

**PARTNERS IN PROGRESS RARE DISEASE SUMMIT:  
AFTERNOON PANELS**

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DAVID KESSLER: We're going to shift our attention to the financing side of treatments for rare diseases, and it's a real privilege to start the afternoon off introducing a colleague. Chris Jennings worked for a decade on the Hill for three United States senators. I had the privilege of working with Chris when he was a senior adviser to President Clinton, 1994 to 2001, involved in everything from SCHIP to HIPAA to FDAMA. In the current environment I think we all look to Chris for guidance as probably the most historic period in healthcare reform lies in front of us.

Chris, if you could give us the lay of the land currently. How are we going to maintain the incentives? the reality is developing a drug that fewer and fewer people are going to use but it's going to work, covering those costs weigh heavily on the minds of everyone in this room and especially upon those patients, their families that bear that burden. And what are the creative solutions that we can think through as health reform takes off over the next several months. Thanks for being here.

CHRIS JENNINGS: David, thank you for having me. And you know, I am proud and privileged to be a board member of NORD, and Peter, thank you for that. It's one of the more inspiring and challenging roles that I play. I wear many, many hats in my life. I guess I want to first commend NORD for bringing this group together. It's an extraordinary brain trust. If you all can't figure it out, I just don't know what we're going to do.

I hope you're not anticipating all the answers here, but I do want to mention, I have been doing this health reform gig for 25 years, more than 25 years. My father told me about six months ago, he reminded me that it was 25 years. He said, you know, not much good has happened. (Laughter.) In fact, it's getting worse, and have you thought of a new profession? I said that I subscribe to the Winston Churchill adage that Americans will always do the right thing but it's only until they've exhausted every option first. I just have to believe in my heart and soul that we have to be close. So I'm paying it in here, and hopefully applying lessons learned in constructive ways to you and all those who are working in this environment.

I think it's really important as we talk about this issue, though, to understand that our current environment, and the environment that is likely to follow it in the absence of broad reform, is much worse than engaging in a thoughtful conversation about healthcare reform. When we talk about patients who have reduced access to drugs, that's what we're seeing today, and that's what we'll see more tomorrow in the absence of reform. We will see cost growth continue. We'll see more cost-shifting from the uninsured. We'll see extraordinary pressures on the federal government to cut healthcare costs not driven to reinvest to healthcare reform, but rather to dedicate it to deficit reduction, which will mean that there will be more pressures on the private sector to find ways to constrain costs and shift costs.

The reason I would suggest that the pharmaceutical industry and all stakeholders are thoughtfully engaged in this debate now is not just because they want to do the right thing but it's because the market share is going to and has declined substantially for the use of their products. With more uninsured people and with more people who have insurance incurring higher and higher cost sharing under the rubric of what's produced unnecessarily utilization,

we're seeing more people have less access to these drugs. That not only hurts them and hurts our ability to manage disease well and leads to unnecessary and expense of hospitalization, it means to the pharmaceutical industry that they're losing market share.

So whether for altruism or for legitimate business purposes, we're seeing, as we saw earlier this week with the president, people coming together to commit to working on collaborations to improve access for all Americans, but to do it in an environment that constrains cost growth with the recognition that if we don't, we'll have less access over time.

So I start this conversation to remind people that failure to act is a policy choice with severe and negative consequences. And there should be as much fear of not acting, if not more, which I think brings us together today, I hope in the most constructive of ways.

Obviously with the population that we care so substantially about in this room, those patients with rare diseases that can't bring market share themselves to the industry, we have to maintain some significant level of incentives, both for innovation and also desire for coverage. We have a situation where the trend line is worse and there is a desire for populations to come together to address that in this debate.

Whether we're talking about the Medicare population and the doughnut hole, where rare disease patients are particularly hit because they have very expensive drugs and they quickly get to that point where they're paying substantial dollars out of pocket, or the uninsured or the under-insured, there is a need to find a way to address this. I think you do have to address both the appropriate incentives for innovation and for offering these drugs, but also for coverage because I believe they complement one another. If we don't have coverage, we won't have resources for investment in these areas.

And where I'm encouraged is that I think there's a growing recognition that you can't do cost containment without coverage, and you can't do coverage without cost containment well. You can't do prevention well, you can't do chronic care management well. You can't eliminate cost shifting. You can't get insurance reforms. This population is also substantially victimized by current medical underwriting practices in our sector today.

It is in all of our interest to recognize that we have to change the system in order to fix the system, and that includes covering every single person. In the absence of which I think we'll have substantial dis-incentives to address this access innovation challenge that we face.

Secondarily, when we talk about innovation, and it's my belief that there is a constructive conversation that has to happen around the issue of follow-on and bio-generics because there's got to be that innovation has rarely been driven in an environment of a monopoly, that we actually have to have competition to spur innovation.

Then you get into this difficult challenge of, okay, what's the tradeoff for that access to competition, and that's a typical conversation about the issue of exclusivity, and I'm not going to get engaged in that today but I'll just say it's far past time that we stop talking and start walking on this issue and get it done. Not just because people need to have access to these alternatives,

and not just because we need to have access to them, but because the only thing that the market hates more than fear that there will be no spheres of exclusivity is this feeling of there's no predictable course of action. We don't know where we're headed, and let's give them a sense of where we go. That requires federal leadership.

As for the issue of off-label drugs and how insurers deal with that, again, in the absence of a meaningful healthcare reform discussion that puts on the table substantial insurance reform regulation, and a very honest conversation about what that means, we will not be able to get to that discussion about what rules we want to apply to the insurance issue industry as it relates to off-label, whether that means Medicare or the private sector.

So my message to you today is that we cannot address this issue well in a silo, that we have to do it in the context of our reform, and should we do so we will be able to look at options like appropriate rules governing off-label use if clinical protocols or compendiums or whatever else dictate that that is the appropriate medical intervention. And I think it will be harder to do so outside that context.

Now, I'm not sure how I'm going to conclude this, other than to recognize that whether this group of people can agree on something or not, this debate is occurring. The mark-ups are scheduled. This is going to happen in June and July. The desire is for the committees of jurisdiction to be conferencing by the time we get to the August recess. So we're talking about another month or so of significant discussions on the Hill about what gets included and what doesn't get included.

And even if it's a hook, even it's just a small level of a reference to this issue to get into conference, that's what you want because I assume that we'll be having long conference discussions if we get that far. Sometimes we have conversations outside the Hill, and sometimes we forget that the Hill does things to us, not always for us, and generally not out of any hostile act but just because they've got to get moving and their timetable is now.

The players who are most prepared and most constructive are the ones who are going to have the door open to them. I would think with this group of people participating today, to the extent we develop ideas and recommendations, it will be a very open door.

I guess, David, I think I'm going to conclude with this. You mentioned in my introduction that I worked for three senators in the first part of my career, in my first decade on the Hill. And my first one was John Glenn. He was who he is. He's this tough Marine, Paul Newman blue-eyed guy who tells it like he sees it. Not the greatest politician but maybe one of the greatest men I've ever met. And I hearken back to a time in 1986 when the space shuttle Challenger exploded. Many of you who were around, and most of you are old enough to remember, it's one of those rare times that you remember what you were doing when that happened because your child or whatever was watching it on TV because they wanted to see the teacher go up in space.

The space shuttle exploded, a terrible disaster in both technology and life, and Ronald Reagan asked John Glenn to go down and comfort the family members. And he did of course,

and he came back to Washington and he called us into his office and he said that this was a very difficult time for him. It recalled many very difficult conversations and memories that he had. And he talked about the odd-man-out fly-over formation where the planes fly over and one plane flies up into the sky. He said, this one was one of the most beautiful ones he'd ever seen because this plane flew up into a funnel cloud as though it was going up into heaven.

As he was describing this, he broke down and cried and it was a very emotional moment. You can imagine this tough Marine in tears. His head went down and his head went up, and he said, but despite it all, if you ever have an opportunity to do something bigger than yourself, seize the opportunity.

This is the opportunity that I think our debate around health reform offers us in this year, and I hope you all will seize it. Thank you.

(Applause.)

DR. KESSLER: Say that a company will invest and develop an orphan drug if there's a sustainable, reasonable business model on the other end. Sometimes that sustainable business model requires the drug to what a reasonable person would perceive is a lot of money. Is that issue, who bears that burden, what's acceptable, how we handle that question, is that an issue for the next several months? Or is that an issue that we have to hold off, or is that part of healthcare reform?

MR. JENNINGS: I think that it's part of healthcare reform and it's part of healthcare reform post-healthcare reform. Because healthcare reform never stops. There's not a static analysis. Just this is part of the bigger debate. I think every time there's a debate around any of the incentives for investment, and if they get integrated into the broader healthcare reform debate then it becomes the debate for today.

So for example, on the so-called bio-generics or follow-on issue, you're going to be talking about what type of special incentives there should be for that. Should there be an application of what we did under Hatch-Waxman for any type of products in that area? Should there be a discussion about insurance reforms to protect special vulnerable populations? I would suggest yes on both fronts.

I think that it's very difficult to break through for a whole lot of reasons. The committees of jurisdiction are predominantly focused right now on the broader infrastructure of healthcare reform and its financing. And very focused specific discussions around special population and orphan drugs, I would suggest, are hard to break through within that context. But that's why I say look for a hook, whether it's insurance reforms, or if they do bio-generics, or if they do any other policy that you think – what I call ride-the-train issues. Don't think you can invent something and say, I want you to do something new on this vehicle. Look at their vehicle and say, consistent with what you're doing on this vehicle, shouldn't you amend it to include this?

It's got to be part of the train. It can be the caboose. It's got to be connected to a larger engine because a stand-alone advocacy piece for something so relatively narrow is going to be a challenge. So it's got to be both a part of a policy discussion with specific recommendations.

And by the way, one last thing, don't expect them to invent the answer. You need to have some answers. Don't go up there and say, I think you should address this problem, and not have an idea as to what that means. Say, here's the issue that you're trying to address. We think what we're talking about is consistent with that, and here's an idea about how best to address it.

DR. KESSLER: So you're looking to save how much money? What have you got to come up with now? What's the latest number?

MR. JENNINGS: We can use one-year or we can use ten-year numbers, whichever will scare you least. I don't care. But just to put this in context, the baseline in health care over the next 10 years is about \$32 trillion or \$33 trillion, national health expenditures. No matter what we talk about here, we'll be probably between \$1 trillion and \$2 trillion in terms of investment over 10 years. So apples to apples, it's a relatively small reinvestment. And if it's in the context of broader healthcare reform, the goal, the objective, the commitment is to slow national health expenditures over time so that it's going to be less than 33, or certainly less than what it otherwise would have been within 15 years from now.

That's why when you hear Barack Obama talk about health reform, he's not talking about the first 10 years. He's talking about the second 10 years, and particularly in terms of maximizing the savings. But yes, you have to have some offsets from the current healthcare system, and probably revenues from outside of it to get this thing done. And to me in so doing it offers the opportunity to rationalize what can only be described as one of the most irrational systems ever created in the world.

DR. KESSLER: Let me open it up. We'll just go around. Dr. Dan.

BRUCE DAN: Chris, I want to take the advantage of asking a question of someone who's spent a lot of time thinking about this. You said the door is open for NORD, but it's also open for the American Heart Association, American Cancer, Diabetes, AMA, Nurses. The president has his campaign promises, the Democrats have their strategy, the Republicans have theirs. What's the chance that by the fall it will get done and get done in a way which will actually be better than we have now?

MR. JENNINGS: I can't imagine it getting worse than what we have now, and certainly into the future I think it will be a huge problem if we don't address this.

I always talk about healthcare reform in terms of comprehensive health reform is always more unlikely than likely. It's just a hell of a lot more likely than it's ever been. To me you judge that by the degree to which you see a president being invested in his policy and talking about it as a priority. I don't know if you could pick an issue on the domestic side that he's talked about more.

You look at the committees to see if they are invested in doing that. The last time around we had a chairman of the Finance Committee who would sooner die than do health reform. Now we have a chairman of Finance Committee who every night goes to sleep and wakes up talking about healthcare reform. He wants to do healthcare reform. All five committees of jurisdiction have made a commitment to move ahead and they have a timetable.

Does that mean that there is one vision of healthcare reform that anyone could tell you today what that will be? I don't think so. Does that mean that they are really on the hook to deliver? I'm pretty sure it does.

And I guess the last point is, look at what the stakeholders did on Monday with the president. It's kind of an interesting development. By the way, stakeholders outside of Washington I think are called special interests, but in just Washington it's stakeholders. I'm a stakeholder, you're a stakeholder.

What happened really is that the pharmaceutical industry, the device manufacturing industry, the insurers, the hospitals, the physicians, labor, SEIU, all got up and they said, we can achieve substantial savings in the healthcare delivery system and we will commit to working with you to that end. And my metaphor about this is, for those of you who swim – I tried this with someone who wasn't a swimmer and they didn't get it – but if you ever remember when you were young and your dad asked you to jump off the high dive and you were really scared, and you did it and everyone knew it was your first time and you walked up to the top and walked out the end of the plank, and you said, gee, everyone's watching me. I really have to jump, I really have to jump. But you could always walk around. You could always go back and go down the ladder, just be as embarrassed as hell.

Well, that's what happened on Monday. All those people went up to the top of the diving board. And sure, they can turn around and go back and not deliver and not be committed, but they will be chastised and humiliated for so doing. And I would suggest that if they just dive together and work collaboratively that it will not be as bad as they fear, just like as it wasn't as bad as I feared when I dived. That's what I hope is going to happen in the next few months.

DR. KESSLER: Eileen?

EILEEN OUELLETTE: I was asked last night to be specific in terms of something that NORD could do. I think one of the things that is emerging in the healthcare discussions is the importance of the medical home, not only in terms of improving care for patients but also as a cost containment issue. I was surprised yesterday to learn that NORD is not part of the patient-centered primary care collaborative.

This is a group that came together about two years ago now, founded initially by the American Academy of Pediatrics, Family Medicine, Internal Medicine, and IBM, ERISA, and has grown both in numbers and I think in importance as a group to try to improve the care for patients while making the case that this is cost-effective.

Certainly those of us in the medical profession in this group are very interested in the benefits it will provide patients by giving them a place where they have a physician who is really managing their whole care and coordinating it, knowing full well that for the insurers and the industry cost containment is really their first and greatest priority.

So I would certainly recommend that NORD become a member of the PCPCC. It's right around the corner in the Homer Building. All you have to do is walk a block and a half. Certainly the AAP would be helpful in having you join this. I think it's a very important and collaborative and something that would really help patients because if anybody needs a medical home, it's somebody with a rare disease.

MR. JENNINGS: I'm glad you mentioned that issue. This is a really important opportunity, yet a very vexing challenge for policy-makers. When people talk about healthcare reform, I always look at Bruce Vladeck when I'm talking about healthcare reform because there's nothing I can say that he'll just say it's so simplistic. But anyway, he knows everything. But you'll hear everyone say, look, the problem is going to be that 5 percent of the population incur 50 percent of the cost, and 10 percent of the population incur 70, 80 percent of costs, and you've got to figure out ways to do that and look at that mismanagement and lack of coordination of the system and how that affects that population.

I think instinctively all of us, and particularly a lot of people on Capitol Hill, believe that and are looking desperately for policy visions to achieve that outcome. But the challenge has been and continues to be that the scorekeepers, the Congressional Budget Office and others, have not seen many models that do much more than improve care but not necessarily constrain costs. I don't necessarily believe in those models but I want you to know that they are what they are and they do create a challenge for policy-makers to come up with the appropriate and most thoughtful way to do this.

As relates to medical homes, that is the theme of the day, theme of the year. People want to do something in those areas in order to prevent and to better coordinate care for the chronically ill. There can be no dispute that anyone who has had a family member go through this system, who could say today that they know how to navigate it, or they don't do anything other than get screwed by it, then they haven't been through the system.

I know through personal experience and everyone else in this room probably does as well, so I think we're quite confident that that can be done better. I would say in particular where there's maybe the best opportunity for managing chronic illness is first and foremost the better management and coordination of the use of prescription drugs, predominantly because we have platforms more advanced through e-prescribing and elsewhere than we have in most other elements of this discussion on chronic care. And secondly because the first intervention of almost any doctor for almost any chronically ill population is a prescription.

We all know that for the chronically ill, there usually isn't one prescription. Frequently there are four and five and six. So coordinating that better, managing it better, stopping the synergistic and interactive and negative effects of mismanagement of drugs actually offers one of the best opportunities in that setting to constrain costs and improve care. And as a consequence,

since obviously NORD patients are disproportionately chronically ill, i.e., they are defined as such, they may well benefit, and that would be an idea that you suggest that's worth taking back to the president. I'm sure he just heard that, Peter just heard that, but I'm not in a position to rubber-stamp anything up here.

DR. KESSLER: Bill?

BILL SCHULTZ: As you know, and as you've just really said, in a lot of the areas of prescription drugs there are various tools you can use and think about to reduce costs. You can think about generic drugs, you could think about comparative effectiveness studies and so on. Unfortunately we are in the area where none of those tools work. We're in an area where typically it will be a single drug for a very, very serious disease, and the traditional tools of competition don't work.

My fear is that there's going to be a real reluctance to get into this area in healthcare because of the cost. Do you have any ideas about how you address that? Or this group should address it.

MR. JENNINGS: I probably have ideas. I think that there are – I guess I would want to define cost a little bit. There's cost to the patient and there's cost to the insurer, the cost to the government. And of course to the extent that you have poor benefits or high out-of-pocket cost, the patients say there's cost to me. To the extent to which you cover those, then it's cost to the payer, the insurer or the government. Then the third way to deal with cost is, can you constrain what you're paying for those particular products. That's really – I think those are the options that you have.

One way of course, and the easiest way that generally we do it is we try to cover more of a portion of those costs for people who are very disproportionately hurt by that. That would include looking at mechanisms on limitations on out-of-pocket costs for particular drugs, or things like that. On the pricing side, you're right. PBMs can't do much about negotiating better prices if there's no competition. And it's very difficult for any purchaser to do so.

One could argue – and I'm not arguing this – but one could argue that when people talk about why don't we have Medicare directly negotiate on pricing, you can go through all these arguments but in the end of the day it's difficult to either pass politically or even argue from a policy perspective that's necessary where there's other drugs out there because at least according to the Congressional Budget Office they argue that the PBMs do just as good a job as Medicare when you have the use of a formulary and you negotiate from a power of that.

But when it's a new drug, or when it's an only drug, that may be the time where you may want to talk about federal negotiation. Again, that's an anathema to many people maybe in this room and on Capitol Hill, but it's something to contemplate. As an advocate of a NORD patient, you really don't care whether the cost comes from the coverage or the cost comes from the payment mechanism. You just want relief.

That's what I can say I think are the most viable options right now. I'm not saying they're easy but that's what I think you could say right now.

DR. KESSLER: Just keep on going around the room.

FRANK SASINOWSKI: Chris, one of the things that has come up obliquely and that you talked a little bit about is off-label use. We're at a point in time in which for many people with rare diseases, their only recourse is to an off-label use of a drug. My son with Tourette's is on an off-label use of a drug.

We see that there are twin threats to continue that option for those with rare disorders. One is the FDA Amendments Act of 2007 which created REMS (Risk Evaluation and Mitigation Strategy), which encourages the FDA to try to restrict the use of therapies just to the labeled indication. So there's a public safety movement that is constraining access by patients to off-label use, which might be necessary off-label uses.

And the other is from what I'm asking you to address, which is, under cost controls, as we're working through the healthcare reform system, is there also a threat that you see in the current pieces of legislation working their way up to hearings next month?

MR. JENNINGS: On the cost containment front for off-label? I don't see any threat in terms of anything new and different in being applied. It is after all a Democratically controlled Congress and I don't think that they would want to constrain. I think that, again, there's an opportunity maybe to talk about the definition of medically necessary as it comes to drugs. A well-managed, clinically run formulary can be good care. I believe that.

That does not mean that you ban or limit or constrain access to people who need the drug if it's medically necessary. That's poor medical judgment. Maybe in the definition of medical necessity or coverage for plans operating in the exchange, for example, in all these models on the House and Senate there is either a federal or a state type of exchange that regulates the insurers and applies insurance regulations, particularly as it relates to access. Access is generally meant to be access to the insurance product, but maybe it could also be defined as to some extent how they administer drug coverage.

Now, that's a heavy lift because they don't love to micromanage how that works, but if you can prove that this is a huge problem, it seems to me that no one on Capitol Hill is going to say that we want to affirm or in any way allow drug coverage policies to be utilized to exclude populations from medically necessary.

And in fact you can use that not just in terms of access piece but also in terms of almost an implicit medical underwriting approach. In other words, you can say if you really are banning the use of medical underwriting – that's what we all say – then in effect you don't want to allow this type of coverage decision because in effect it's sort of a pseudo-medical underwriting. It's saying, don't come here, right? Anyway, that's at least my instinctive response to that.

DR. KESSLER: Tim.

TIM COTÉ: Chris, taking for a moment the more modest proposal, because you're suggesting that the community come forward with very concrete proposals of universal coverage for all on-label use, for drug costs for products that are actually approved for orphan indications. We know that there are 339 of them right now. There are databases which should allow us to calculate what those costs are.

Has that been done? Do we know what that cost is? Because it should be right out there and if you can ask for it, we should know what it is.

MR. JENNINGS: Well, my instinct is not to ask for it. But you know, people don't know what it is and I'm not sure you want to know what it is.

DR. COTÉ: I would suggest that it's a very small proportion of all drug costs.

MR. JENNINGS: My experience with the Congressional Budget Office is they tend to over-estimate costs and under-estimate savings. There's also, by the way, a question that we should look into, and I don't know the answer to this, which is the degree to which all or some or few plans do block access to off-label. I mean, I don't know the answer to that.

I'm sure it exists and I know that plans do that. I don't know whether it's everyone or how it's done. Before I ask anyone to score it, I would try to get an answer to that because I don't want to pay for things that are already being paid for. Know what I'm saying? I'm saying be careful with that one.

DR. KESSLER: Steve, then Bruce, then we'll go on.

STEPHEN CROFT: One of the problems with so many patients with rare diseases confront is getting the diagnosis. After they get the diagnosis, which is problematic, how do we ensure that the patients actually get into the hands of practitioners, medical healthcare providers who understand the disease, who can give them the best quality of care? It's something I think NORD's tried to work on in improving the education of the healthcare providers in the country, but that's another issue for later in the afternoon.

How will this play out? Will they have access to the specialists who really do understand the disease? It may need referral up the ladder two or three stages from the normal referral patterns.

MR. JENNINGS: Well, my instincts, just from hearing you, I concur that's a huge issue. Workforce issues are an issue that's pandemic to this whole health reform issue. I mean, one could say you're talking about access to appropriate specialists who really understand what they're doing. Most of the debate and discussion right now is that we don't have enough primary care people that people can access, and there's a fear that if we do cover everyone, we will be under-manned on that front.

I do think there's a whole workforce challenge that needs to be addressed. Again, my belief is that it can be addressed through two things. If I were listening to you and responding initially without thinking about it, I would say, well, go to the Health and Energy and Commerce Committees and talk to them about you're doing something on workforce issues. Have you thought about the adequate training of specialists in these areas? So you have the front-load discussion.

And the back end discussion is access to those people. Have you thought about that in terms of insurance coverage or rules or parameters? So you kind of front end/back end it as a policy.

I think there will be a hesitancy by those on the Hill to do too much writing and drafting and crafting in this area, predominantly because if you do special access to specialists for one population, how do you deal with it in another. They're worried about too much micromanagement in the drafting of this language. And one of the lessons learned is that there's a belief that if you weigh down this bill too much you won't be able to pass it at all.

I hope I'm giving some just general guidance as to how I would deal with it, recognizing where they come at this as they're drafting these specific provisions.

DR. KESSLER: Dr. Vladeck.

BRUCE VLADECK: Let me just reinforce Chris' last point. It will be a miracle if we can get everybody covered. That's a lot to ask in one piece of legislation and they'll have to figure out how to pay for it. This is not going to solve all the problems of health care. Health reform is not going to solve all the problems of the healthcare system. To the sense that anybody tries to see to it that it does, it's going to reduce the chances that we'll get everybody covered.

The Congress is not going out of business after this fall either. So I just hope everybody understands that you don't fix a system as complicated and multifarious, with as many interests as the healthcare system, with one piece of legislation, no matter how important it is. Let's get people covered and figure out how to pay for it and then next year we can start fixing everything else.

The other thing that's troubling me about this conversation is, and it seems to me a reflection of how badly screwed up our thinking is on all these issues. In terms of adequate payment for care for persons with rare diseases, whether it's for drugs or for other kinds of services or things of that sort, as somebody who used to run a big insurance program, my reaction is, well, they're rare diseases. And what health insurance is, ought to be, is a way of pooling risk such that the minority of the population that has very considerable expenses has some mechanism to defray them other than their own resources.

So in fact, if we have our heads screwed on straight, paying for the costs associated with people with rare diseases is the easy part of designing a healthcare system because that's what insurance is supposed to do. I mean, everybody talks about 20 percent of the patients account for 80 percent of the costs, as Chris referred to. That's because costs are distributed along a log

normal distribution, like every other phenomenon in the world. Eighty percent of the area of the curve is under the right-hand 20 percent of the distribution.

Our problem with healthcare costs is not what we're paying for those 20 percent. It's what we're paying for those other 80 percent. As my successor Tom Scully used to say, it's not the real life-saving drugs that are killing us. It's Nexium that's killing us. (Laughter.) It's not the rare biotechnology products that are killing us. It's the brand-name statins. That's where the money's going in this system.

I think if to the extent that NORD and its constituent organizations are worried about somehow being singled out in cost containment because of the visibility or the unit costs and so on and so forth, I think there's a relatively easy case to make that it's only thoughtless, dumb cost containment that focuses on a very small number of cases. The big money is in the middle of the distribution.

Having said that, I just would put one modifier or caveat to that, which is that if I ran a pharmaceutical company, particularly one that had a range of products, I would figure out that rational insurers aren't going to beef at all about the \$100,000 a dose drugs for the rare diseases. They're going to be much more concerned about the competitive drugs, while I've got to do pricing strategy. I think there is enormous public image and political vulnerability on the part of the pharma and bio industry from very high unit prices, even if from a macroeconomic point of view they're not really a serious problem for the payer. So I would just qualify the general statement as that.

But again, in terms of NORD's relationship to health reform and cost containment, I think the fact that you're talking about rare diseases, if people understand the basic economics of health care and health insurance ought to be a very considerable asset that you ought to be able to talk about in those terms.

MR. JENNINGS: Just one response to Bruce's point. You're not going to see this Congress produce a defined benefit package. But I think what they will do, and maybe should do, is to say there should be, under any benefit, catastrophic protections. That's what insurance is. There should be prescription drug coverage because if you don't have prescription drug coverage, you're not going to manage the chronic illness well anyway.

And if there is a catastrophic benefit, it might be in the discussion of a cap on out-of-pocket costs. If there's a cap on out-of-pocket costs that applies to prescription drugs – in other words, some of these insurers, they don't apply the drugs to the out-of-pocket cost. There's all this sort of games playing. You may want to think about protecting people from those types of cost burdens in a significant way.

Again, there are different ways to skin this cat here. That may be one of them.

DR. KESSLER: I want to go on. I think you set this up, Chris, brilliantly in the discussion. I want to go on to our other speakers. But by the end of the day I want you to come back to this point, if there is a catastrophic benefit, what are the tradeoffs that we as patient

advocates or innovators, what do we need to be able to trade in to make people comfortable, if we're asking for these catastrophic costs to be covered, that we're being responsible to?

What's sort of the policy that we could advance this time around? So just think about that and we'll come back by the end of the afternoon to that.

Sol Barer, who is CEO and chairman of Celgene, an organic chemist by training.

SOL BARER: It's a pleasure to be here. Thank you for inviting me. I'm going to make some remarks, so just one caveat to my remarks. I'm generally pretty unsubtle in terms of what I say, so it's pretty direct, and I have some strong beliefs on this, and some are very consistent with what we heard this morning and some may not be.

But I come to you not as a public policy expert. What I do come to you as is in a dual role. One is a chairman and CEO of a biopharmaceutical company, a company that I've essentially worked in my whole adult life, and focused on discovering and developing and commercializing drugs largely for rare and orphan diseases. So this is a very important area to me professionally.

I also come to you as a father of four and a grandfather of up to 10 now – it grows every day – and with children and grandchildren that have rare diseases. So I have a dual role. And my personal passion is finding drugs for serious debilitating illnesses. We focus on orphan and rare diseases. So please recognize that.

I'm going to divide my presentation into three pieces. First is just talk about some facts which we've already discussed, which everybody knows, but which I think bear repeating. Number two is, I've identified four things that I think inhibit access, development of drugs for rare diseases. And the third is some things we may do, either strategically or specifically that will help access and the development process for rare diseases.

I'm not going to solve healthcare reform. I leave that to wiser minds. But hopefully some of what I talk about will be helpful as we develop drugs.

Some obvious truths. And you know all this, but there are 6,000 rare diseases, 25 to 30 million patients. And it's easy to say the words "many are profoundly debilitating and fatal" and they affect some of the most vulnerable members of our society, our children. But staring into the face of a child who has one of these rare diseases – I got home late last night before I got on a train this morning and I was at a children's brain tumor foundation. Those words are bad enough, but when you stare into the face of a child that has a brain tumor and is five years old, it gives you an emotional impact. I think that's what drives a lot of us in this industry.

So of these 6,000 we have been tremendously successful with our orphan drug products, with NORD and the Orphan Drug Act. We would have very, very little compared to what we have now, but still out of the 6,000 we have a few hundred therapies. There are thousands of diseases that have no therapies, and how many therapies are there that truly change the course of

a disease? So there's a lot of work to do. I think we've made a lot of progress, but there's a significant amount of work to do.

So another truth to me, and a passion for me, is that drugs are developed by companies. The NIH does great work, many of it in combination with companies. Academia does wonderful research and without academia I don't think this process would go on. I think there's governmental input that is very, very good. But at the end of the day the ball is given, whether it's on the five-yard line or the 95-yard line, to the company and it is the company's responsibility to bring the drug to patients. If the company can't do that, it is out of business.

I've said many times, our mission as a company is to make sure that we develop new, not incrementally better therapies but significantly better therapies for patients. If we can't do that, we're out of business, we have no role in society. But I think also as a corollary to that, companies like ours, we need to make a profit and we need to show a return on investment. Make no mistake about it.

So the development of therapies, orphan drugs, is incentivized but there are areas – and we touched a number of these that really could be improved. We have orphan drug exclusivity. I think it could be better, and I'll give you one specific example of that. I think that the reimbursement for oral drugs is an issue for patients. Their access to that is a problem, certainly as compared to other modes of therapy. Patients should not be discriminated against if the only drug they have is an oral drug. I'll mention that in a couple of minutes.

In addition, we've talked about off-label. Complicated subject, but nevertheless many of the orphan diseases are treated with off-label drugs. My son also takes an off-label drug for his condition. It's not a great drug but nevertheless reimbursement can be an issue associated with this.

I do want to mention intellectual property because I think intellectual property is an important subject, and we haven't talked that much about it but I think it's worth speaking about.

So let me talk about orphan drug exclusivity. We all know that currently there's a seven-year exclusivity. This is compared to European Union, which has an up to 10-year exclusivity. That is really an apples to oranges comparison. They are not the same. At the end of the day you do have exclusivity but there are some bells and whistles on one which there aren't on another one.

But I don't address that as much as addressing the fact of a specific example where if a company develops a drug for a rare disease, they get exclusivity for seven years. If that drug, and it's probably more common than people think about, if that drug has activity in another orphan disease, they then have to develop and they can get orphan drug exclusivity for another seven years, which extends it.

But the truth of the matter is, and practically speaking, the drug goes generic after seven years, so there's just no benefit for any company to develop a drug for more than one rare

disease. So that's something for us all to remember. And it happens in more cases than people think it does.

We need to understand the influence of orphan drug exclusivity. The Office of Orphan Drug Products at the FDA has been fantastically successful, with the Orphan Drug Act and NORD, in bringing this to a new level. But I think we really have to examine is there a way for us to even go to the next step.

Oral drugs. This is a quote actually that was in the New York Times by a brain cancer patient, called, "Because it was a pill, I had to pay, not my insurance." So there's a unique situation, and I'm sure many of you know, especially in terms of Medicare Part D versus Part B, is that if you take an oral drug – and sometimes that's the only thing that's available – a patient has a higher co-payment and a patient also has to pay through his doughnut hole. This is thousands of dollars for a patient with a rare disease.

For full disclosure, we sell oral drugs and we sell IV drugs. We sell more oral, but we sell hundreds of millions of dollars worth of IV. So for me it's a question of equity; it's a question of a level playing field. One can actually make the case that many of the oral drugs are more patient-friendly. They involve less visits to hospitals or doctors, and then from a pharmaco-economic perspective are better. But at the end of the day I think it's important that we level the playing field, so that a patient can get reimbursed for his disease, or what she needs, regardless of the modality of the treatment.

Another point is off-label. Rare diseases are often treated by off-label drugs. It is a very challenging reimbursement challenge and not all payers will pay for off-label drugs. It does vary based on peer review publications and other things. And I'll make the suggestion later on in terms of one approach that can be used. And companies like ours do give out free drugs for people who cannot afford it. We do have a variety of clinical trial programs but they can only go so far in terms of what is needed.

Intellectual property is in essence the bedrock of much of the pharmaceutical industry. Our founding fathers made sure that part of our system is that when you make a discovery, you make an invention, you get a protected period of time to practice that invention in essence. After that, in the case of a pharmaceutical company, that drug goes generic. It is given to society. But that is under attack for a variety of reasons. I won't go through the legalities of it. It involves making a newly issued patent more vulnerable, existing patents will have less of damages if somebody infringes, and existing patents can be attacked more freely.

So I think it's very, very important from an intellectual property perspective to understand the implications of weakening that intellectual property.

I just want to give one personal example. There is an NFL linebacker, Elijah Alexander. If you know football players – if you don't know – this is an imposing guy. He's 6'7", 6'8", really looks like a strong guy, not somebody you want to have an altercation with. At the age of 35 this guy, at the peak of health, at the peak of physical fitness came down with multiple

myeloma. He discovered all of a sudden, now I need a drug and there are no drugs that are available during that period of time.

Nineteen thousand Americans are diagnosed every year with multiple myeloma. Equivalent amounts proportionally around the world, 10,000, 11,000, roughly half of them will die every year. If you go back to 1998, you had an average survival of two to three years for this. There had been no new therapies in decades.

We saw an opportunity in that rare disease, though it is a more common disease than some of the very rare diseases we're talking about today. We commercialized the drug thalidomide. That was a very famous approval. Dr. Woodcock, who was here this morning, played an instrumental role in that and by doing so really changed the course of medical history. It was approved for a rare condition, erythema nodosum leprosum, which is an inflammatory condition of leprosy, and then it was eventually approved for multiple myeloma in 2006.

Today the average lifetime is double at least for myeloma patients. It's by many estimates greater than seven years if diagnosed early and if appropriately treated. There are three drugs on the market right now for it. Part of the reason is, yes, there's a regulatory path where there wasn't one before, and we understand the clinical aspects of it.

But there's something more. Many small companies, and there's about 20 of them who have drugs in the pipeline, looked at (other) companies that have been successful in this disease, like Millennium and Celgene, and say we want to be successful to. We see a pathway. We're going to develop a new compound and we're going to be just as successful. Whether they're right or wrong is a separate issue, but they're incentivized in which to do this, based on success.

So what do we need to do? I think in terms of orphan drug exclusivity, in one way or another, try to incentivize additional research on compounds that have activity in certain orphan diseases. There are a number of ways in which we can do that, and it's not a huge thing but I think it's very, very important because I happen to be a believer, despite chairing an \$18 (billion), \$20 billion company, I'm a scientist at heart and truly believe, against much evidence, that at the end of the day science solves many, many problems.

If you look at 6,000 orphan diseases, many of those diseases you can probably lump together in terms of mechanism of action of the disease, the pathology of the disease, the science behind the disease. So as you start solving some of those problems, it's going to have implications in other related diseases.

I think it's important for all orphan drugs to be reimbursed equally, regardless of modality associated with it. I think reimbursement of off-label has to be looked at very carefully. There are a lot of implications. But for example in the area of cancer, if it's listed in a prestigious compendium like the NCCN, the National Comprehensive Cancer Network, and has peer review publications, then that should be something that is good enough as a basis for argument's sake for reimbursement for some really rare diseases, and intellectual property has to be respected.

So at the end of the day it's important for us to take action now. Just let me summarize by saying that in my heart I believe very strongly that we've made significant progress in science. We heard some great things this morning about the interaction of academia and government agencies and private industry. I think if we do that, we will indeed find treatments for many, many more diseases than people currently anticipate. Thank you very much.

(Applause.)

DR. KESSLER: Thank you. David.

DAVID MEEKER: I think most of the points have been touched on today, but I'm going to go through it quickly. It's probably worth reinforcing a few of them. Starting out with this question of access, and it's worth asking the question of what are we trying to preserve access to. The drugs or the treatments that we're talking about here are almost universally potentially lifesaving medications. I'm quite confident that there's no rash out there that affects 100 people for which there's some biotechnology company that's working hard to develop a therapy there.

So almost by definition the therapies that get selected for pursuit in this area are ones that are potentially life-saving. Is there a system we're trying to preserve here, or is there something we're trying to improve, the ability to access potentially life-saving medications?

We've seen this need in many different forms. We've done a fair amount of work in what's called lysosomal storage diseases.... I'm going to argue that virtually everything traces back to rarity, so I'm going to spend a minute exploring that concept again. I talked about approvability this morning, this idea that what disease is too small, and as a public company, for-profit company the simple flat, straight-out answer is, is it approvable? If it's approvable, I would say in today's world I have a reasonable level of confidence that we could figure out a business model that would make that work. If it's not approvable, it doesn't matter.

Is it sustainable? Again, if the world changes in such a way where this business model is no longer sustainable, our challenge is once you develop a potentially life-saving drug, there's a moral obligation to continue to make it available to patients who need it. It's very hard to pull back from that scenario, but I can guarantee you that the ability to then pursue the next drug is gone, and the interest of the community who is watching you as a company get stuck in that position has taken that lesson to heart. So all of this of course when you get it right links to innovation.

So what is rare? Orphan drug legislation, 200,000 affected individuals. Fortunately I think we've heard the Nexium and Lipitor story but I think it does frame it. Millions of individuals taking these drugs, \$12 billion a year spent on Lipitor. And you get down to the point where some of these diseases are in the hundreds of patients that we're treating.

I'll just highlight Serazyme is a bit of a poster child for this area, the treatment for Gaucher disease. It costs \$200,000 a year. After 15 years on the market approximately 1,500 patients are on therapy. That's the sum total. There are 100,000 patients with Gaucher disease,

half the number that would be required to fit the definition of an orphan drug. The cost of this drug would be proportionately less. So again, rarity is on a continuum.

The point here is that many of the diseases, we talk about are small diseases. Here's Duchenne muscular dystrophy, 10,000 infected individuals. You hear about large diseases being shrunk and now they're orphan diseases, because the genotyping has identified a subset that allows it to qualify as a disease. Here's an example where an extremely rare disease, Duchenne's muscular dystrophy, PTC therapeutics, who we're partnered with, has developed a drug which treats only 13 percent of that 10,000. So again, that has shrunk even further.

So the rarity challenge is awareness, and this has been highlighted, and again I would urge NORD and all of us to think about doing a small number of things extremely well. Awareness in a rare disease space is one of the biggest barriers. Fifteen years in the Gaucher disease space, and there are still patients with advanced disease who are being discovered at a time when there's a drug that's available, if you were treated early you had a potential of living a normal life. Can't make the diagnosis if you don't think of it. Simple things like where do you send the test. Expert centers have been highlighted.

And this idea that knowledge is limited and that's the world that you start out in, and simple things like is there an animal model against which you can test. And one of the take-homes which I'm going to highlight is the natural history. The value of knowing that natural history as you embark on this is just tremendous.

So you go into the regulatory pathway, again discussed this morning. Rare disease efficacy proving a positive, safety proving a negative. Numbers are small. You have a disease like Gaucher disease where you can reverse something and the response is fairly dramatic, that clinical trial paradigm may not be so difficult. And in fact, Therazyme was approved on a 12-patient clinical trial. The reality is the world doesn't look for the most part like Gaucher disease, and the therapies that are being approved don't have that kind of visible reversible effect.

This is Pompeii disease. This is the infantile onset form of the disease. Ninety percent of these infants die at one year of age. We started out developing an enzyme replacement therapy along with a number of other interested parties around the world. The question was how do you do the trial. With 90 percent mortality obviously you don't have a placebo control group. The FDA said can you get the natural history. So the natural history, although it was understood, was not understood at a level that met the regulatory guidelines.

So we went back and retrospectively put together the natural history study. That was the first thing that we did. We then ran the clinical trial where we had this result, which dramatically changed the natural history of this disease. So three years, four years out, 50 percent of these children are still alive, so fairly dramatic. That's fantastic. The reality is 50 percent of those children are still dying, albeit not as rapidly as originally thought, so not the best outcome.

Then we had a study which was done in Taiwan, so we wanted to know if the natural history in Taiwan was any different. But what they did in Taiwan was they did newborn screening, and in Taiwan they were able to screen virtually 100 percent of the population. These

patients were identified at birth. In our original trial, we knew you had to be treated early, and to get into that trial everybody had to be enrolled by six months of age. To get 18 patients, which was the size of that trial, we ended up flying patients as soon as they were identified, from wherever they were in the world. So a patient from Latin America was flown to Duke. A patient from Japan and their family was flown to the U.K. Two patients from the Middle East were flown to Germany, all so they could participate in this trial and we could get that trial done.

The beauty of the Taiwan example is by newborn screening and being able to treat patients within weeks, they now have an outcome which is dramatically different. Again, it highlights how little we know when we start pursuing research in the area of rare diseases.

This is Fabray disease (slide). This is a family. All those individuals in this family are affected. There's 100 total. These are the 40 patients in the family who are affected.

They don't look like the Gaucher patients. Some of these patients are on therapy, some aren't. They don't look different before and after being on therapy, so that kind of reversal is not so obvious. When we started doing this trial, again, we knew nothing about the disease. What we didn't understand is the fact that these patients scar and they scar early. So when we ended up running our trials, this was the result – a p-value of .058 -- and after vigorous debate with the regulatory agencies, we did not make it. The drug was approved but we do not have full approval because we came up short. We came up short because we didn't understand the disease the way we might have.

I'll leave you with just a couple of thoughts on this concept of sustainability. These are all stakeholders, the patients in the center (slide). The biopharmaceutical industry, healthcare system, academia, and the economy, which is struggling to support the needs of a healthcare system. And this is the way that picture often looks, and we have discussions with governments around the world where the minister of trade and industry will come in on one side and say, it would be just great if you could invest in our country and we're going to give you a few tax breaks, and won't that do it?

Then the minister of health comes in and says, in a totally unrelated conversation, you've got to give us a price break and we're not going to reimburse your drug or whatever, and it's a totally disconnected conversation. The reality is that the world should look like this. This is a world that is totally aligned once the debate is properly framed. One of the things that worries me, and we as a community, is we have to learn to talk about this in a way which shapes the debate in a way that it doesn't get distracted or hijacked by people who have their own agendas. As you can see, the major thing for the biopharmaceutical industry is this: tell me we have a market. If we have a market, we can figure the rest out. We'll be willing to invest enormous amounts of money to get to the goal.

The healthcare system, they want innovative solutions. I mean, having a disease cured can't be a problem for the healthcare system.

Academia, they follow the money, research funding. And again preserving the ability to have that in place. And economies at the end of the day, high tech jobs out of the healthcare industry is not a bad thing. .

Mainly this concept of the circle is sustainability. All of these things are linked and you end up at the end of the day with more medicines. So I'll stop there.

DR. KESSLER: Terrific. Thank you. (Applause.)

Dr. Javitt, what I'd like to do is I want to tackle two issues on access and cost and see if we can get some consensus on them. In about a minute I'm going to turn it over to you and ask Francis (Collins) to come back and sit up here because we're going to ask what the future world of genetics is, the implications for all rare diseases and whether everybody's going to be a rare disease, what we will end with.

But I want to focus on access and cost, and I want to focus on two very specific issues. The first issue is the lifetime limit, and I want to follow Chris' advice, is why I pressed him. For now it's either healthcare reform I or healthcare reform II, whenever it's the right time. Let's see if we can deal with the issue of how we're going to deal with lifetime limits, the need for catastrophic coverage, and if there is catastrophic coverage, or a guarantee of no lifetime limits, is there a reasonable way to manage those patients and say, look, as long as there's catastrophic coverage we need that, but in trade for that there is a patient home, there is coordinated care, there is some way that we are managing that patient well. That's the first question.

So I want to go around. Is there a consensus on what we need to do on catastrophic care/lifetime cap? And second, I want to talk about off-label use. Should the position of NORD be off-label use needs to be reimbursed, and then the question becomes, is the tradeoff to the payers, there needs to be some peer-reviewed publication, there needs to be some compendium, what's the tradeoff. So those are the two issues that I want to see for the next half-hour we can give you advice, so either in this next round of several months as part of healthcare reform there are openings, there are hooks, or they are later. But where are we on both of those issues? Who wants to start? Feel free to do deal with both of them. Tim.

DR. COTÉ: Thank you. Dr. Meeker, this is directed at you. I've been in this position for about a year-and-a-half and I do a lot of speaking. One thing I can consistently count on is the level of outrage that people have when they talk to me about a therapy that costs \$200,000, \$300,000, \$400,000 per year for a patient. Of course my first defense is to hide behind the fact that FDA doesn't regulate price. Eventually that wears thin, so my response instead is, well, exclusivity lasts seven years but knowledge is eternal.

Can you tell me what you think is going to happen when exclusivity runs out? Is there actually going to be competition on these products? I know we don't have a lot of experience with this, but I'm hoping that the prices will come down. Do you have any view on that?

DR. MEEKER: Yes. First and foremost I would just say pricing is not a deep, dirty secret, and I often find it's one of those things you say, well, don't talk about pricing, or the company's afraid to talk about pricing. If we're afraid to talk about pricing, it's too much.

Where I started this morning's conversation or discussion was that that price point, I'm going to argue, is what has driven the willingness of a phenomenal amount of investment in the area of orphan diseases because it's what supports this concept that there is a sustainable business model.

Now, if you take Gaucher disease, which is \$200,000-plus per year, it's based on a per-kilogram basis, 1,500 patients puts you in the range of \$300 million-plus, is what the United States, different payers pay for the treatment of Gaucher disease. MPS-1, which is also in that portfolio, is 100 patient-plus at \$200,000, so that's in the range of \$20 million a year, which we share with our partner, BioMarin, so that's a shared economics.

We would not have been able to invest in the MPS-1 opportunity if we had not had Gaucher disease in our portfolio. So the first answer to the question is, I do think that this is a price point that allows that business model to work, and I think that observation's been validated. Now will competition come in? The answer is I think, yes, and the competition is here.

If you look at Gaucher disease, which is a much larger opportunity around the world, the reason it's a much larger opportunity is because we make it available in 100 countries around the world. So there are two other companies who are pursuing that. Is there competition in the MPS-1 arena? No. My guess is I'm not sure there will be. I think that opportunity is just too small for others to come in and do that. But at the end of the day it's a very small amount of money that's being spent on 100 children with MPS-1 and the opportunity to have their lives transformed.

DR. KESSLER: Help me on the two issues. Catastrophic/lifetime cap, off-label use, reimbursement for both. What should the policy, what should NORD advocate? Bruce?

MR. VLADECK: I'm missing something. I don't think it's a hard problem except in academia. As a practical matter, we have, for example, stumbled into it but we have hundreds of thousands of Americans with severe developmental disabilities who are in their 40s, 50s and 60s, supported both in terms of income support and healthcare by public funds, not as well as should be in a variety of cases, although most of them get pretty reasonable medical care because there's no alternative for a civilized society.

DR. KESSLER: Translate that into policy.

MR. VLADECK: I think there are real questions about qualitative improvement in both the nature of the income support and the quality of the health care which don't get addressed because they're not as politically visible as they can. But you can point to all kinds of folks who incur enormous expenses on the healthcare system every year for years and years and years. No one would seriously argue that we stop paying for their health care, even though without it their mortality would be pretty rapid. I just don't see that as a debate.

The issue has been, absent universal health care, the desire of payers to shift the responsibility onto the government. People understand that they're not going to be liable for killing a patient who hits the \$1 million cap because Medicaid's going to pay for the rest of that patient's life.

DR. KESSLER: Just articulate it. For patients who have rare diseases.

MR. VLADECK: If they have health insurance coverage, if we have universal health insurance with catastrophic coverage going in, I can't imagine a situation in which there would be a cutoff.

DR. KESSLER: So that's the policy? No cutoff, no lifetime cap, patients with rare disease –

MR. VLADECK: And if it gets into health reform inadvertently, we can fix it real fast because I can't imagine any elected official condoning such a policy.

DR. KESSLER: So we're set on that?

MR. VLADECK: No. We have to have health reform in order to get – (laughter).

DR. KESSLER: No, I understand that, but as part of healthcare reform, NORD has to advocate for catastrophic coverage with no caps for patients with rare diseases. Right?

MR. VLADECK: No. NORD has to advocate for catastrophic coverage with no caps, period.

DR. OUELETTE: We need more than that. Only 1 percent of children ever need catastrophic care, but 100 percent of them need preventive health care, and they need immunizations. We can't just look for catastrophic care because they won't be covering the children in the 99 percent of children, in addition to the children who have rare diseases, who need a different benefit package and who need more comprehensive benefits package.

So I would urge NORD not to simply look for catastrophic care, but certainly at least for children to make sure that the benefit package includes first dollar coverage for preventive health care.

DR. KESSLER: Bill.

BILL NOVELLI: David, I know what you're trying to get us to. It just seems to me that this Bruce is correct, and that it has to be a given, a going-in position on NORD's part, I think, on the community's part, that as Chris Jennings said, this system, this reformed system has to bear the burden for vulnerable populations. We cannot have care being rationed in any way. I don't think the public would stand for it.

There are some things that are, as you say, tradeoffs. We should be working for secretarial (of HHS) negotiating authority, especially for monopolistic drugs. The biogenics and follow-on biologics, the medical home, those kinds of things. Try to help to get those into place because they will have cost containment implications.

DR. KESSLER: Steve.

MR. GROFT: I guess one of the issues I see too is the need to really determine what the prevalence is of many of these disorders really are. I mean, we don't have any idea. If we could come up with some way of obtaining reliable data, say of perhaps we could identify these diseases, how many patients have the disorders, we could get a little bit more accurate estimate of what this is all going to cost us. I don't think we have that information right now on so many of these disorders.

I don't know how to get it. There are multiple systems that perhaps we could start to tap, but I think we need to find some way to generate that information, that we can counter the arguments about how costly this is going to be to provide that coverage for these patients.

DR. KESSLER: Help me on the nonapproved use, reimbursement for nonapproved uses. Is that simple to you also, Bruce?

MR. VLADECK: Again, I come at this differently from everybody else. To the extent that off-label use for a whole variety of conditions is a growing phenomenon, and I don't know if it is or it's just increasingly talked about as a phenomenon, then it seems to me again there is something systemic going on that is much more basic, that has to be addressed. I mean, why is all this stuff going, and why have drug companies, although they no longer do that but in the past spent hundreds of millions of dollars a year promoting off-label use for a variety of things?

Well, something is wrong with the approval process for labeled use that has so much off-label use.

DR. KESSLER: This is the debate.

MR. VLADECK: I mean, if there is good data suggesting that there's an appropriate indication, then why is it so difficult for a manufacturer to get those indications approved? I mean, is that a function of the inadequacy of the bureaucracy, or the inadequacy of the process? Or is it more profitable for them to promote off-label use?

DR. KESSLER: While that is happening, the patient is stuck in the middle.

MR. VLADECK: But there is not a perfect answer. If you look at the incredible bureaucracy that CMS and others have set up to determine which off-label use is okay, and which off-label use is not okay, and which compendia do you use and how many peer review articles do you have to use, this is a surrogate for an FDA that is not functioning the way the FDA is supposed to function.

DR. KESSLER: He only says that after they leave.

(Laughter.)

MR. VLADECK: We've got a couple of folks still here.

DR. KESSLER: Bill, thoughts?

MR. SCHULTZ: Yes. I think this may be a case where orphan drugs need to be treated differently than other drugs. For other drugs I don't see why the problem is the FDA. If you're a drug company and you can get away with selling drugs for off-label uses, and you can get the government to reimburse it, why should you take the risk that if you do the studies it will turn out that the evidence just isn't there, that they're not working?

I mean, I think the system is set up with the wrong incentives. But I would imagine that for the drugs for orphan diseases, there's going to be a serious issue as to just whether it's going to be worth it for the drug company to do the testing. –

DR. KESSLER: So you would advocate a policy that said what?

MR. SCHULTZ: I don't know the data for orphan drugs, but I think you have to look carefully to see whether the problem is that it's too expensive to do the trials, in which case you need to try and find a policy that identifies off-label uses that at least have promise. I would not advocate a policy that just reimburses for all off-label uses. But somehow you need to find something in between an FDA approval and simply no data.

DR. KESSLER: Question. Maybe you can enlighten me. I wouldn't say the majority, but an overwhelming amount of drugs that are prescribed to patients without rare diseases are reimbursed with co-pays. You don't have to have a diagnosis on your prescription. Are rare diseases any different? Why wouldn't you reimburse for off-label use?

MR. SCHULTZ: But they're not all reimbursed. I think –

DR. KESSLER: But the question is, why wouldn't you? Not the reality, but why should they be treated any differently than hypertension, depression, or anything else you can think of?

MR. SCHULTZ: Well, I think outside the cancer area it's often difficult to get reimbursement for off-label uses. But you can imagine under national health care there's going to not necessarily be just unlimited reimbursement for approved drugs, regardless of whether their use is approved or no.

DR. KESSLER: Let's take a couple of points from the audience on both the issue of lifetime caps and off-label uses, and just take five minutes.

DR. MEEKER: I think this debate doesn't need to be framed around the orphan drug situation, what's different? If you have a mainstream drug which may be in the orphan drug

legislation but with little to no incentive for the biopharmaceutical industry to go there, but in a risk-benefit analysis, the drug's approved because there's an enormous amount of safety data, and so the idea that this could be looked at in a very specific way by the FDA would seem to be high.

Q: Just a comment. Bill Allisky (ph) from Simon Cooper Partners. The question is why orphan drugs are different than regular drugs and require prior authorization. You have a system because some of these drugs are so expensive that the insurance company has set in place a kind of a demand control. So they prior authorize every patient who goes on the drug. So a drug that has a potential for being used for off-label won't be used because it doesn't meet their criteria.

DR. KESSLER: Thanks.

Q: (Inaudible) It really is a concern to me that somebody who wants to be productive in society and work, as I do, would be forced to leave employment, divorce his wife, live in an apartment somewhere legally so her income and my income wasn't included to apply for Medicaid, apply for Social Security for disability, and then have the government take care of me until the time that I die.

What really concerns me is how this is going to play out in the future with comparative effectiveness. Lifetime caps should be eliminated for people with chronic conditions, especially rare conditions because without insurance I couldn't afford to pay for my medication. Therefore, I would die. So thank you.

(Applause.)

DR. KESSLER: One more comment?

Q: I'm sorry. I have something else to say. That was very great message and mine doesn't even compare to yours. But I will say that we need to be very cognizant of the necessary costs that are required by individuals with rare diseases. My son has 27 mandatory physician appointments a year. Chronic illnesses need to be recognized for their insurance needs in the health system because, first of all, I agree that the proper diagnosis is necessary, and appropriate research and referrals, lending itself to appropriate treatment options so therapy can be more efficiently developed in turn to potentially decrease those costs.

We are fortunate in our family that my husband has a great job. We only spend approximately \$9,000 out of pocket per year in addition to \$2400 annually for insurance. So fortunately we can afford to do that. I have a lot of friends with children with Russell-Silver that are unable to pay for their healthcare costs. I have been effective in getting certain off-label drugs approved just because I'm pretty good at it, and I'm good at getting other things approved through insurance. But a lot of other people aren't as good at that as I am. Those drugs cost for us between \$20,000 and \$40,000 per year. Just to give you an idea.

DR. KESSLER: I think we have a general consensus, is that fair? Bill?

MR. SCHULTZ: If there is to be reimbursement for off-label uses, which seems necessary, there also ought to be some thought given to doing the testing to figure out whether those off-label uses are actually working or not, and figure out what the right dosage is and what the right populations are and so on. If there's reimbursement, the drug company won't have incentive to do it. So it seems to me there needs to be thought about it.

I mean, often you can have several possible drugs that are all off-label and there's just no evidentiary basis for knowing which one is the best one.

DR. KESSLER: But sometimes as a physician you want to use a drug in a situation for an off-label use and no one's interested. You need to try it on a patient and no one's interested in studying it, you don't have the opportunity. So I'm not sure you can mandate the protocol or the study in every instance.

MR. SCHULTZ: I wasn't suggesting mandating it at all. I think thought needs to be given, and maybe some of this is the government doing it, but thought needs to be given to the importance of that –

DR. KESSLER: So there would be some monitoring of the nonapproved use. So at a certain point if it does add up to significant dollars then that can be studied.

MR. SCHULTZ: You can imagine there'd be actually savings to doing this, so you could just –

DR. KESSLER: Right. Just something you can actually offer up on that side.

I think there's one more comment, and then we're going to go on to the future.

Q: Hi. I'm Muriel Finkel from amyloidosis support groups. It's a rare blood disease that can be fatal when it strikes the heart. It's similar to multiple myeloma in that it is a plasma cell dyscrasia disease. However, unlike multiple myeloma it's not a cancer and it doesn't stay in the bones, it does affect the organs. But we do get a lot of our drugs from the multiple myeloma family and we thank them for that.

We are eight in a million, so truly it's a rare disease. We consider multiple myeloma a great big cousin or uncle because they get maybe 50 in a million or something like that. But because we're eight in a million, there isn't a lot of money for the drug companies to invest in trials for amyloidosis, so we get our drugs from the trials for multiple myeloma. Because of that there is some off-label use there, and there's some playing around with the envelope, pulling, pressing against the envelope, pushing the envelope, looking outside the box, looking the other way, whatever you want to call it. Playing the system.

But if you find the people that treat amyloidosis – and that's the key, is finding the centers that know amyloidosis. Every doctor had it in medical school for one paragraph. Very few remember it, and I'm sure that's the case with most rare diseases here. So when you do find

centers, like Boston University or Mayo, that know amyloidosis and know how to treat it and you want to get people there and you want to work on awareness, but that's a whole other thing.

The point is, we don't have treatment unless we have those treatments from multiple myeloma. So we have to maybe not necessarily tell the truth all the time to get what we want. I can remember my uncle when he was diagnosed with amyloidosis in the 1990s, the doctor changed his diagnosis to rheumatoid arthritis so he could have access to a particular drug that they felt might work on him.

So I think it's very important that we realize that we have to look outside the box and we have to push the envelope when it comes to rare diseases. As sad as it is to see pediatric diseases – we all see Lori Metcalf with all the makeup off, doing that wonderful five minute thing for the children overseas -- and gosh, makes me want to adopt them all and I'm sure all of us. But we don't all have a Lori Metcalf without makeup with our disease. Therefore, we have to do what we have to do to get it done. That's all I have to say. Thank you.

DR. KESSLER: You just made the case for health reform.

Why don't we move on to the future, and Francis, come on back on the panel. Gail Javitt, a lawyer, masters in public health, director of the Law and Policy Center at Johns Hopkins University.

GAIL JAVITT: Thank you, and thank you for including me in this. Before we look to the future, unfortunately there are some things in the past and present that I think we have to clean up, so let me tell you some of those things. I think together with your help we can clean them up, I should add.

I'm in this funny position on the program of talking about genetics and talking about access, and I had sort of a similar reaction to Dr. Meeker. Access to what? And access from whom and by whom? And so my answer to those questions we want access to genetic tests that are valid and reliable and informational, informative, and also information that is truthful and not misleading to consumers and patients. And then access to interventions and therapies informed by those genetic tests.

And of course, once we have those tests we want to make sure they are paid for, but without the baseline valid test, there is nothing to pay for.

Then looking at from whom, there is a need for high quality laboratories to perform those tests and get those diagnoses, and those laboratories must have personnel that are adequately trained to communicate the information about those tests. Then access by whom gets us to the issue of privacy of the information that's provided by genetic testing.

So thanks to Dr. Collins and NHGRI, we now have many more variables to consider when dealing with diagnosing, treating, preventing disease. It's really a tsunami of information we don't yet know what to do with most it, but we will. And the way you get this information is by doing a genetic test, a genetic analysis. And these tests, as you know very well, can be used

to diagnose disease, reproductive decision-making, to determine prognosis, predict risk of future disease.

The holy grail of pharmaco-genetics, of course, is to help select optimal treatments that are safer and more effective by identifying risk for adverse reaction and figuring out what dose an individual patient needs. So this is the future – personalized medicine is the drug that's for you, but we're not there yet.

In terms of how many genetic tests there even are to do all these things that we want them to do, there's been a huge growth in genetic tests. There are now tests available for more than 1,500 diseases, but I say that number advisedly because there is no requirement anywhere to register if you are performing genetic testing. So these numbers are based on a voluntary system of registration. There are likely many more but we may not know about them because there is no obligation to be transparent. Here transparency is a theme that I'll come back to.

So who's in charge? That's a complicated question and there are many potential players, actual players. There is not a lot of coherence, and a lot of things falling through the cracks right now. So to the extent that there is oversight of genetic tests today, the locus of oversight is within the Department of Health and Human Services, and specifically FDA and the Centers for Medicare and Medicaid services, which we think of usually as the payer. What we've been talking about mostly here is CMS as payer.

But there is a teeny, tiny little part of CMS that oversees laboratories and the quality of laboratories. That's through a statute called the Clinical Laboratory Improvement Amendments, which always makes people fall asleep so I'll say quickly. While it's perhaps mind-numbingly boring to read, it serves a really important purpose, which is to make sure that the information that you get from genetic tests is accurate.

Then on the FDA side obviously we've talked a lot today about drugs and new therapies. To some extent, but a very small extent, FDA also has authority over genetic tests and other test use in diagnosis if they are regulated as what's called a test kit, that they are sold to laboratories to perform testing. So there's the bare bones of it. What are the problems?

So the vast majority of genetic tests are not in fact provided as test kits and do not in fact undergo any third party review by FDA because they're developed in-house by clinical laboratories. So most genetic tests are so-called LDTs. FDA has taken the position, and its position has evolved and switched over time, but overall it takes the position that while they could regulate all laboratory tests, they are exercising enforcement discretion, which means that they don't, except when they do.

There have been a few cases where FDA has stepped in and said to a laboratory – and I'm not trying to say there weren't good reasons but it has been somewhat episodic and quixotic where FDA hasn't taken action, which has led to a lot of confusion and consternation about what is the appropriate regulatory status of an LDT, and if you want to invest in developing a new test, or the company who wants to develop a new test, you're not sure what you face.

Dan Schultz this morning talked a little bit about the IVDMA, which stands for In Vitro Diagnostic Multivariate Index Assay. That's why we say IVDMA, which is a very small subset that about three years ago FDA issued a draft guidance to try to regulate. It was the first time FDA had ever sort of lifted the cloak of enforcement discretion in a non-episodic way, but tried to set a standard for a very specific kind of genetic test, one using a lot of different variables to give direction such as take this drug, or undergo this treatment.

It caused a lot of consternation and confusion within industry. It's still not finalized. And has, at least some have argued, caused disincentive to innovation because the playing field is very uncertain if you are trying to make investment decisions. And it also, as you see, there is not only uncertainty but lack of parity between the way genetic tests are regulated, depending on just the local of performance, how they are performed.

Most recently in the ongoing saga of this unlevel regulatory playing field, Genentech filed a citizens petition with FDA in December 2008. Genentech, as you know, makes Herceptin, and that was the poster child for this concept of co-development of drugs and diagnostics. Herceptin, you are given it if you are HER2/neu, which you find out through a genetic test. However, there are laboratories that are able to do Herceptin testing that have not gone through FDA, and that's the point that Genentech was making in its petition.

Then also on the issue of personalized medicine and the question for personalized medicine, I give you the label of abacavir just as an example of what we hope will be standard and not unusual down the road. Abacavir is an HIV drug, but if you have a specific rare mutation, you shouldn't take it because it could have very adverse consequences. We are doing a study right now to try to figure out what is the pathway by which pharmacokinetic information should get into the drug label. What we are finding is it's really not very consistent or coherent. If personalized medicine's going to succeed, you need tests that work that you can be sure of, and you need a pathway to get the information into the label and to physicians.

So on the laboratory side, I mentioned CLIA. CLIA was intended to improve laboratory quality after it came to light that PAP smears were being misread and women were being misdiagnosed as a result. At that time in 1988 there was no such thing, for the most part, as a genetic test but subsequently a lot of laboratory testing are genetic tests. But CMS is kind of stuck in 1988, when there is a need to update the regulations to ensure the quality of genetic testing laboratories.

When we started our initiative to try to promote better oversight we thought this was a no-brainer but we're still fighting that fight. Specifically because there is no genetic testing so-called specialty, there is no requirement that genetic testing laboratories do what's called proficiency testing, which is a way to spot-test the laboratories, pop-quiz them and say, are you getting the right answer. Again, it seems like a no-brainer that there should be, and many labs do have that system for themselves, but there is no mandate that that occur.

CMS has said we can't do it because there aren't enough programs to allow us to require it. The PT providers, such as the College of American Pathologists, say we can't develop them

because there's no mandate that laboratories do them. So what you have here is sort of a chicken and egg problem.

Just in the interest of trying to understand how you might go about assessing the quality of laboratories, in theory, or at least in statute, the CMS is required to give data on proficiency testing performing for laboratories that are subject to proficiency testing if they do other than genetic testing. So for example HIV testing. We asked them for the data. It took about a year to get the data on proficiency testing. We looked at it and saw a lot of labs seemed to be failing, which doesn't mean they were failing. It could mean anything from they weren't required to take the test and got a zero, or they failed.

So we don't know what it meant, but the problem is not that. It's that CMS couldn't even tell us what it meant. So again, going back to lack of transparency, you need to be sure that the laboratory that is doing your testing can get the right answer. Accuracy matters for diagnosis, for prediction, for treatment, for selecting a therapy. It's something you probably do only once and then it's in your record and may be eventually in your electronic record so getting it right really matters.

You all know the GINA was passed last year, and we all know what GINA does. But what doesn't it do? It doesn't change the situation once somebody has a diagnosis of disease. It helps you before. It was privacy protection before you were diagnosed. It doesn't mandate coverage. So going back to the access issues that were talked about before. And the protections are limited to health insurers, not other kinds of insurers.

Then just a quick word on what's called direct to consumer testing, because the old model is you go to the doctor, the doctor gives you a test, you get consultation and then you have the information. But the Internet has changed all that and there are many companies out there offering genetic tests, from the frivolous to the very, very serious. One in particular is a product that hasn't launched yet but it will soon. It is called the Universal Character Screen. It is a direct-to-consumer carrier test for more than 100 diseases, including rare diseases.

There could be an active debate about whether you should need to go through a doctor, or you should be able to just get this on the Internet with your credit card. But in the context where we don't have assurance of the safety and effectiveness of genetic tests, there are certainly concerns about having this completely outside the system and nobody looking at the claims that are made, or the interpretation, or who's providing the interpretation.

And while we are aware of claims, particularly by DTC companies, that are troubling, there really has not been any action against them. The Federal Trade Commission did a few years ago issue a warning, essentially buyer beware, but that's the extent of it. There have been some legislative attempts but nothing to date.

In April 2008 the Secretary's advisory committee on genetics, health and society, which Dr. Collins was on, issued a report saying there are real gaps in the oversight of genetic testing that have potential risks for patients. They recommended updating proficiency testing requirement, having a mandatory registry so that if you're offering a test you have to show your

work, show your data. Oversight by FDA based on the level of risk of a test but not how the test was performed. More enforcement for noncompliance, and a way to assess the clinical utility of tests. All excellent recommendations.

Just a couple of weeks ago we and 21<sup>st</sup> Century Medicine Coalition and many other groups sent a letter to (HHS) Secretary Sebelius, probably before she even took her coat off in her new office, saying please help us create a holistic regulatory system here for genetic tests.

Just to recap my recommendations for this Blue Ribbon panel. We need test oversight that's based on the level of risk and not the method by which the test is performed. And laboratory oversight needs to make sure that we get accurate tests, and we need to have data to measure whether we're getting accurate tests. There needs to be transparency in the data that underlies the tests that are being offered. We need pharmacogenetic information to be rapidly integrated into drug labels. We need to demand truth in advertising and claims about genetic tests, and GINA of course should be quickly and rationally implemented. Thank you.

(Applause.)

DR. KESSLER: Thanks, Gail. So let's build on that. Tim, if I come to you and I take in a relatively common disease and my drug is only effective in a subgroup of that common disease, and I have a diagnostic that I have co-developed with, and it's less than 200,000 patients, but this drug is going to work on that subgroup –

DR. COTÉ: I think you're asking the question about whether it would be qualified for orphan status –

DR. KESSLER: Are they going to become members of NORD?

DR. COTÉ: If there is a common condition for which there is a medically relevant subgroup for which there can be a test and that it's clear that the drug would only work in that subgroup – let's say a cancer for which you've developed a monoclonal antibody and that is a presenting antigen that is in perhaps 5 percent of breast cancer cases, then indeed that therapy would qualify as an orphan product.

Likewise, if you had a gene and you developed an oligonucleotide against that gene and that gene was in a small subset of a common cancer – a common disease of any kind – that would indeed qualify for orphan status and would be considered a rare disease or condition.

DR. KESSLER: So the incentive, to be more precise develop a subgroup, find efficacy in that subgroup, even though I'm limiting the number of patients that I might be able to sell to, is that I could come in to you for exclusivity.

DR. COTÉ: That's right, and that's absolutely true. Some have claimed that, oh, maybe someday everything will be a rare personalized medicine. That hasn't happened. Personalized medicine is indeed much better than impersonal medicine, so we're looking forward to those

movements because it will be better. But right now that hasn't been the reality that we've had to deal with.

DR. KESSLER: So Francis, take us through where this is heading. You can actually see the future, right? (Laughter.) In some of that genetic information that you have. How does NORD think about this, and how do we think about this in the context of do we want to incentivize that kind of work as well as the more traditional view of rare diseases?

FRANCIS COLLINS: Well, I think Tim's going to need a lot more staff because it may not have happened yet, but if you look at the way in which common diseases are being stratified by discoveries about their underlying pathogenesis, much of it built upon understanding at the DNA level that there are subsets and those subsets are going to have different natural histories and different responses to drug therapy, then diabetes and heart disease and certainly cancer, especially cancer, are going to be broken apart and already are being broken apart now.

Talk about cancer for a minute. We now know that virtually every tumor has at least a dozen mutations in it, most of them somatically acquired, some of them hereditary. And we're not far from the time where every tumor will be analyzed to figure out what's the exact fingerprint of those mutations in that tumor. Then what one will want to do is to take that list of mutations in the tumor and the genes that they involve and the pathways those genes are part of and intersect that with the armamentarium of drugs that are known to hit various targets.

When you think about that matrix, it's not likely that very many patients are going to have exactly the same outcome. Now, this is going to stress our system and we should be prepared for that because it will of course result in circumstances where market size is going to be diminished because subsets are developed instead of blockbusters. And it will also challenge us to develop drug trials for combination therapy especially for cancer, if you know your tumor has three different serious pathways deranged, are you going to be happy if only one of those is being approached when in fact there are drugs available for all three? I wouldn't be, and I think as caregivers we wouldn't want to stop at sort of monotherapy if we could do better.

But the clinical trials, obviously, the combinatorics are going to be pretty scary in terms of how you design a trial, how you get companies to work together if different companies are producing different compounds. All of those things are going to come to the forefront, which will make what we're talking about for single gene disorders where you're just thinking about a target sound kind of simple in comparison. So get ready.

But I do think basically the world is going to be coming to this same discussion over the course of not terribly distant time. It hasn't happened in many instances quite yet. We're just sort of on the brink of that, but in the next four or five years clearly things that used to be thought common are going to be increasingly seen as a collection of less common or even rare subsets.

There's a lot of discussion about the economics of that. Will that in fact result in an increase in cost because of the fact that no market is big enough to be able to recoup the investment? Or will that be balanced, or maybe even end up in a positive direction as far as reducing the cost by the fact that you can run clinical trials with smaller subsets that have been

specifically identified on the basis of knowing that they're different, and then being able to assess efficacy with a smaller number of patients? Obviously that's going to require a lot of interactions with FDA.

So, yes, we're on the cusp, I think, of a very different view of common diseases, and many of the things we've talked about all day today are going to be highly relevant for diabetes and heart disease and cancer.

MR. SASINOWSKI: We heard Mike Astrue at lunch talk about how 50 years ago, physicians would diagnose people as having the disease of melancholia, and pulmonologists about 100 years ago would talk about consumption. Francis, you're talking about how, because of your work with the Human Genome Project, we're going to have much more granularity to our definition of what disease is in the very near future.

With respect to whether our new definitions of disease will yield new orphan diseases, this will depend a lot upon FDA's interpretation. For instance, there may be 400 different alleles for some condition and you know through in vitro tests that your drug is going to hit five of them. So you want to go out and test your drug in those five, but if to designate you as an orphan you have to prove it doesn't work in the other 395, then you might be able to get FDA marketing approval for those five but that drug may not be recognized by FDA as an orphan disease if the aggregate prevalence of those with the 400 alleles exceeds 20,000 persons.

As we tease through this, this is like the proverbial onion with its many layers as we peel away the layers of what you unearthed with the human genome project, and how those new definitions of diseases may affect the world of rare diseases.

DR. COTÉ: When we talk about alleles and monoclonal antibodies, the FDA is not really in the business of making people prove that their drug doesn't work. That's really not our business. But a monoclonal antibody is directed against an antigen and so we would expect that it wouldn't work in the other – it's a reasonable expectation. So every one of these cases that comes in for designation is done on a case by case basis but they tend to be pretty straightforward.

DR. KESSLER: Gail.

MS. JAVITT: I just want to bring up another issue that affects incentives to do the research to figure out which drug works or doesn't work, or is safe or effective for which patient. The ideal situation is you do this all prospectively when you're doing the drug development, you collect the samples. In reality a lot of times there's already a drug on the market and you have to go back retrospectively to figure out whether there's a connection between a variant and a response.

There's right now a tension within FDA about what level of evidence you need. Of course the gold standard is the prospective trial, but in reality that's not always going to happen. So I was struck by the parallel on the drug side we were talking about this morning and this

situation. There really needs to be a rethinking of what kind of data the agency is going to be willing to accept for pharmacogenetic claims.

DR. COTÉ: Just one other comment is that the flip side of this is that we are charged with protecting the integrity of the Orphan Drug Act. People are here in this room today because it is the goose that is laying golden eggs of incredible miraculous drugs for patients with rare diseases. We do not want it to be usurped by people who are trying to use it for common diseases. That's the reason why we're pretty specific about coming up with a clear answer to the question, what is the disease or condition, and then is that less than 200,000.

MR. SASINOWSKI: To answer Gail, in terms of the pharmacogenomics, I've dealt with a number of companies who have been negotiating with the agency over getting exactly what you're asking for, getting more of that information in. Often, right now, it hasn't resulted in getting into the label. And the reason is the FDA has had concerns either about sensitivity or specificity.

So it's the reliability of the assay system that has been an impediment because you don't want to put something in labeling that's going to indicate that the drug should only be for a certain kind of person and then that's only 80 percent accurate. That would mean that 20 percent of the people who should be getting the drug won't get it because they test out by your assay. I think as we evolve the systems and we have more accuracy in those assays, then I think there will be a greater receptivity to have that kind of information that you're asking for, that is, the pharmacogenomic information, in labels. We're going to get there.

DR. KESSLER: Bill, when you did the Orphan Drug Act back 25 years ago, you didn't think through this one, or maybe you did know this one was coming. Does it give you any pause? It's a good thing if you have diagnostics and more tailored, targeted therapies that work. We're all pushing for that. We're concerned that the pharmaceutical industry doesn't have enough incentive to do those diagnostics today and really limit. So maybe this all is aligned.

MR. SCHULTZ: With the Orphan Drug Act, although I was little involved in it. But 25 years ago the most expensive drug was maybe \$10,000 a year. We're in a completely different world than we were in 25 years ago. So the answer is no. I don't think anybody is imagining this.

DR. KESSLER: Tim?

DR. COTÉ: I'd just like to add that Dr. Collins' concern about my level of staffing is correct. (Laughter.) I share that. In 1982 orphan drugs represented zero proportion of all drugs that FDA approves, all FDA approvals. In 2009 it represents somewhere between 30 and 40 percent. It's been growing pretty rapidly and we really are the future. This rare disease community and this increasing personalization of medicine is the future of the agency. It's where we're going.

DR. KESSLER: This morning we've talked about research, innovation. This afternoon we talked about access, and now the future genetic testing. I think it's been a most fruitful discussion.

Just closing comments on any of what we've talked about today. Why don't we just go around the table and then I'll turn it back to you, Peter, if I may. Bruce, why don't we start with you?

DR. DAN: It just seems to me we've come to the moment in time which is propitious for all of us, and as I can repeat the quote that Tommy Thompson made. Governor Thompson said that basically when a concerned group of people get together, they can do what they want to do. I think what I've heard today is that this is a very good time, if not the only time we'll have in the near future for a collaborative group of people – not just NORD but NORD working in collaboration with other agencies – to put together a program and a process that as we were given the goal to identify those policies and principles that will move the organization and patients we care about forward.

MR. NOVELLI: I have found this to be a really important and instructive day. I'll too go back to Tommy Thompson and then go back to what Tim just said. This whole healthcare reform situation this year is critically important. It is an enormous opportunity and it's full of risk. We could really mess this up, and at the same time we could get healthcare reform that would be comprehensive.

It seems to me that the rare disease community has the opportunity here to play a substantial role and to achieve a great deal. If rare diseases and personalized medicine really are the future of where things are going, it makes it all the more important. I really like this idea, again as a layman, Peter, I really like this idea of strength in numbers of a comprehensive overview set of strategies built around the science, built around the advocacy, built around the public outreach, and not think of this as a series of tiny, fragmented diseases but think of this as a community and advocate as such.

DR. OUELLETTE: I would certainly agree with that and with what Bill just said. And again, I'd like to make the point that Bruce also made, which is children are not small adults and they need something entirely different in the health reform package. It's important that all of us who are advocates remember that. We talked about the fact that they need preventive health care and not just catastrophic coverage.

The other point I want to make is that the issues about workforce are exactly the opposite in children as they are in adults. In adults there's a crisis in not having enough primary care doctors, but they have a lot of sub-specialists. In pediatrics, we're doing fine in primary care but we have a critical shortage of pediatric sub-specialists, especially in the cognitive sub-specialties such as neurology, rheumatology, et cetera. I know from pediatric neurology more of us are retiring than are going into the field, and there's already a big shortage.

So we're looking to have part of the healthcare reform include incentives for our young people to go into the pediatric sub-specialties, which is going to mean that they can postpone

their huge amounts of debt, mostly about \$150,000, because they're not going into sub-specialties because they can't absorb more debt.

MR. SCHULTZ: Let's not forget this is an extraordinary organization. I think it's true that before 1981 all food and drug legislation was basically passed after negotiations between industry, between government, maybe some cases consumer groups. But the Orphan Drug Act was passed on the initiative of an individual representing patients. This organization has enormous credibility in this debate.

I think the two parameters need to be maximum access to products and products that work. There was a big debate in the discussions around the Orphan Drug Act about whether the safety and efficacy standard should be weakened. Basically that the problem is FDA. We can't get these products through the agency. The decision was made early on, and I think everybody involved has really stayed to it, that we want to keep the standard the same because we don't want just products. We want effective products. And I think as long as we keep that in mind and access in mind, we'll get to the right place.

MR. SASINOWSKI: One thing that struck me listening this afternoon to the speakers is that I heard Dr. Barer talking about, for instance, that there hadn't been a drug for multiple myeloma in 30 years. Then, Celgene developed one and now there are several others being developed. I commented on that phenomenon earlier this morning, with pulmonary hypertension, because the first approval reduces the regulatory uncertainty. I heard the same thing from Dr. Meeker's talk about the value of knowing natural histories, so that if you know the natural histories, then, we may have endpoints that can reduce the regulatory uncertainty. Just think about what that may mean.

We have 200 diseases for which there are drugs approved, 200 orphan diseases. That means there's 6,800 others for which there are no drugs. Yet people are willing to go out there and develop a second multiple myeloma drug because of the reduced regulatory uncertainty to developing a drug for this condition after the first drug has been approved and blazed a regulatory trail for others to follow. That means companies are willing to forego having an orphan drug monopoly that they would have if they develop a drug for one of the 6,800. Talk about a business model! Think about that! Corporations are willing to forsake the opportunity to be a monopoly drug. Instead they would rather try to take market share away from another product. This is because the regulatory uncertainty barrier is so high that it's more attractive to get the second orphan drug in a disease like multiple myeloma than fight through the regulatory uncertainty of blazing a trail for the first drug to treat one of the other 6,800 rare diseases that today lacks any drug therapy.

So that's why I was captivated this morning by all the discussion about how important it was for patient groups to work with the scientists at FDA and NIH and with academics to try to develop natural histories, and to try to develop pivotal study endpoints, and that's where I mentioned that, and Bruce Vladeck picked up on it, that it's like "Field of Dreams." I'm picking up on that third brick wall that Francis talked about: the clinical endpoints. If we can reduce that wall by developing natural histories and pivotal study endpoints and thereby, reduce regulatory

uncertainty, then maybe we as patient advocacy groups will be able to draw more companies in to begin to develop therapies for those other 6,800 diseases.

I know, David, that this observation is not directly germane to the topic of healthcare reform, but it's a common thread that I've heard throughout the day.

DR. COTÉ: This has been a fascinating discussion, and thank you, Dr. Kessler, for leading it. Our candidness in contributing to questions about policy aside, it's really not our position to promote or establish or even suggest policy. It's really from NORD. As all in this room know, NORD and my office have an incredibly close relationship. In fact, I've commented at several venues, including yesterday's talk that I gave to the NORD board of directors, that this is the nonprofit organization and governmental organization that seems to have the closest relationship of any that I've experienced, in my career at least, and I'm very grateful for it.

NORD established the Orphan Drug Act, at least was very instrumental in the establishment of the Orphan Drug Act and its predecessors, and I tell my staff on a daily basis that NORD, Genetic Alliance, and the people that they represent more importantly, are the reason that we all have jobs. So whatever policies come out of this – and I've heard some good ones, and I've yet to hear some that I'm sure will be at least as good coming forward in the future – we stand ready, just as humble public servants, to implement them.

MR. GROFT: I agree with Tim, and I'd just like to mention to Gail, there is a set program or collaborative genetic test development program, and I think it's not that people are not paying attention to this. We are looking very closely at how do you develop genetic testing, the information that goes back to both patients and physicians. So I think this is very, very critical.

I think for many of the rare diseases to have every test be regulated by the Food and Drug Administration in the sense of kits, I think it would be very, very difficult to accept that over a period of time because it's just not going to happen. It's too expensive and too time-consuming, and there are too many patients looking for diagnosis, and sometimes laboratory tests are the best we can do, and the same with laboratories that are CLIA certified. So I think we have to work around that position there and a little bit better perhaps.

But I just wanted to let you know that this is developing, continues to develop, and we're looking forward to expanding it even more.

One of the other issues I think we haven't really talked about is access to information. Before you really have treatments, or before you can get treatments you have to know that treatments exist, whether they are under investigation or whether they've been approved. And so I think a couple of the tasks for NORD to think about would be the education of healthcare providers about the services that are available from so many different agencies, from so many different patient advocacy groups.

I think if you talk to most physicians, have they heard of the Orphan Drug Act? Maybe. Have they heard about rare diseases? Perhaps. Many times they don't think of a rare disease as

the type of information that might be available to make dealing with that rare disease better for them and for their patients.

Several years ago Francis and many of us were involved with NCHPEG, the National Coalition for Health Professions Education in Genetics. And so I think trying to come up with some type of educational program about rare diseases, orphan products that we can make the resources better known to all healthcare providers because so many of the healthcare providers, just not physicians but everyone in the healthcare providing chain who will have access to the patients, they can direct them to this information.

I think right now we don't quite have that. We don't have that one point person that a patient can go to and they can then distribute information about all the services that are available, including information about clinical trials, information about these services that the patient advocacy groups provide, information about the type of services that are provided by organizations such as NORD and the Genetic Alliance. I think we have to do a better job of making this known to healthcare providers and their patients.

And the other thing I mentioned earlier was the education of the leadership of patient advocacy groups. This is so significant, and without having a good track to run on and a good pathway to follow, many of the patient groups just do not understand what their steps are, where do they go, how they facilitate research advances into treatments and interventions. I think this is a big issue for many of the organizations. I think whatever we can do to help them I think would be very, very useful as we move forward.

I guess the last point, and the experiences we've gained from our rare disease clinical research network, it's a small network relates to the natural history or longitudinal studies of rare diseases. And for many years these types of studies were not well accepted by the scientific community. People said they really are useless. They aren't going to give you very useful information. I think the reality is now they do give us good information.

If we can factor these types of studies into any type of research or clinical research studies that are funded by the NIH, by other organizations, we should look for ways to incorporate a natural history type study that they can follow patients over a period of years. I think it will give us information that includes biomarker development and so forth. Then I think we can really use reliable information, and it's the understanding that perhaps many of the products that will be used in investigations may never make it to the approval stage. I think that was recognized back in the early days of the consideration of the Orphan Drug Act. Many drugs would stay in the treatment IND state.

So we have to think of that and just think of how we can put things together a little bit better for everyone. So I'll end it with that.

DR. KESSLER: Thank you all. And Peter, thank you for the opportunity for the day. I turn it back to you.

PETER SALTONSTALL: David, let me say I would like to thank everybody in the room for participating, and especially everyone sitting at this table, and including people who were here this morning for the absolutely stimulating and insightful conversations, thoughts, and ideas that came out today. When we started the morning I said we were trying to help set the policy for NORD moving forward and I must say it's a fairly potentially long list here, although I think we're well positioned to help lead some and be a very active player as healthcare reform begins.

We now have some clearer ideas of where we may want to go. I will tell you that we will publish the results of this one-day summit on our Web site. All of the slides will be on there in about a week, as a matter of fact. And we are looking to produce some documents with the help of Frank and a number of other players that are sitting around this table.

I hope that that will help me set my direction a little bit. I have some key ideas, but as we were going along today, I have about 400 additional ones now, so we really need to try to focus that down to understand the impacts that affect our audiences and where we can have the most bang for our buck, if you will.

So more will follow. Keep track on our Web site, if you will, but again, thank you to everyone for giving us their time and their energy and their thoughts today to make this a very successful day. So, again, thank you and applause for everybody.

(Applause.)

(END)