've done in England and elsewhere has been an exemplar of this. So and others of your companies have done this too. But as you begin to look at changing your business model, disruptive innovation to the current thinking is what we really need to move forward. And then build our relationships with other organizations that you need to have to be successful. The same applies for Mayo. We're building more relationships too to get this job done.

Now, when we move to the infrastructure for decision support, because after all there's another way to look at personalized medicine, and it could be viewed as just the decision support tool. To help us make on-the-spot correct decisions about prediction, prevention, more precise diagnosis, precise treatment, the [Lee hood four P?] type of example.

So how do we do something like that? Well, this is our concepts that we're working on at Mayo Clinic and what we're trying to construct. We start overall with the idea of the patient. When a patient comes, what are the outcomes that we really have to try to generate from the patient's view-point. What are their expectations when they go to the doctor or especially when they come to an organization like us? Because they have expectations. They really like to have a cure, if they've got a problem. They'd like to stay well if we can't cure them. They like to have a good quality of life. They're really looking for some value. And sometimes the value we bring is we don't change their outcome, but we are safe. We're very safe organization. We provide excellent service. And the service component alone may satisfy some people. If you have compassion and you care for them, you can't change anything, that in itself is viewed by people as some value at that time in their life. So that's the business we're in is looking at the total patient. So if that's our endpoint, here's when we start. Somebody walks into my office and I'm sitting down talking to them. You start with the stuff that you already heard alluded to there. But we start with some of the key components of the data that you have available to them. And that data would be in the phenotypic area. It's going to be the raw data, be the clinical information that you obtain from the data. It'll be some of the biologic, the testing, the imaging information. And then of course in that front-end, we

also have a bio-banking process, where we have access to maybe tissues that they either brought with them, or tissues of people who are like them. So we have that in the background. So we built a bio-banking that sort of fits over there somewhere in this diagram.

When we collect that information, all that data, we pull that data into what we call an enterprise data trust. That's the name we use, because we don't use simple names. We always look for something hard. Basically what that is is pulling together all of that data that I talked about, collecting it, storing it, collating it, and making it be retrievable. Then, once that is there, we're able to say, OK, let's say that's a group of women with breast cancer just for the sake of discussion. So that's great to be able to tell that patient you're like other people that have breast cancer, but there are at least 125 types of breast cancer that we can identify now. Eight or nine that we treat differently. So where does that patient fit becomes the question. Once we have pulled that data all together, what we try to do is to use the data and then in that enterprise data trust, it comes back and we use this to make a medical decision for the patient. That information that we've created from the data is helpful in making the next decision for the patient. But, what we really want is not just the information to make a decision. We want that information to compare it to what we think to be true. What is the knowledge that is available to us or anyone in the country. So we need some kind of a process being able to do the computational biology that needs to be done to understand what is the current state of knowledge for that population. And then where does that patient fit into that population, given the knowledge base that's there. Patient may not fit in. Patient may be on the brink of helping us make new knowledge, as we begin to analyze this as we go forward.

Last century, the Enterprise Data Trust was our unified paper record. Mayo Clinic's unified paper record was started by Henry Plummer in 1907. And we've had that in place for a long, long time. We switched to the electronic environment about 1995. So now that's collected electronically. Last century, that computational component was the minds of physicians, who particularly went to our Harwick building, where all the records were kept, and they would spend weekends going through records of patients that had a common disease, like Wegener's Granulomatosis. You'd thumb through all those records to try to make some connections if you could using your mind. Can only handle about seven parameters at a time. And try to come up with some knowledge, and we would publish it and we'd use it going forward. As you all know, that's not going to work this century, because there's thousands of pieces of data and

information we need to look at. So that box is the tough one. Computational bioinformatics is the tough one. How do we really do this? We heard that alluded to, Johnson & Johnson does that in part of its activities. But we're talking about a patient-care delivery system, and we're talking about it as a national vision. How do we do this? Groups are doing it, but this becomes I think the biggest challenge, because when you're done with that, you now have a decision support tool that can be at your desktop. It can be a push technology, help you make decisions with the patient wherever they are, in the world, when you need to. And that becomes useful to make clinical decisions, as I've pointed out over here. Maybe in the area of prediction, prevention, diagnosis, prognosis, treatment.

But it's much more valuable than that. And remember, I'm emphasizing value. This can be used to help us in research. I only gave three examples. There are about 20 different examples under research, with the work that Frank Prendergast has been doing in our individualized medicine center, there's tons of opportunities in research for us. That's of value right there. Education. Being able to take this to the patients and to the staff that are caring for our patients is a form of education. Actually, with our push technology we use now, we're going to be giving CME credit for physicians who actually use this stuff, as we go forward. I'll say I'm going to meetings. So we're building that. And then getting out to the public and the profession, and then going global. Taking this global is not a hard step. As a matter of fact, it'd probably be easier to go global than it would be to do it in the United States, because of rules and regulations in our own country.

And then finally, all of this gets fed back, and you have a continuing cycle, and you get one last benefit out of it is there are business opportunities here, tons of them. As we look at that. In the area of education, laboratory testing, imaging, all the things you're aware of.

So that's sort of a concept, and we are tackling this whole spectrum in those blocks within our institution. We are building each one of these. And I tell you, we're way down the road on everything except the green diamond. We're doing the green diamond, but it's still not fast, efficient as we'd like it to be. We're searching for partners. We've got partners. We've got the highest speed blue-jean is in our project, still not exactly where we need to be yet. But we're getting there. And I think the whole country could do that if you focused on it.

OK, so that's kind of a picture of the issue of the structure, infrastructure to maybe make this all work.

The third thing I'd emphasize is the comparative effect of this. I think, and I'm going to show you another diagram where this might fit in, but I would encourage you all to really be positive about comparative effectiveness, because if we do this right, in teamwork, I think we have an opportunity to accelerate new discoveries through a translation process of some kind, identify where it'll actually work. If it's worthless, fine, let's find that out early. But if it's useful, if it's useful in a blockbuster, that's wonderful, but that would be shocking. Right, if we believe in individualized medicine, unless you all think we're all the same, the blockbusters are going to go away. We got to think of where are the 10% that it would work, or the 15%, identify it quickly, and get that out. Get paid for that and move on to the next. And you begin that process. And you turn all the work that is being done into a vibrant enterprise for the United States, where we are looking for comparative effectiveness. Where are the incremental values that we're generating. And the price we pay, some things won't work. But the quid pro quo is you can get an accelerated process to find out where it does work. Now, I don't know how much this will play out, but I know there's a commitment to make it happen and I'd encourage people to get involved rather than hope it doesn't happen. Because something like that's going to happen and you might as well get in and get engaged.

And then finally, I hope I've made my case that as you look at this, that these elements that we've talked about, to the extent it produces value, we should be making the case that the folks that are talking about controlling cost in the United States need to really start talking differently and talk about let's get value in the United States. Get the waste out. Get rid of that 30% that is worthless or 40%, or maybe 50%. But then from then on, if you're getting high value, what's the difference what the real "costs" are, or what the consumption is of the gross domestic product. It doesn't matter if you're getting high value. That's what I hoped the President would have said in his speech, instead of saying we're going to control cost, I wish he had said, "We want to be number one in the world in our outcomes, our safety, and our service, and for controlling our costs." You got to bend the curve, I agree. And Peter Orszag is right: you can bend the curve. There's no question. Because there's a lot of waste. But you bend it and then you grow back up on the value curve, and you go to whatever extent is necessary to provide value.

Now, I'll leave you with one final set of thoughts for you to try to pull all this together, and maybe see where some of us are picturing where personalized medicine might fit in. Going to look at what healthcare looks like today. You can see where it can be improved when I'm done, I hope. I've divided up into just three simple domains in healthcare today. I'm taking a systematic approach. I'm looking at this as though we were to design a healthcare system. Let's go over the three domains. The first domain over there on the right is what I call the knowledge domain. It's where inside that universe, there are all kinds of people doing research. R&D for drug manufacturers, device manufacturers. Academic medical centers. The National Cancer Institute. NIH. You get the idea. All of these places in that universe are doing some research. And when you look within the universe -- and by the way I'm just describing the domains. My goal is not to get into the domain itself in much detail, but how they interact with each other. But I'm going to make a comment about what goes on inside each domain. The first one is here. When you just look inside that domain, if you look carefully, you'll see some connections. Some of the nodes are actually connected. It's not a very good neural network, but it's probably the best we're going to get when I finished showing the rest of them. For instance, Mayo Clinic sits there and we interact with Hopkins. We interact University of Minnesota. We interact with Arizona State and Stanford. We've got some connections. But there isn't any systematic attempt to make them all connect, except on the internet one and internet two. There's some attempt behind the scenes to make it work, but it's not a conscious effort, to really make this thing flow.

Anyway, that's the knowledge domain. Second domain is what I call the care delivery domain.

Yesterday, somebody said we should change that to, remember what it was? I think it was your idea, Larry, wasn't it? OK, that's right, Larry suggests we call that the consumer provider domain. But you get the point. There is that universe, patient's in the middle of that OK. And inside there, there are a whole bunch of small stars, big stars, and some galaxies. And the small stars are all the individual doctors and nurses are trying to take care of people. Then you got the small practices. You got bigger practices. You got integrated group practices. You got hospitals. You got groups of hospitals. Academic centers. You get it, get the idea. When you look inside that though, if you look carefully, you'll see there's some connectivity around certain galaxies. And that connectivity probably is only around their own little galaxy, like Mayo Clinic has connectivity. We're pretty well connected. It's not perfect, but it's pretty good.

Keiser, University of Minnesota, University of Pennsylvania. They each have varying degrees of interconnectivity. But there's really not move connectivity among the galaxies and all those stars. There isn't any attempt to make that happen. That's a huge opportunity for information technology and distribution of knowledge. Huge opportunity, but I'm not here to talk about that. Just give you an idea of how that would look.

And then the third domain is the pair domain. In that, you've got individual patients that may pay out of pocket. You got Medicaid. You got Medicare. You got private commercial insurance. You got employers. You got the United States government with the VA system and you got the military, [champus?], et cetera. And when you look inside that, you can't make any order out of it whatsoever. There's no connectivity. Nobody knows what's going on. It's just a chaotic universe if you will that just sits there.

All right, now if we draw a little box around that, and you now say one of the roles of system engineering is how do you look at the interfaces between complex interdependent systems? That's what system engineering's supposed to do: try to make them work better at the interfaces. OK, let's look at the interfaces then, between the two domains on the left and the two on the right. There are two interfaces here. One I'll just call the translation, and the other is the reimbursement sort of interface. Now, when you look at that, here's the price we pay because there is no person or body or group that manages either one of these interfaces. It is really no conscious attempt to make these interfaces work. There's no conscious attempt to try to make these domains sort of function across each other. And when you look at that, here's the price we pay for not paying any attention over on that left side. Through the knowledge domain, there's all kinds of things coming out. It's like pouring out like crazy. Money goes in. Great ideas that need to be tested, evaluated, et cetera. Here's the price that we're paying for paying no attention to that whatsoever. In about 17 years, a few things will get the practice. And when it does get into practice, about 50% of the time, the patient will get the right advice. That's what the country is paying for. Now, I tried, I've just done a little napkin thing at a Mayo Clinic, and I would put probably, we do pretty well at that interface, but probably, depending on what you look at, it's probably about two years for our translation capabilities to really get it embedded into our practice. And even then, I'm not sure that I can tell you it's 50% or not. I don't know that. We've never really studied that in our institution. But we're

probably down to about as low as people get. But we still travel to international meetings, or other meetings in the country, and our neighbor, orthopedic surgeon, who may be one floor below me, is presenting something I didn't have any idea they were doing. And it's even worse. It could be my next-door physician partner in the same field I'm in giving a presentation. "I didn't know you were doing that." You've lived through that, haven't you? We've seen it. So the distribution of what do we actually know, nobody really manages in a way to compress this to one second, to get it down to a click of a button. That everybody knows what everybody knows in Mayo Clinic. We are building a program to make this work. We call it our enterprise learning system. And our goal is to have it be available click of a button. It is up and running. We're planning to use it as push technology in addition. And that is up and running for ten diseases. And we've identified, Fred Smith asked us to use, he funded part of it. He runs FedEx. And we call it in his honor the Code Purple. For that, if it's ten diseases, that if the patient doesn't know that they have it, and the doctor isn't aware of it, the patient could die in a week. And there's push technology bam, comes right to the computer and says, here are the experts at Mayo Clinic. Here are the phone numbers. Here's what you need to know. And you read it and it's just one little page. So anyway that's that interface over there on the left-hand side. Then we come out over here where we have the care-delivery domain producing a bunch of products. They've come out and they hit that interface. And some of the products don't even get to the interface, because nobody's going to pay for it, like caring for people at home on the internet. Try to get Medicare to pay you to take care of people in non-traditional settings. Only reason doctors are recycling patients in their offices is that's the only way you get paid by Medicare. So it's kind of a self-defeating interference with the way we might be able to generate value, because we have to practice a certain way to get paid. It's kind of crazy. The sicker you are, the more money we make. You go figure. So that interface there has a bunch of products that sort of hit the interface. And then as they get through, the height of the arrow reflects the amount they're paid. Many things are underpaid. Some things are overpaid. There really isn't a real rational balance to try to figure out what is of value and how do you pay for the value. So anyway, that's just a model to think about. And I would leave you with the final concepts that we started with. The first is I want to show you where Mayo Clinic's strategic priorities fall in this construct. Because we created those strategic priorities about four-to-five years ago. And we've been following

them. And this slide is relatively new since last September. But Shelly [Mayo Media Relations] is here, she said, "Let's see where our strategic priorities fit." And when we did that, we found that those four strategic priorities that we talked about: creating value, and the coordinated integrated care we felt was probably in the care delivery domain if you will. I got to put it somewhere and I put it there. And then individualized medicine is over there at the knowledge side, pushing stuff out. But actually, when you think about it, in the diagram I showed you, individualized medicine comes all the way across into the pair domain. Not into the pair, into the provider domain. But for our purposes at Mayo Clinic, we focus our efforts on individualized medicine down on the knowledge side. And then, that interface is there, that science to healthcare delivery. How do we actually bring it through and apply that stuff that's being discovered, as quickly as we can? So our four strategic priorities actually of interest circulated around those two domains, and probably because those are the two we understood. We didn't create the strategic priorities because of the diagram. We had the strategic priorities before. But it kind of reflects the fact we're a provider. We understand the knowledge side. And we understand something has to be done at that interface, try to make that work better.

Then Shelly asked the next question, she said, in our health policy center efforts, where we have been engage over 2,000 people and about 1,000 people who are patients, individuals who spoke for themselves, and another 1,000-2,000 people who come from places like your places, who are vested interest, members of the sectors of healthcare. And we've gone through almost three years coming up maybe in May. We would've been working on this. And through all the meetings we've had, 15-to-17 meetings, four cornerstones have been resonating and have stayed as cornerstones. Now, look where they fall out. Here are the four cornerstones that came out of our health policy center. Getting everybody covered with insurance. Paying for value. And then creating value and trying to get integrated coordinated care. It's very interesting how the overlap came. And the process that we've run these programs, by the way, they're not directed by Mayo. We convene and we run them. A few of us get a say. But it involves everybody else. And these are the four priorities. So I'm not sure what that tells us, but it kind of confirms part of that diagram I showed you before. But it shows you in this diagram how important it is, if we want to really get new knowledge, new discoveries, take it through translation, get it

applied into practice, we better be generating value. And we better have somebody on the other end ready to pay for it, be willing to do that.

So I'll leave you with those two thoughts around how individualized, personalized medicine should demonstrate-ably generate value, and then make the case that we ought to be focusing on it and making sure we're paying for it, and not pay for the inverse of value. So thank you very much for listening, and I'll stop and see if you have any questions.

(Applause)

Should I take any questions you think? I'll be happy to take any. I think there's a microphone. I heard somebody say there might be. (Pause)

Q:

Hi, I'm Michael [Kidder?] from Pfizer. Also practicing internist. My question for you is really about the translation of this. And when you were talking about comparative effectiveness, we've seen that there's a lot of studies come out, there's a great deal of evidence. There's a great deal of medical literature coming out all the time. So the best practices are out there. But when you have the patient in your office, how do you actually get people to follow those guidelines? I think the Mayo Clinic and probably academic medical centers are almost like an idyllic setting. But how do you do that kind of maybe for an individual provider or smaller group, how do you maybe enforce the findings, for want of a better word, of comparative effectiveness research?

DENIS CORTESE:

Two points. One, I don't like the word force, but to get what you want, if you start paying for value and focusing on value, then the knowledge becomes a tool to get better value. And that becomes the key driver in Mayo Clinic's environment. That's first point. Second point, I'm not talking about guidelines at all. We don't use guidelines in our practice. It isn't a guideline type thing. Because as you all know, as soon as you get the guideline done, something's changed. And what we're trying to do is be on that cutting edge and making the knowledge available to our individuals. Give you an example. When our enterprise learning system, which is a desktop thing that people can go to, let's take patient has atrial

fibrillation, is in with the doctor. And there might be a reminder saying your atrial fibrillation somewhere in history. This information available if you want. If the patient or the doctor clicks on that, we start with the list of the top doctors in Mayo Clinic that you can call about what's current in atrial fibrillation. The first neural node we want to connect to is the people's brains. Because you can't get it all distilled on paper. Then we also have what are some of the current treatments. What are some of the literature that you've got. What are some of the clinical trials, et cetera. It's all rolled out in a single document that people have access to. And we're providing helpful information for them to apply. It's the outcome that you measure that makes the difference, however. Because that information may not even be germane for that particular patient. It's just information. Or better, it's the knowledge. This is the state of what we think to be true. And what you apply to your patient is up to you and the patient to decide. But if we are measuring the outcomes, if you're getting better outcomes, that's what you should be rewarded on. You don't have to apply the knowledge per se. The knowledge is a tool to get better outcomes, better safety, and perhaps better service, but certainly lower cost. Keeping people healthier over time. So that's the first set of concepts. And in our institution, if we were using guidelines, and people say you have to go down the guidelines, we'd have a riot in our staff. They're not any different than all the rest. Just because we're an integrated group practice, and we do try to work together and respect each other doesn't mean we're ready for guidelines and cookbook medicine. This is not cookbook medicine. This is ongoing process of updating the knowledge base as we do it, and then apply it to our patients. So that to me is the only way to get there. And having that knowledge in the hands of the individual doctor in a small rural town in Iowa is a challenge. But it's doable with information technology. Quite, quite possible. Yes sir.

Q:

Thank you for your remarks. [Guarberto Ruwano?] Genomis, Hartford. The learning said that you have acquired through your practice, as you appropriately call it, it's relevant to Mayo Clinic in Rochester. The question is how do you see it being exported to other populations where people will say, "You don't have the evidence base in those other populations to apply the rules you learn in Mayo or at Rochester." What I'm getting at is, if you're going to impose a regulatory hurdle, as you translate outside of Rochester, that hurdle may be insurmountable, given the requirements of evidence.

DENIS CORTESE:

Right, well first of all, we're not talking about a regulatory hurdle. And we're not talking about a requirement. And we're not talking about telling people how to practice. I firmly believe that the way practice needs to be done has to be embedded within that particular environment. What works for Mayo Clinic in Rochester doesn't work for Mayo Clinic in Arizona or in Jacksonville. We're not asking them to practice the same way. This is a very important point. They have to design and use the same tools and skills to do what they need to do to get the results for their populations. But, we expect the same results in all three sites. We expect the same outcomes, the same level of safety, same level service, and the same costs, if we can get there. We're pretty good on the top three, but still there's variations. For instance, in our own institution, the very best transplant program, just take the one transplant program. The best transplant program we've got is in Jacksonville. It's a small practice, but it's a huge transplant program. It's the biggest in the country right now. Do the most number of livers. The lung transplant program is outstanding. And they are our cheapest, least expensive outcomes. And they're the best in the country. We turn to our other sites that do transplants, Arizona and Rochester. And we say, you got to get the same results. Now, if you can study their processes and you want to use their processes, that's your business. I don't care what processes you use. We're measuring the results. And that's what I'm talking about nationally. Let's measure results. Not, you know, a lot of the pay-for-performance we're hearing people talk about is pay for compliance with process. All right? You can get great compliance with process and still get bad results. Happens all the time. Compliance with process is not what we're looking for. We're talking about let's measure the outcomes, the true outcomes. And then that's what we should be striving for. And the different processes will be different at each place. What works at Cleveland Clinic isn't going to work for us. What works at Johns Hopkins is entirely different than what works here. But you better believe we're comparing our outcomes. We're comparing the outcomes. We're not measuring our process internally. Just to give you one small example of a benefit of doing this. When we did this with Hopkins, we did it with 12 centers a few years ago on a specific project on open-heart surgery. And we found that one center was getting better outcomes -- the outcome was lower use of the ICU after open-heart surgery. And they couldn't figure out why, so they drove into it, found they

had a lower rate of post-op atrial fibrillation. They drove a little lower and they found there was one doctor in that one center doing it. Happened to be at Hopkins. We got all our cardiac surgeons to go to Hopkins, figure out what they were doing. Found out he was doing an infusion of magnesium-sulfate, and it was getting a lower rate of atrial fib. And their own staff didn't even know it. Didn't even know it among their other cardiac surgeons. So we're searching for outcomes that are better than others. And then you begin to drive in and figure out, how are they getting that? What are they doing to do it? So the goal is measuring outcomes, measuring the results, and then the purpose of process is to get those results. But the process can be quite different no matter where you're working in the country. So I'm not here insisting on common processes at all. People who know me know that I have not been a proponent of that in any way. But I am searching for those people to get the very best outcomes. And as I say to Mayo Clinic, our only competition is anybody who's better than we are. And that hopefully is somebody down the hall, in our own institution. So you got to measure those outcomes, and that's hard to do. It's easier to measure process. Yes sir.

Q:

Doctor Cortese, thank you for sharing with us your extraordinary strategy on the field. I think it was Claude [L'Enfant from DNH?] who said a few years ago, talking about translational research, that this country doesn't apply everything it knows.

DENIS CORTESE:

Right.

Q:

And that's one of the key problems we have on this. So Mayo Clinic perhaps has one of the most powerful educational platforms of any medical center in this country. I think that's one of your, if not your best asset, the educational platform you have. You lead in many areas. And people go to Mayo to learn and look for guidelines. How do you see that platform being instrumental on the acceleration, on the

[catalysis?] of the personalized medicine examples that are well-known for certain niches, but are not really known in the real-world out there?

DENIS CORTESE:

Well, if you look at personalized medicine, in the broad spectrum, go back to my little pyramid diagram. Notice I said individualized medicine, which was more the science-based discovery. And then I had right next to it the science of healthcare delivery, which is engineering science, which most physicians sort of resist. But that is the important component. You're exactly right. We have a lot of active ingredients. But we don't have the processes that deliver them very well. The delivery system, and I'll just take a minute to tell you a quick story. I know you want to cut me off but this is worth hearing. Mr. Pratt has been a benefactor to us for our science of healthcare delivery. So now I'm on that other side, how we deliver. He challenged Mayo Clinic. He comes in and he's actually funded one of our programs now to do this. He came in, he's the gentleman who started the Cutter insect company. And here's what they did. They had their product. And in the product was the active ingredient. It was DEET or something like that, 0.001%. It was cheap, effective, and it was the smallest component of their product. The rest of the product was a hydrocarbon solvent that you had to dissolve the DEET in, so you could spray it on your skin. The delivery system was the most toxic and the most expensive part of his product. The active ingredient was what worked fine. Looked at all his competitors, and every one of them was doing research to improve the active ingredient. He comes along and says, "We already got an active ingredient." He hired somebody to fix the delivery system. About three months, they came back with an aqueous solvent that would dissolve this stuff. It was one-tenth the cost, eliminated the toxicity. That's what we need in healthcare. That's the science of healthcare delivery component of it. And he said, "That's what you really need, because you got two things. You got more active ingredients, but we got a lot of them that are not applied correctly." So you have to meld the two that we're talking about. New discovery with how do we deliver it. The delivery science component. The two have to go hand-in-glove, because of just what you're saying. And education can do that, and that's what we're teaching our students.

Edward Abrahams:

I think everybody agrees that Doctor Cortese has laid out a compelling vision for personalized medicine. Implicit in what he also said is that there's an agenda for action. It's an agenda that the PMC is dedicated to addressing in 2009. It was not noted, but this year is obviously going to be critical for the future of healthcare. And I'm hopefully that everyone in this room and beyond can join us in effectuating that agenda, making personalized medicine even more a reality than it is today. And that conversation will begin in the next room. Right now, please you're invited to join us for drinks. So thank you very much. And join me in thanking Doctor Cortese.

(Applause)

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