Repurposing Off-Patent Drugs: Research & Regulatory Challenges

Bobbie Ann Mount:
My name is Dr. Bobbie Ann Mount. I work for New Therapeutic Uses at the National Center for Advancing Translational Sciences. It's my pleasure of welcome you to our off-patent drug repurposing workshop today. We've put a lot of effort into this agenda in collaboration with the Food and Drug Administration. Heather is standing -- Heather Stone is standing right here. She's been my partner in crime on putting this agenda together, and we've also had a lot of support from the Regan-Udall Foundation for the FDA, who put together our printed materials.

It is my pleasure to introduce Dr. Christopher Austin, who will kick off this event. He's the director of the National Center for Advancing Translational Sciences.

[applause]

Christopher Austin:
All right, well, this is a very important meeting to us, and I hope to all of you. And I want to be able to look back at the end of tomorrow and realize that this is a start -- this meeting was the start of a new era. Most of us in this room, or many of us at least, have been interested in and/or working on this problem that we're going to talk about for the next two days for many years, and have probably started out thinking, "Well, gosh, you know, this is a really simple problem." And the more we've gotten into it, the more we've realized the kind of intellectual, scientific, regulatory, reimbursement, evidentiary quicksand that this problem presents. But the reason that we've stuck with this is that the public health significance of what we're going to talk about is truly enormous.

And so, NCATS, as an organization, has been interested in this problem and committed to this problem since our start. I don't know if you noticed because she said it so quickly, but Bobbie Mount is part of an organization -- part of our organization called New Therapeutic Uses. There's a whole group called that. So, we've been -- had a number of efforts in this area. But it's become clear to us that this is -- though there are scientific issues in this space and there are some funding issues in this space, significant ones, there are other issues that go beyond the research space. And I just mentioned some of them. So, we decided, with the help, the guidance of our Cures Acceleration Network Review Board, which I'll tell you about in a second for those of you who've never heard of it, to go all-in on this problem. And invite all of the constituencies that we could think of that, depending on your point of view, are either the roadblocks or the sources of the solutions to those roadblocks. Of course, the people who are best at identifying those roadblocks and then figuring out those ways around them are experts in the field, so that's why you're here.

This meeting is a typical NCATS meeting. For those of you who are not used to NCATS meetings, they are a little different than, perhaps, your fathers' NIH where everybody sits quietly, does their email, is very polite. You know, we like to be polite, most of the time. But really, what drives us is patient benefit, and sometimes when one thinks about patient benefit, sometimes you have to be willing to skewer some sacred cows, perhaps say things that, oh my gosh, you know, might be a little controversial. My heavens, if we can't be controversial to improve patient lives, I don't know why we're here. So, please, be polite, be respectful, but don't be bashful. We really want to air all of the issues that you've run into, realize that there's a tremendous variety of experience in this room. So, though something may be obvious to you and the world that you live in, it may be completely unknown. Even the problem may be completely unknown to the person sitting next to you. So -- and that's also been a secret of NCATS success, that, the
more diverse the group is, the more we find that what's impossible to one person is trivial to another because of the fact that they come from -- they have different skill sets, they come from different backgrounds and have different experiences. So, I hope you will engage deeply in this. If I thought I could do this without resulting in -- without having to hand out, you know, group valium, I would ask you to all turn off your electronic devices and don't look at them for the next two days. But I realize I probably couldn't even do that. So, I won't do that. But I hope you will come as close to that as possible. So, what I have for you is just a few slides to give you just some background, get you thinking.

So, this is the problem that NCATS works on. It's the problem that, I think, is the biological problem of our era. That is this yawning gap that has opened up over the last 30 years between ethical advances in fundamental research on the left side, and the really, for the most part, underwhelming advances in health of individual patients or the public on the right side. And to the degree that health improvements are based on understanding of fundamental biology of humans and health and disease, it's really curious that this has happened. And so, that's really -- that's the translational problem. It's the problem that, as we like to say at NCATS, to quote Matt Damon out of the Martian, we're sciencing the heck out of this problem, or use more colorful language if you remember that movie. But -- and this problem is an exemplar of the problems that we work on, because NCATS problems are rarely just scientific problems. They're usually about half science, half operational, or other issues that are not strictly biology, chemistry, physics. They're IP issues, they're credit issues, they're incentive issues, they're ethical issues, they're regulatory issues, they're reimbursement issues, they're access issues, et cetera, et cetera, et cetera. And so, this problem is a typical one.

So, what is our mission? And again, you're now part of this mission by being in this room -- is to come up with innovative methods and technologies which will deliver more treatments to more patients more quickly and more efficiently. And so, we're all about new ways of thinking, new ways of doing things, new ways of -- new technologies, which are not diseases specific. Our disease, if you want to think of it this way, is the translational system that is very sick and does not work very well. But the problems that we do, and again this meeting is classic for that, is not specific to cardiovascular disease or my own field of neurology and neuroscience or oncology or anything else.

So, what is translational science? We're the National Center for Advancing Translational Sciences, so translational science, just like any other science, it's a field of investigation. It is a field of investigation that seeks to understand what the general principles are by which this process happens, with a hypothesis that, if we can understand the general and operational principles, then this process will be transformed from an empirical, trial and error, phenomenological, sometimes almost astrological, process where we're dependent on luck and those kinds of things, into a predictive science. And that's why we're all here. And again, this problem is an exemplar, an exemplary of that system.

So, when I first thought of this back -- thought about this seriously back in, I don't know, it gets lost in the sands of time. But let's call it 2008 because this comes from a slide in 2008. You know, I was thinking about this, like a lot of you, in a very simple way. I thought of -- this is the chevron you've all seen a thousand times. At the end of this process was FDA approval and once you've done that then everything's good. And I thought, "Well, gosh, you know, you could do it the usual way. Start out with 400,000, a million compounds, whatever you want, do a [unintelligible] screening, do a lot of med chem, [unintelligible] Ten to 15 years, fails 99 percent of the time, cost $2 to $10 billion, depending on how you do the math, et cetera." Oh, but wait, then it was obvious to a lot of people, myself included, and this was probably all of you in this room, that another way would be to take all the drugs that FDA and
other regulatory agencies worldwide have approved already and say, "Well, gosh, you know, as I was taught when I was --" before I came to NIH I was in pharma.

And we had this saying in pharma, that every -- and it was generally used to warn people of toxicity and it applies there too, but it was always said that every compound, every drug has two activities. And I heard this, and I thought, "Okay, I'm going to sharpen my pencil and write this down." Two activities, and I thought, "Only two activities?" They said, "It's the activity you know about, and the activity you don't." And so, I thought, "Well, you know, that kind of could be bad if it leads to toxicity." But it's true. But it can also be good, leading to a different therapeutic effect, because of course, for mother nature, a target is a target is a target. And we're the ones who say whether it causes efficacy or toxicity, right, so we thought, "Well, gosh. What could be simpler. We'll just put all these drugs together in a collection," which actually didn't exist at the time, and we said, "Well, gosh, within a year or two, once we do the screening," which we knew how to do, and animal models, which we knew how to do, then we'll just trot over to the FDA, and they'll say, "Yay." Approve your new indication, change the label, and CMS will shower reimbursement on all of us and world peace will prevail, and we could go on to another problem.

Well, here we are. As we all know, it's not this simple. But when we thought about, you know, gosh, you think about this at the larger level. I just want to stick this in your head because it's a problem that continues to bedevil me on a regular basis. First of all, the drug repurposing seems tantalizingly simple. It would be simple, faster, cheaper than new medical entity development or chemical entity development, with a potential to develop many unmet medical needs, given that, you know, every compound has two activities issues. And, you know, when you think about, you know, the ultimate application of this, if we take it to the extreme, as most of you probably know, they're about, conservatively, about 6,500 human diseases which have no regulatorily approved treatment whatsoever. You basically have two choices if you're going to do this. You can develop a [unintelligible] entity, which has those numbers that I told you about. Ten to 15 years, 99 percent failure rate, $2 to $10 billion, et cetera, et cetera, and did a calculation a few years ago at the current rate of progress, which is not insignificant, but given the scale of the problem it will be 2,000 years before every human disease is treatable. Two thousand years. That's not acceptable. There are some people who would say, "Well, gosh, you know, it's the nature of the problem." I don't accept that answer and you should not either.

So, what other opportunities are there? What alternatives? So, one alternative, not the only, but one alternative is to say, "Well, gosh, what about all the drugs that have already been approved?" And the question we've wanted to understand, wanted to know, we just currently have no idea, but do the thought experiment. What percentage of those 6,500 currently untreatable diseases is ameliorateable [spelled phonetically]? Maybe not curable, but amelioratable, to some degree, by a drug in the current pharmacopoeia that you can go get at the Walgreens? And the fact that we have not identified that and not made those available to patients suffering from disabling and lethal diseases, shame on us if we can't figure out a way to do that. This is an eminently solvable problem, and so that's why we're here. And so, that's what we hope to identify through the course of the day. You know, why have so few, particularly off-patent drugs, been repurposed. If you ask yourself, outside of the developing world and work amazing organizations, like DNDI, the Drugs for Neglected Diseases Initiative, who have successfully repurposed long generic, long off-patent drugs for diseases, mainly parasitic diseases in the less developed world, why -- in the major markets, why has this been so rare? What's the problem? And as it turns out, in a problem like this, of course there's not one problem, there's many problems.

So, I mentioned, in case you're interested in this and you're interested in looking at some of the things
we do, we have a whole section of our center and our website, of course, that talks about repurposing drugs at various stages, and you'll hear about some of that through the course of today. But one of the first things we did -- this is going long, way back, but it was done by a number of the people who were in this room. Was to do what we thought would be necessary but not sufficient, that is, to put together a complete non-redundant list, emphasis on non-redundant, of every drug that had been approved by regulatory agencies worldwide. So, it's not just FDA, but the EMA, Japan, Canada, and the first version of this was in 2011, and it's continued to grow and be refreshed every year. It's -- and the paper's published, and there's a website and all that stuff, so you don't need to worry about that. So, you can go look at it and I hope you will. But, not surprisingly, because his is a -- integral of all drugs approved, of course, given the fact that patent clocks are what they are, 90 percent of this or more, they're off-patent. And there was just a paper published last month about -- this was the reference in Drug Discovery Today, about the use of this collection. You'll notice -- you can't see this from the back, but those maps are all the countries that have used this collection either with us or independent of us, and number of papers published, and there's hundreds and hundreds and hundreds. But if you ask, "Well, how many have been approved?" As far as we know, the answer is none. So, science is not the problem here, or hypotheses is not the problem here. And we have the obligatory list, this is a long list of indications, most of which are completely untreatable or poorly treatable, the drug, the stage that it's in, and the reference. So, if you're interested in what this collection can do, what a collection like this can do, there it is. It's a 10-year experience. And this is the obligatory pipeline chart or [unintelligible] chart of where these are. And you'll notice that none of them have been approved, most of are stuck in what's incorrectly called lead-op. But that's the term that people use. So, essentially these have died waiting to figure out how to get into the clinic. Sometimes there is, you know, different formulation or toxicology or other things that needs to be done, but the point is that, the folks who have done this -- most of these are not just us, they're our collaborators or folks who have done this independently of us now that -- once the discovery's found -- have tried to take these forward. And most of them have met their demise at, one stage or another, short of patients. So, again, why? Why has this happened?

Okay, so, what is this meeting focused on? Though we work on, and probably a lot of you work on various stages of what's been called repurposing -- repurposing is a lot like translation, people use it in lots of different ways. So, I want to be very specific about what this meeting is about. That there are three potential -- at least three potential phases when one can think about repurposing.

The first is in the purple chevron there, unapproved drugs that have failed for their initial indication, or otherwise dormant, they've been shelved for business reasons or what have you. That was the initial focus, it still is much of the focus, of the new therapeutic uses program that Bobbie mentioned. And it's an important program, don't get me wrong, it's an important program, it's a collaboration with a large number of pharmaceutical companies, to repurpose their investigational drugs. But these are drugs that are still on-patent -- they're actually not drugs, they haven't been approved yet. But they're [unintelligible] that are still on-patent, have failed, usually for efficacy or business reasons.

And then there's the second, which are -- they're approved, but they're still under patent protection. So, in those cases, there actually is a commercial champion who will take the floor. Somebody with a commercial interest in developing these drugs now, because they can coup the return -- they can get a return on investment on all of the work that has to go into the preclinical and manufacturing and all the clinical trial work that has to go in to get these approved, because they're still on-patent. But the majority of the drugs fit into the last one. They're approved drugs that are no longer patent protected, and of course every year there's more of these as drugs go off patent. So, we're not going to talk about this. It's not that it's not an important problem, it's a really important problem, but we're not talking
about this today. We're going to focus on the worst problem, we're not going to worry about this either. We're not talking about approved now, these are approved drugs that are no longer on-patent. Sometimes you call them generic, but really, they're off-patent drugs, and that's why the title of the meeting.

So, after screening -- think about this collection. After screening and cells, which, now that we have a collection, once we put that together, you know, you can do this now. In our collection, we can screen all 3,300 compounds and 15 concentrations in a day. So, this is not the problem. In testing animal models, animal models can be limiting, can be misleading, but of course they exist and can be done. Off-patent drug repurposing faces a litany of roadblocks that we're going to talk about to clinical utilization, including just some of these that are just a preview, a lot of which you're going to hear about. Disease and population of specific toxicology, which several folks will talk about, GMP manufacturing of the API and the dosage form. This seems like a trivial thing, this is not trivial, believe me, it is not trivial. It kills projects very effectively for clinical studies. That's just to do the clinical studies, that's not to market it now, that's just to do the clinical studies. Availability and adequacy, particularly for old drugs, of the drug master file, if such a thing exists.

You know, it may not be available, the innovator company may no longer exist, then if the DMF -- if the drug was approved 40 years ago, the characteristics or the requirements that the FDA had then are very different from what they have now. So, even if there is a DMF, it's not going to be good enough for a new indication, even if you can find it. Funding for testing the therapeutic hypothesis in humans, that means their clinical trial, clinical study, and then funding for the definitive clinical trials to satisfy the various constituents, and they're different, as most of you probably know. The requirements for regulatory agencies are one standard, the standards for a payer are a different standard, and the requirements for physicians to actually use them may be a different standard. And so, those clinical trials may be very different and who's going to pay for those? And I can tell you that NIH does not like to pay for these. I love my colleagues dearly, but they do not like to pay for these. Why? Because it's not viewed to be innovative science. It's not -- it is hypothesis-based, but if you can't show people, you know, biochemical signaling pathways and a promoter being bashed, it's very hard, I must say, to get these things funded. Which is distressing to me because we do these studies in mice all the time, and NIH pays for them, right?

But you try to do the same study in a human, and it won't be paid for. Which I find incredibly curious, but there it is. It is the reality that we have to deal with. And we can continue to argue to the funding agencies, and I continue to do this, you should continue to do this, but it is the state of the art now, I can assure you. And philanthropic organizations would love to do this, but they just don't have the money. Just even a small trial could be, you know, $50 million. $50 million for even the most wealthy of advocacy organizations is really tough. And then, beyond that, a big problem, drug availability of low margin, off-patent drugs. This is a huge problem -- forget about repurposing. You know, think about normal saline and vincristine. This is an ongoing problem that FDA and the whole world have been dealing with. But all of these drugs fit into this category, so nobody's going to make any money manufacturing them either.

So, here we have this curious situation where we have drugs that are cheap, probably effective, at treating all kind -- we think, treating all kinds of untreatable or poorly treatable diseases, and we have no way to do it. So, we got to solve this problem. Identifying all these roadblocks and suggesting solutions to them is why you're here. So, I told my staff when they were doing this, typical boss thing, "Don't bring me problems, bring me solutions." So -- I love saying that. But of course, we need to know
what the problem is too, because sometimes you're focusing on the wrong problem, so don't go right to the solution, but we're really interested in what would you do, and why is that? So, this is the part we're going to work on.

Okay, so, before I turn this over to the next group, I got to tell you how this started for us, because it's important for you to know what's going to happen out of this meeting, at least at NCATS, and of course we're co-sponsoring this with the FDA and Reagan-Udall, and they have their own action items, but as far as NCATS is concerned. The Cures Acceleration Network, aptly named, is as program with NCATS -- within NCATS has been created specifically by Congress as a part of the ACA to advance development of what they call high-need cures and solutions to barriers to successful translations, such as what we're talking about. It has a number of really cool and innovative funding mechanisms associated with it, quite unusual. And we have an incredible board, that's separate from our council, that was indicated by Congress in a remarkably prescient way, I must say, that spans the fields of all these things. Basic research, translation, drug device development, medicine, venture capital, private equity, biotech, pharma, patient groups, all of these folks. And this idea to launch a renewed frontal assault on this problem, came out of a discussion of the CAN Review Board when we do what we regularly do, which is to have the CAN Board from their point of view -- not from our point of view, not from NCATS and going to the CAN Review Board and saying, "What do you think?" But the CAN Review Board who are customers or entities outside the NIH to say, what do they think the problems are? And they brought this to us, and I particularly want to thank Scott Weir, who you'll hear from later, and Harry Selker, who you hear about later, and many others, Ron Bartek, Lynn Marks, remarkable people within the group who helped advance this and brought us to where we are now. Importantly, also, the CAN Review Board has representatives from FDA, NSF, DOD, VA, et cetera, very unusual for an NIH organization.

Okay, so, this brings us to the outcome of the meeting. What are we going to use this meeting for? It's going to be used by the CAN Review Board, this board which I just told you about, and NCATS to help devise an actionable research agenda. This is not a talkfest where everybody goes home and congratulates themselves for having an intellectually stimulating conversation for two days and you pat yourself on the back that you have solved the problem just because you've talked about it. No, you don't get credit. We have to come up with an actionable research agenda -- that is, you have to come up with an actionable research agenda to overcome the identified repurposing roadblocks. So, I may have lots of opinions about this, and I certainly do. That's not why I'm here. I'm here to listen to you. We need all of your help to devise this research agenda. So, this has been a typically NCATS team effort to get us here. I do want to call out Bobbie Mount on our side because she's really done a lot of the heavy lifting from a scientific point of view, but many, many, many others, and they're all on this list. Some of them -- many of the names that you'll recognize because some of them you'll hear talking during the course of the next two days. And again, I want to thank our colleagues at FDA and Reagan-Udall for doing this with us, and these people -- in a good team, you don't indicate what organizations they are. They're from both organizations.

And lastly, the sentence I have to do, and I will say this with my most impressive bureaucratic voice, "The views and opinions expressed by invitees at this workshop should not be considered an endorsement by any government agency." How'd I do? Was that good? But seriously, that is the message that you have to realize. And it's not only important for something I need to say, but it's also important for us to have free and, you know, open discussion, that you're not talking on the behalf of your agency, or even the organization that you're from. These are your personal opinions and that's why you're here.
So, welcome. Put your thinking caps on, your action caps on, your engagement caps on, and welcome to the repurposing scrum for the next two days. So, thank you for coming.

[applause]

Bobbie Ann Mount:
Thank you, Dr. Austin, for that introduction. Our next speaker is Shira Strongin. She is a rare disease patient who has been both benefited and harmed by the use of an off-patent drug. But ultimately, her life was saved by repurposing an off-patent drug, so she is free to go on with her life. She's an intern at the FDA Office of Medical Policy, and she's currently a student at George Washington University. We look forward to hearing what she has to say. She's -- we're here because of patients. We wouldn't be working as hard as we all work if we weren't trying to find treatments that actually help patients at the end of the day.

[applause]

Shira Strongin:
Good morning, everyone. Oh, my voice just cracked, it is too early for this. But thank you so much for being here, and thank you so much to NCATS, FDA for giving me this opportunity. It's such an honor to be here at this truly just groundbreaking conference. So, a little more background on me first. I'm a student at George Washington University majoring in political communications with an intended minor of human services and social justice. So, basically what I'm doing now is what I would like to be doing for the rest of my life. I am a rare disease patient. I have an undiagnosed disease that I will talk more about later, but for now I'd like to more mention my policy side.

So, I got bit by the policy bug when I was 12 and went to the Hill for the first time, never looked back. I worked on 21st Century Cures legislation, which some of you might be familiar with, and was lucky enough to work with that on OPEN ACT, which was specifically about repurposing, so this is a huge passion project of mine. My goal with this presentation is to humanize the issue of repurposing drugs. I think so often we just talk about the data points, and that data is astounding. In my community of rare diseases there are almost 7,000 plus rare diseases with more being discovered every day. And of those 7,000 plus diseases, only five percent have approved therapies, and I'm in that 95 percent that don't. And I think something that's shocking about that is, as much as those statistics are hard hitting, it still doesn't explain the stories. So, today you will hear from me and my story, and later you will hear from the amazing Dr. David Fajgenbaum, who is sitting over there. Fun fact about Dr. David Fajgenbaum, and I actually was doing a little bit of Google searching last night and turns out we have the same birthday. So, not only are we rare diseases patients, we were both born on March 29th, so I'm expecting birthday cards from everyone just considering how much we appreciate the gift of aging, more than the traditional population.

So, to kick this off, who has heard of South Park or has watched any episodes of South Park. Anybody? Okay, good, so you'll understand this reference. All right, so, there's this episode with the underpants gnomes, and they had this brilliant business plan where they were going to collect underwear and they were going to make a profit. Here's the problem, they had no phase two. They didn't know how they were going to make that profit; they just knew that if they collected the underwear, they would make a profit in the end. Well, repurposing is kind of like that. We have all of our stakeholders here in phase one. We have NIH, NCATS here, we have FDA, we have patient advocacy groups, we have biopharmaceutical companies, we have so many people who all want to get to the same solution. We
want to get to repurposing, but we have no idea how to get there. And that's what this conference is for. Like I said before, my goal of this presentation is to kind of humanize the issue because this is a critical component of it. However, there's a much broader conversation that needs to happen about how we can actually go about getting drugs to patients. So, hopefully you'll stay with me there.

So, these pictures are from the past few years. We don't have the time for me to go through my entire medical journey because we need to actually be productive throughout these two days, so instead I'm going to break to down a little bit. Over the past few years, I have travelled to 13 states. Technically 12 with one district, but that's a separate policy ask, seeking medical care. I have received 10 transfusions, I have been in the hospital on nine major holidays, not including birthdays which have also been spent quite frequently in hospitals. I have relearned how to walk about five times, and yes, I'm here wearing heels today. So, just needed to throw that out there.

[laughter]

I've had four major surgeries, and of those major surgeries, only one was in my home state, and even then, not in my own country. And I spent a year of my life relearning how to read, write, and speak as a result of neurovascular events. Again, that's all statistics, numbers, data. But let me tell you about my real story.

A few years ago, I was slipping down the barrel of a very, very quick downslide. I was wheelchair bound. I was having major neurovascular events multiple times a day, about five, 10 seizures at some points. TIA's the night before the Common App came out, which is the application that you apply to college with. I ended up in the ER with a really transient ischemic attack that they ended up keeping me for, thinking I could have a major stroke. Also ended up with that on my mom's birthday a couple years ago, so, sorry, Mom. I was not only losing function of my body, I was losing function of my mind, which was quite honestly a lot more terrifying. I was losing my ability to speak, I was losing my ability to read, to write, and as somebody who obviously has a political communications major, highly values communication, this was truly terrifying. I was losing my memory. They were thinking -- they, being my doctors -- were thinking that a possibility was me getting early onset dementia, probably about the age 25, which I was not super thrilled about being a teenager. I was losing my personality too. I was very anxious and angry all the time. And while, definitely, part of that was from the experience that was going on, it was also neuro events were just altering everything that was going on and it was truly terrifying. My doctors kind of came to a standstill. They didn't know what options we had left, and so they decided to throw a couple of chemotherapeutic agents at me and a blood thinner. Interesting choice, considering I have a platelet disorder, which means my platelets don't coagulate properly, but since I kept getting blood clots they were like, "We've got to do something." It was a hail Mary and thank god it worked.

So, I could tell you exactly how well I'm doing, though hopefully you can see now that none of these pictures are exactly where I'm at today, but I thought I could just show you instead. Let's see.

[video playing]

Shira Strongin:
I would like to point out I was wearing an NIH sweatshirt in the video. Always repping, just a little bit.

[laughter]
If you asked me about a few years ago where I would be, I honestly would have said dead, and I would not have been exaggerating. That was where my life was headed. Today, I am interning at the FDA in the Office of Medical Policy under the amazing Heather Stone. I am a full-time college student. I run a successful non-profit called Sick Chicks, which is dedicated to united and empowering women with various illnesses and disabilities. I live across the country from my hometown of California. I do trapeze. I go rock climbing sometimes, too. Really fun. My doctors are not as big of a fan of that one because of all of the bruising but, you know, we make do. And, even a few years after being on the protocol and regimen of these therapeutic agents, I’m lucky enough to be able to cut down on my dosages and now only on one chemotherapeutic agent, which makes a huge difference during sick season for me.

Potential solutions. So, this a super complex issue. There is no simple solution. In the legislation that I worked on a few years ago, 21st Century Cures, one of the bills within it that I mentioned earlier, OPEN ACT, was very big on increasing biopharma incentive. And that’s just a small piece of the solution. I know today a lot of people are here from biopharmaceutical companies, and we’re so grateful for you being here, but we need to recognize that that is not everything. Instead, we need to focus on collecting and making data accessible for decision making. I talked about the ways my life has been saved by repurpose drugs, I’ve also been harmed by repurpose drugs because we didn't have this data to look at of how it could affect my body. Ultimately the pros greatly outweighed the cons and I am forever grateful. However, this could have been organized so much better for patients not just like me, but any patient in any community.

Later today, you'll be hearing about an app called CURE ID which does directly this with infectious diseases, and hopefully we'll have other applications later and I'm so excited for you to hear about it. We need to use real world evidence to direct clinical trials, which Dr. Fajgenbaum will be speaking about later. So many of these patients, including myself, with rare diseases, we’re not going to get clinical trials very easily. We have tiny patient populations, we don't have the funding, we don't have the backing, but when we know that there are medications that are currently being used, we all know that everybody is repurposing medications, we can direct them to clinical trials more effectively after showing efficacy. Well, suggestion of efficacy. We also really need to work with physicians and insurance companies to remove the barriers with prescribing. This is a big one. I am beyond lucky that my physicians were willing to take a chance and prescribe this hail Mary for me. I'm beyond lucky that my insurance covered this hail Mary. I'm beyond lucky that, even if my insurance hadn't covered it, my parents could help to afford it. Most patients aren't that lucky. A lot of physicians will not be prescribing off-patent drugs because they are afraid of the consequences. A lot of physicians and insurance companies will not then cover it, which means patients won't have access to it, and it's a big spiral. So, I’m so looking forward to hearing some of the ideas for solutions here today.

One thing that I want to touch on really quickly. There's this phrase that gets thrown around in medicine a lot, and, using the specific example of chemotherapeutic agents because that’s personal at home here, is the patient failed chemo. How messed up is that? The patient failed chemo. The patient didn't fail the drugs. The drugs failed the patient and, by extent, we as a system failed the patient for not getting them access to other options. We cannot let this happen. So, today I implore you guys to change the way this system works. We have to find out of the box solutions for out of the box patients, like myself. I wouldn’t be here today without repurposed medication. I am so grateful for it. But there needs to be a better, streamlined process. I cannot wait to hear what everybody's ideas come from and see what the action items are. So, thank you all.
Bobbie Ann Mount:
Thank you, Shira. Next, I'm going to cover kind of the overall structure of the meeting as we planned it. Miss Heather Stone is seated here in the front. She's on the agenda as doing this with me, but she's actually going to cover her part in the afternoon session when we get more into the clinical experience spectrum. Trying to advance the slide. There we go.

So, this slide is the overview of what we'll be talking about on day one. So, Dr. Austin covered much of this already, but we are focused today on already marketed drugs that don't have any patent life and they don't have any regulatory exclusivity. In an ideal world, we would like to solve the problems that exist between somebody coming up with a new idea for a therapeutic indication pair and actually getting that indication on a drug label. We've asked all the speakers to identify challenges. Every step along the way we're going a GPS landscaping exercise today, and I probably have to give a disclaimer before I show an ice slide that I'm from northeastern Minnesota, I grew up near Lake Superior. Jamie Zigterman helped me with the slides, she also grew up near the Great Lakes in Michigan. So, we don't see large volumes of ice as something that can't be solved if we don't all work together, come up with a solution. So, we sometimes talk about the challenges in this space as roadblocks, but I feel like roadblocks gives a misperception that you can just go over a hurdle or go around it, but the problem we have is that nobody owns that problems and we can't even see the whole entirety of the problem. So, that's why we're doing a landscaping exercise of everyone in the healthcare ecosystems perspective today on what the challenges are in capturing the solutions that people have in mind. We want to even capture solutions even if they're not viable so we can bust urban myths about problems that seem like they're easier to solve than they really are, and perhaps there are some challenges we think about impossible to solve, but if we just talk to the right people they will have solutions.

So, after my talk we will have a regulatory 101 to get everyone on the same page for what the regulatory pathways are. We also will have a panel discussion after the regulatory session where we'll talk about the lack of incentives and decisions that companies make when they're deciding whether or not to update drug labels with new information when there is a therapy that could really help patients. We also can't ignore the fact that there's a lot of economic challenges in this space. As government agencies, we actually don't have any control over how drugs are priced. But we don't want to do something that makes things worse, so we want to at least understand what the economic levers are. And, of course, there are a lot of scientists here, there are a lot of data challenges that we're going to be talking about. In the morning, we'll start more in the preclinical space. I realize all of these drugs have been in humans, but sometimes we still have to do some preclinical work if there's not enough information for the new use for that new indication in humans, and I'll get to that on the next slide.

So, we consider what we're going to talk about for the data challenges as levels of evidence. And what you consider to be suitable levels of evidence really depends on the perspective you're coming from. If you're a patient that has a disease that doesn't have an effective therapy, your perspective is not going to match with somebody who's making a decision about regulatory approval is going to be interested in. But we would like to solve some of the challenges in data quality and data inoperability in order for the existing information that we have available to actually get on drug labels. So, we'll start in the morning on the first box on the top of this slide. We'll be kicked off our intramural program, Christine Colvis will be doing the hypothesis research introduction where some regulatory studies are needed before you can even consider testing a drug in humans. It could be that a drug was developed for cancer and they just have short term consideration data, but they need long-term safety studies before you can consider
a clinical trial. And then in the afternoon, we'll get into the evidentiary standards more in the clinical experience spectrum, starting with the situation where there's a limited amount of information for clinical data, and I'm letting Heather Stone cover this in more detail because that's really her expertise. She works in the Office of Medical Policy and that office is actually trying to get some guidance in place for using real-world evidence and real-world data to update drug labels. So, we'll get into a session on real-world evidence, real-world data, how electronic health records might not be ideal right now, but how might they be more useful in the future for research. They were developed more for payment information, but there is some data there that we can use and how can we improve that going forward. So, we'll have discussions about data access, quality, and sometimes the data's there but you just need somebody who knows how to aggregate that, so we have Matt Might talking about that later on today. So, as you can see, we have a diversity of perspectives that we'll be hearing today.

And then on day two, that's when we're going to come up with solutions. We're going to prioritize the problems that we heard, so our goal is to figure out, with all of these problems that we've heard, is there a shortlist of problems that if we solve these we would make the most progress at getting more treatments to more patients more quickly? Are they actually addressable in the short, medium, and long-term, and who owns them? We would have solved these a long time ago if we knew who owned the problems, but we don't know. So, if we can find some space where different organizations are willing to own pieces of the problems and to find a shared space where we're going to have to work together to accomplish the mission, that's what we'll be doing tomorrow. And at the end of the day tomorrow, we hope to have a research agenda and a list of problems that we need to solve to actually do that research agenda. We have a picture on this slide of an icebreaker ship. I don't think we have built the icebreaker ship yet, but that's what we're tasked to do so that we don't have an impenetrable series of icebergs, but we have this ice that actually looks like an icebreaker ship can sail through and actually make some progress.

So, with that introduction I'm going to then turn things over to the next session. There's going to be a session where Miss Katherine Schumann will introduce the regulatory landscape so we can all be on the same page for the what the possibilities are. And then we're going to have a panel discussion from three attorneys who will cover some of these overarching issues that can't be ignored about the incentives about the considerations that people make for label updates. And just the general, what's the problem? It seems so simple in the popular press, but use patents aren't enforceable. And they've come up with a lot of other questions that I've seen by email that I'll let them handle. So, I'll turn it over to Miss Schumann now.

[k applause]

Katherine Schumann:
Okay. I wish I had worn my higher heels, I need to, like, stand on my tiptoes. Great, thanks. Excuse my voice today, but thanks very much for the opportunity to be here. I'm Katie Schumann, I'm the acting deputy director in the Division of Regulatory Policy in the Office of New Drug Policy of FDA. And I'm here to give you all some background on new drug regulatory pathways to set the stage for some of the conversations of this panel and for the rest of the two days. Let's see. So, the disclaimer that, I think you've already heard, these views today are my own and don't represent FDAs.

Okay. So, today I'm going to briefly talk through the new drug application process, give you a brief overview, go through the three regulatory pathways to market a new drug in the United States, and briefly touch on, because I think it would be of interest to anyone interested in repurposing, post-
marketing responsibilities of applicants that submit new drug applications to FDA because those may be things that folks need to consider when they're thinking about the feasibility of repurposing.

So, the Federal Food, Drug, and Cosmetic Act requires anyone who wants to market a new drug in the United States to submit a new drug application, an NDA, or an abbreviated new drug application, an ANDA, to FDA for approval before marketing. And Section 505 of the act describes three types of applications. The first is a 505(b)(1) NDA, and that is what we consider a standalone NDA. The second is a 505(b)(2) NDA, that's the intermediate pathway that I think most folks thinking of repurposing would be interested in. And then there's the 505(j) pathway, which is the generic drug pathway which is what are essentially duplicate drugs. So, when FDA receives an application from someone who's interested in marketing a drug, certain information is required to be provided to the agency for its review. And these include forms and administrative information, including proposed labeling, patent information, summaries of data for our review, product quality information, which includes drug product and drug substance information and manufacturing and facility information, nonclinical study reports, including in vitro and animal studies, and then clinical study reports, which would include case report forms and data sets. And this is all required to be in an electronic format called the electronic common technical document.

So, applicants also are required to pay a fee for FDA to review an NDA, and that has to be paid before the application is received. For applications with clinical data, that changes from fiscal year to fiscal year, but it ranges from $2 to $2.5 million for an application with clinical data. Once FDA receives the application, a multidisciplinary review team is convened with experts in various fields, and they evaluate the NDA to make sure it's complete for review and can be filed, and then the team decides on whether it will get a standard or priority review clock that is six or 10 months. If FDA determines it can be filed, each of the reviewers on the team will conduct a full review of their section of the application. During that same period of time while FDA is reviewing the application, the agency may decide to send personnel out to clinical studies sites or manufacturing facilities sites to conduct preapproval inspections. And, if the information in the application raise novel questions of safety and effectiveness, FDA may decide to convene a panel of experts for a public discussion and an advisory committee meeting. At the end of the review cycle, FDA decides which official action to take, and that can either be an approval action or a complete response action. If it's a complete response, the letter to the applicant will detail the deficiencies that the applicant would need to address in order for the application to be approved. And this slide is a slide of the NDA review timeline. For the sake of time, I'm not going to go through the details today, but this is the timeline and some of the various steps that we go through when reviewing an application.

So, now I'm going to transition to the review pathways for new drugs. As I mentioned, 505(b)(1) NDAs are considered a standalone NDA. This is what you typically think of when an innovator would submit an NDA, for example, an NME. So, a 505(1) NDA contains full reports of safety and effectiveness -- of investigations of safety and effectiveness, and those investigations were conducting by or for the applicant, or the applicant has gotten a right of reference or use to those studies, and those include clinical and nonclinical investigations. So, this means that the person submitting the applications owns all the data.

The 505(b)(2) NDA pathway is that immediate pathway, and it's probably of greatest interest here because, while the 505(b)(2) NDA still contains full reports of safety and effectiveness, at least some of the information required for approval of the drug comes from studies that weren't conducted by the applicant and for which they don't have a right of reference. So, that means they're relying on someone
else's studies for part of their application, and this allows for flexibility in the characteristics of the proposed product, relative to an approved product, but also allows the applicant not to have to conduct studies on what is already known about the product. So, in this case if we're talking about approved drugs, an applicant may not have to conduct, for example, basic toxicology again when that information of the drug is already known. So, when a 505(b)(2) comes to FDA, it typically relies upon one of two things. The first would be FDA's prior findings of safety and effectiveness for a previously approved drug, a drug that is listed in the orange book. So, a (b)(2) applicant is permitted to rely on FDA's findings of a previously approved drug, only to the extent that the proposed product shares characteristics with that approved drug. So, for example, the same active ingredient or other characteristics. The applicant also is expected to establish a bridge to the approved product in order to support and justify reliance, and typically that's done with comparative bioavailability data. One challenge that can arise with establishing a bridge is when a particular listed drug to which you're trying to bridge is either the NDA is withdrawn or the product is discontinued. Because then, for example, the product may not be available to conduct NDA studies.

In addition, the applicant must include their own data sufficient to support any difference between the product they're proposing and the previously approved drug. So, for example, if a 505(b)(2) NDA is submitted for a new indication relative to the approved product, the applicant may need to conduct studies of safety and effectiveness for that new use, and that information would come in the application. The second thing that a 505(b)(2) application can rely upon is published literature, and in that case the applicant is also -- needs to provide a bridge to establish why reliance on that published literature is scientifically justified. So, is it the same active ingredient and the same type of product and why would FDA be able to rely on that literature to support that drug?

There are a few additional considerations for submitting a 505(b)(2) NDA. So, filing by FDA or the approval of the 505(b)(2) NDA may be delayed to patent or exclusivity protections covering an approved product. Additionally, 505(b)(2) applicants are obligated to provide appropriate patent certifications or a statement with their NDA to patents listed in the orange book for the previously approved drug. I think the agenda for today is focusing on products where this wouldn't be a concern, but it is something for potential (b)(2) applicants to think through. And here are examples of differences that could be supported between a proposed product and a listed drug via the 505(b)(2) pathway. So, FDA has seen new dosage form and routes of administration come in, new indications, which I think primarily is the interest today, different strengths, different dosing regimens, different fixed combinations of active ingredients, and different formulations to the extent that those formulations would be permitted via the generic drug pathway. So, that is the (b)(2) pathway in a nutshell.

And just for completeness, the last pathway is the 505(j) or ANDA pathway for generic drugs. Generics are generally required to demonstrate that the proposed product and the reference listed drug are the same with respect to active ingredient, dosage form, route strength, conditions of use, and labelling. So, it's a fairly restrictive pathway and I think probably wouldn't be useful, for the most part, in what we're thinking about today. ANDAs must include sufficient information to demonstrate that the product is bioequivalent to the reference listed drug, which is not always required in the (b)(2) context and ensure identify strength quality and purity. Like the (b)(2) pathway, ANDA receipt or approval can be delayed due to patents or exclusivity and FDA generally won't accept a 505(b)(2) application for a product that could be approved via the generic drug pathway.

So, lastly, I just wanted to touch on some examples of post-marketing responsibilities of applicants because I think that anyone considering the (b)(2) pathway for an approved product would need to
consider these obligations when considering the feasibility of repurposing. So, once an NDA is approved, applicants throughout the lifecycle of the drug do have obligations. They need to periodically provide safety reporting to FDA, they need to provide annual reports to the agency, to the extent that there are changes made to the product over time they may need to submit supplements to the agency to support those changes, over time they would need to propose any revisions to update product labeling, they would be obligated to fulfill post-marketing commitments or requirements -- for example, pediatric studies under PREA would apply -- and then there are annual PDUFA program fees that are separate from the initial application fee that are required to be paid.

So, here I've listed a few resources that go into the topics I've covered in much greater detail if you're interested. So, the draft guidance on (b)(2) applications, determining whether to submit an ANDA or a (b)(2) application, and lastly there's a guidance there on requesting a meeting with the agency. And I would say that for anyone interested in repurposing a particular drug and what might be needed to submit an application for FDA, a meeting with the agency is the best first step and we look forward to discussing those issues with you. And with that, I'll turn it over to the panel.

[applause]

Matt Fedowitz:
[inaudible] Well, then I'll just talk loud. My name's Matt Fedowitz, I'm [inaudible] in Washington, D.C.

[inaudible commentary]

Matt Fedowitz:
Yeah, Matt Fedowitz of Buchanan Ingersoll & Rooney in Washington, D.C., and I'm also a cofounder of the group called the 505(b)(2) Platform, which is a non-profit dedicated to developing and helping organizations and companies develop (b)(2) products. I think this topic is incredibly timely. Over the last year I've been at a number of conferences across the U.S. where we've had C-suite executives from pharmaceutical companies and other executives and high-level individuals that are incredibly interested in this topic of new products. In fact, next week I'm going to be in India speaking about this to companies there who are very interested as well. And I think, to dive into this, we have Kurt Karst from Hyman, Phelps & McNamara, who's going to talk about some industry or legislative perspectives. Then we have Jim Czaban, who's the chair of the FDA practice at DLA Piper in Washington as well, to give an industry aspect. But before we get started, if you guys want to tell a little bit about yourself, just a background?

Kurt Karst:
Sure, thanks Matt. So, my name is Kurt Karst, I'm a director at Hyman, Phelps & McNamara, we're a boutique FDA law firm in D.C. And I've been doing this for about 20 years now, and really my focus is, and I'll be talking about, so I'll probably have undue or slightly biased opinions, on incentives. Do a lot of work with the Hatch-Waxman amendments, patents, exclusivity issues, and, as I've learned over time, incentives are perhaps not the key, but certainly a very important aspect when it comes to repurposing.

Jim Czaban:
Thanks, Matt. I'm Jim Czaban, I'm chair of the FDA regulatory practice at DLA Piper, which is quite the opposite of Hyman Phelps in that we have 4,000 lawyers worldwide and are anything but a boutique.
And I've been practicing in this space, FDA regulatory, my entire career. Kurt and I do a lot of the same types of things over the years. We've been across each other in court, next to each other in court, and we have similar backgrounds, maybe different perspectives. I'm going to give maybe a little less of nuts and bolts than you'll talk about, but it's great to be here on this panel, I appreciate it.

Matt Fedowitz:
Great. So, let's get started. Jim, what's the general industry perspective on repurposing of drugs?

Jim Czaban:
So, there's a lot of interest out there in the pharmaceutical and biotech industries. But there's challenges, and I think we need to really start by recognizing the enormous and ever-increasing cost of investment needed to bring novel drugs to the market, and really think about the long-term outcomes of that increased investment. In particular, despite really significantly increased amounts of R and D investment over the last several decades, the number of new drugs, novel drugs approved relative to that investment has not increased. Now, Dr. Austin alluded to this a bit in his opening remarks, but since I'm an attorney I can actually cite to a law to illustrate this phenomenon. Specifically, something called Eroom's Law. Eroom's Law was coined in a 2012 Nature Reviews Drug Discovery article by Jack Scannell, and it describes the observation that the number of new drugs to market by the biopharma industry per billion dollars of U.S. R and D spending has declined steadily and consistently for more than 60 years. And the numbers are pretty eye opening if my slide works. I'm going in the wrong direction. Can we get - - sorry about that. I'm going to show you a bit of a graphic, if we can find it, of Eroom's Law.

[inaudible commentary]

Jim Czaban:
Anyway, so, while they look for that I'll just -- for those of you who have heard of Moore's Law in the computer space, Moore's Law describes -- in the 1960s it was coined to describe the observation that computer chip power, the number of transistors that can be put on a single chip, has doubled every two years for many, many decades. So, it's a very steeply inclined, increasing chart, whereas Eroom's Law, which we may or may not see, has the opposite effect. So, with that you might realize that Eroom is actually Moore spelled backwards. It's a very clever article if you want to look it up and read it. But in the broadest sense, including the two subtypes of repurposing that Dr. Austin mentioned and mentioned -- not actually the topic of this workshop, repurposing is an attractive thing for industry. Repurposed drugs can generally be approved much faster than novel drugs, at lower costs, and with a much higher success rate for FDA approval.

The cost difference between bringing a repurposed drug to market versus a novel drug is vast, some figures I've seen have cited approximately $300 million for approval of a repurposed drug versus $2 to $3 billion or many times more that for bringing a new novel drug to market. According to BCC research a few years ago, the global market for drug repurposing was close to $25 billion in 2015 and was projected to reach over $30 billion by next year. And an imperfect bit of evidence to support the amount of activity in the repurposing space is that roughly twice as many drugs approved in recent years have been approved under the 505(b)(2) process as opposed to the 505(b)(1) full NDA process. So, I think the bottom line is there is interest, there are reasons for that interest, there are, of course, a number of obstacles.

Matt Fedowitz:
So, Jim, if this is so attractive and easy to do, why are we here?
Jim Czaban:
Well, that's a good question, and if I painted too rosy a picture, I will shatter that. Oh, I see --

Male Speaker:
There it is, there it is.

Jim Czaban:
There's Eroom's Law. Okay, great. Just to go back, you can see the vertical axis is number of drugs approved per billion dollars of R and D spending over time on the horizontal axis, and you'll note the nonlinear scale on the vertical axis. So, more and more money and effort is being spent every year, the number of drugs coming out of that effort have not increased proportionately. And then the next slide, just to close it out, comparing -- who's got the button?

Male Speaker:
It's up there.

Jim Czaban:
I'm going to break it again if I push it. Yeah, so there's just a comparison. The Moore's Law computer chip technology advances, drug success has declined relatively. So, those are my only two slides. The question, though, why are we here if it's so easy? And the answer is, of course, it is not so easy. The reality of life in this space is that for many drugs the expected return on investment for a repurposing effort simply isn't there. The title of the workshop, and Dr. Austin's emphasis on the repurposing of off-patent drugs, illustrates the hardest part of the repurposing manscape, if you will, which is, of course, why we're here. And for those sorts of drugs, they're the ones that most often fall into the ROI trap. There's just not enough return on investment expected. And there's two -- in part, there's two elements to this problem. One is the way that generic drugs are approved, marketed, and dispensed in this country. And the other part overlapping is that there are limitations on the existing legal and regulatory incentive mechanism to reward and incentivize the repurposing of off-patent drugs.

Just by way of a little bit of background, and I expect most of you are not lawyers, so congratulations, but patents, generally speaking, give the owner the right to prevent anyone else from making, using, or selling the patented thing. Now, in the drug world, there's three types of patents that we're most interested in. A patent that can cover the actual chemical of the active ingredient, patents that cover the specific formulation of the finished drug product, and patents that cover a method of using that drug. In other words, an indication for that drug. And a patent has a term of 20 years from the filing date of the patent application. So, for all the drugs where any patents on the API or the formulation on the approved uses have expired, generic versions can be freely marketed, subject to FDA approval of course. Now, regulatory exclusivities and other incentive for innovation, and particular in the drug space, can block FDA approval of generic versions for varying amounts of time, depending on which exclusivity we're talking about. And there's two of particular interest and relevance for repurposed drugs. That would be the three-year exclusivity period for drugs that -- new uses of drugs that are approved based on new clinical trials, and the seven-year orphan drug exclusivity for rare diseases, and Kurt I think you're going to talk about the orphan angle on this because it's actually very important and complex.

So, although both new patents and regulatory exclusivities can both cover a new use, a repurposed use of a drug, the reality is they don't protect the company that made that investment in any meaningful way. And that's because when a drug, or a branded drug, or a repurposed drug has more than one
approved use, a generic product can be approved and marketed with labeling that only includes an unpatented or nonexclusive indication, and the labeling would leave out the patented or exclusivity protected indication. Even though -- and this is called skinny labeling. But even though the skinny labeled generic does not have the patent protected or exclusivity protected indication, in practice that generic will usually be substituted automatically at the pharmacy when the patient brings in the prescription, regardless of the indication for which the doctor prescribed it to that patient. So, the generics end up being used for the patented, repurposed use. And in that way, with the skinny labeling, the generic product and the generic manufacturer, is not subject to patent infringement liability even though the use of the generic drug for a patented repurposed use is technically an act of patent infringement. Now, in essence the patent holder has no effective remedy against this type of infringing generic use. Now, it's not really an option for a repurposed drug to then to just be sold as a generic product for generic prices. Generic prices can be 10 percent or even less than the price or an original branded drug, and there's often a lot of other established generic companies with competing products that's never going to satisfy the necessary return on investment.

So, those are some of the barriers to, you know, and the incentive structures for repurposing, and especially in the subcategory that we'll be talking about today and tomorrow.

Matt Fedowitz:
Right, so, why don't the patent owners sue the doctors and pharmacists to keep them from prescribing?

Jim Czaban:
Well, as I said, it can technically be considered patent infringement for a doctor to prescribe a generic version for a patented use of a repurpose drug, and similarly for a pharmacist to dispense it, but there's really no practical way to enforce that patent. A drug company is going to be very low to sue its best customers, i.e. the doctors and the pharmacies, that it relies on for selling its product. But there's an interesting analogy of a case in England recently where the -- a very successful branded product was at the point of facing approved generic competition, but it more recently approved more purposed indication, which had a method of use patent. And in trying to assert that patent against generic companies, the brand company asked the court for, and the court granted, an order requiring Britain's National Health Service to instruct doctors and patients to only prescribe, by name, the branded product when they were prescribing it for the new patented use. It caused a lot of consternation among the pharmacists and doctors because they weren't getting paid for the extra work required to identify which prescriptions applied for which patients and so forth, and to have to send back a prescription for the doctor to rewrite it for the brand if it had been written for the generic. Ultimately, the patent was found to be invalid by the highest court and the NHS order went away. But the question is, would that ever be possible here in the U.S.? And I think probably not, given that the National Health Service in Britain is a unified nationalized health system. It can be done in one order whereas we have 50 states with 50 sets of pharmacy laws and substitution laws. But it's a least a very interesting scenario.

Matt Fedowitz:
Great. Kurt, so what is Congress doing to address drug repurposing?

Kurt Karst:
You know, actually, Shira set me up very well because she -- I think you nicely illustrated what I guess I'll call the South Park Underpants Conundrum, which is this phase two. How do we get from the ideas and the data we have to drug repurposing? And while you mentioned that incentives are certainly not a panacea, and they're not, but they are a very important part because companies need to be able to
recoup their investment. And an -- the incentives really come down to two things, and really, at the end, one. I mean, time and money. If you can save a company either time or money, and because time is money, I guess money, that is an important incentive that is needed. And while the statute does, as Jim mentioned before, already include several incentives for companies to obtain periods of exclusivity here for non-patent or off-patent products, whether it’s three-year exclusivity for new indications, seven-year exclusivity for orphan drugs, and there are some other statutes that provide add-ons, the fact that we don’t have a robust repurposing industry is problem indicative of the fact that the current incentives in the statute, at least the way the system is running, is not sufficient enough for companies to make the needed investment to have robust repurposing drug industry. And Congress, of course, they’ve taken notice of this, and it moves at a glacial pace as well all know. But -- and so, it’s going to take some time, and there have been various initiatives over probably the past eight years to really look at repurposing and address it, potentially, in different manners.

So, you go back to 2011, 2013, there was something called the Modern Cures Act, the modernizing our drug and diagnostics evaluation, a regulatory network Cures Act. We’ll just call it the Modern Cures. And prior to that, there would have patent and exclusivity enhancement for companies who looked at dormant therapies. And I know Dr. Austin said we’re not here to talk about dormant therapies because they don’t meet the criteria here, but some actually do. There are dormant therapies without any patent protection. Where exclusivity, which is, again, non-patent, it’s a marketing type over data exclusivity, can provide the incentives that are necessary for companies to make these research efforts. And as part of that bill, would have actually directed the HHS and IOM to conduct a study in terms of what are the available incentives right now, do they need to be changed, do they need to be enhanced to incentivize companies to pursue repurposing? And then a couple years later, in 2014, 2015, we had the Dormant Therapies Act which was kind of a redo of the Modern Cures Act. And the Dormant Therapies Act was going to look at products that have insufficient patent protection and that show promise to be repurposed. It would have created his new 15-year period of guaranteed, I guess, market protection for a product. Products that have very little or no patent protection, to the extent there is -- there was patent protection, companies would have to give up their patents. But they would have this guaranteed 15-year period to market their repurposed product.

More recently, as Shira noted, the OPEN ACT, the Orphan Product Extensions Now Accelerating Cures and Treatments Act, and that bill would have authorized FDA to designate a drug as a product approved for a new indication provided that, prior to approval of this application for this new use, this drug was already on the market but had never been approved for this new use. And as part of that OPEN ACT, the incentive there was to add-on a period of six months of exclusivity. And while you may think, "Okay, six months isn't that big." it can be. If you happen to have half a billion dollar a year drug, that ends up being a lot of money per day and acts as an incentive for companies. And of course, there are other ways to do that.

Now, all of these bills have been proposed, and they've gotten through various stages of the legislative process, but none of them has made it over the hump yet. And the most recent initiative was probably last year with Senator Hatch before he retired. He proposed a bill called the MODERN Labeling Act, which would have addressed repurposing in a different way, where you have brand name products that are no longer on the market or no longer being marketed, but there are generic versions of those products out there. And over time, it’s become apparent that those products do have utility for other uses, but because generic drug manufacturers are constrained from amending their labeling from adding anything new in there, because it has to be the same as the brand labeling, they're unable to add this information to labeling. So, this bill would have allowed, if there's sufficient medical literature,
sufficient information on a use of a product, it could be actually be added to the generic drug labeling. And various avenues to address these repurposing issues, old drugs for which there is no longer an interest, which there is generic competition already out there, and for companies to seek approval for new uses of old drugs. But the incentives need to be there to do that.

Whether, again, it's time, creating some type of a voucher for companies to be able to get faster approval at FDA, a tax incentive, a market exclusivity incentive, but of course it has to be meaningful. As Jim mentioned, there are issues when it comes so-called skinny labeling, where a brand company gets approval for a product for a second use, that product -- once the generic is approved, if it's approved only for that first use, the non-protected use, it is going to appear in the orange book as a fully substitutable version of the brand product. And because state laws don't differentiate between indications, they simply refer to the orange book, and if FDA said its substitutable, then it's substitutable. Those substitutions are made without any regard to indicated, therefore really gutting that exclusivity at the end of the day. So, there has to be some type of meaningful exclusivity to be able to incentivize companies to repurpose products.

Matt Fedowitz:
Kurt, so, in the repurposing space, why are rare diseases so attractive?

Kurt Karst:
Actually, I think it comes back to the time-money issue. So, in the rare disease space, one, there doesn't tend to be as much competition when you tend to get into smaller diseases, those with very little prevalence. An orphan disease is generally defined as one with U.S. population or less than 200,000 persons. And of course, you can get into ultrarare diseases, less than 10,000 or less than 5,000. So, there tends to be less competition as an initial matter. But, the exclusivity periods, the statute the law allows for rare diseases, are much more significant than they are for your run of the mill drug for a very prevalent disease. You have tax credits, you have a protocol assistance, you have user fees at FDA not being applicable. And for a small company, a $3 million fee to submit an application to FDA is a pretty significant expense, so that's taken away. And of course, you have seven-year period of marketing exclusivity at FDA. And I guess, finally, in the orphan drug space, to get a period of exclusivity there's no requirement that you even conduct clinical studies if there's sufficient literature out there. You can get an approval of a 505(b)(2) application. A literature-based 505(b)(2) without having conducted studies get approval, get a seven-year period of marketing exclusivity. So again, time and money being major factors there.

Matt Fedowitz:
Okay, and so, despite these incentives, there seems to be some criticisms with regard to what's going on with the orphan space. Can you explain that?

Kurt Karst:
Yeah, this is kind of the double-edged sword here. I'm going to read you a quote. So, you tell me how relevant this is to today. "Critics in Congress and in the pharmaceutical industry and patient groups say that, while the orphan drug act has generally worked, it has proved to be a bonanza for the makers of some very big drugs allowing them to charge higher prices than there would have been with competition." Sounds like something ripped out of today's headlines with the drug pricing debate going on right now in Congress, but yet, that was from 1990 in the New York Times article.

So, the issue of -- or at least the concern over drug prices, it's cyclical issue. A few years ago, it was
relatively non-existent, and then we had Turing Pharmaceuticals and some other incidents which really
raised the profile of drug pricing, that has of course now lead to legislation being introduced, being
considered right now but Congress to address some of these drug pricing issues. And part of some of the
critics there have said companies getting approval for new uses for old drugs and then charging X
amount for these products is unconscionable. I won’t commit on the unconscionability or not of drug
prices, but on the one hand you have Congress saying, “We need to stimulate repurposing, we need to
get these products approved for new uses,” and the on the other hand, we have Congress saying, "But
be careful what you charge.” So, there’s a rub there, and how do we deal with that and talk about
incentives at the same time? Certainly, right now and in the current congressional atmosphere, it’s
difficult.

Matt Fedowitz:
Jim, what type of legal or regulatory approaches have you seen proposed that will incentivize drug
repurposing?

Jim Czaban:
So, we actually have options under the current law where a repurposed off-patent drug could avoid to
some degree, perhaps a large degree, the skinny label generic problem I described. And that's to get a
generic drug approved, as Katie described in her presentation, the generic has to be the same dosage,
form, strength, route of administration as the branded drug. So, if an existing drug is out there in, you
know, a capsule form at 100 milligrams, what have you, and the repurposed drug for a new indication is
or can be made in, you know, a topical form, or injectable, or a different, you know, dosage strengths, or
different routes of administration, those would not be interchangeable under the typical state, you
know, pharmacy laws. They would not be A-rated to each other in FDAs orange book. So, that's an
option in some cases. It wouldn't completely eliminate things because, you know, a doctor could still do
a therapeutic switch of a generic version despite the differences, it would just be more difficult.

There's an interesting proposal I read dealing with the patent rights, if you will, and that proposal was
essentially to use the prior authorization type model along with big data, electronic health records to
identify when a drug has been prescribed to an individual patient for a patented new use. And to then
make that individual information available in the aggregate to the owner of a patent so that they could
recoup their patent royalties, if you will, based on the number of otherwise infringing prescriptions.
Now, this law review article, there's sort of two drafts of it out there from a couple years ago. Incredible
amount of detail and discussion. I'm pretty skeptical that it could work for a lot of reasons, but it's
creative. Whether the political climate would allow such a, you know, windfalls as it might be
characterized to a drug company is probably pretty questionable. And there's others out there, and Kurt,
you probably heard some other proposals.

Kurt Karst:
There are many. Again, on the incentive front, there's the concept of what's called wild card exclusivity,
which has been discussed, whereby a company, let's say, getting approval for a repurposed drug for a
rare disease would get some short period of marketing exclusivity that they could apply to any one of
their drugs that they want. Now, that could be really controversial. If I've got Lipitor out there, it's off-
patent now, but the best-selling drug in the world at one point in time, $8 billion, $12 billion a year,
whatever it was. And suddenly, generics are ready to come on the market and there's now a six month --
an additional six-month period of exclusivity. I mean, it is a massive incentive, therefore, for some
companies, but you also have to consider the effects of delaying generic competition and the savings
that would naturally come from that. It's always going to be a give and take; it depends on what needs
to take precedent.

Matt Fedowitz:
Interesting. So, on the -- Katie had mentioned the different types of drug applications. On one end of the spectrum, you have (b)(1) brand manufacturers, on the other end of the spectrum you have (j) manufacturers, generic drug manufacturers. Do you think these two ends of the spectrum need to sort of relearn or change their thinking about their approach and what they're going after? For example, perhaps the generic manufacturers are used to just a formulaic approach to putting a product on the market and a brand manufacturer wants to just seek a blockbuster product. Do you think they need to change their mindset?

Kurt Karst:
So, from my perspective, I think that change has largely occurred already. You know, if I -- the three applications that we're talking about, if the 505(b)(1) is that wallpaper over there and the ANDA is that wallpaper over there, the 505(b)(2) application is all of this room in between. It is the most malleable type of application. There is -- it can be used for almost anything. Something that is very close to a generic. Maybe it's a formulation difference that's not permitted as a generic. Maybe it's a new chemical entity and there's a lot of published literature out there. Almost anything can be a 505(b)(2). I used to teach a course at FDA, going back to 1999, and I always asked the question, "Who knows what a (b)(2) application is?" And the first few years I'd have one, two hands raised, and by the end of my tenure doing that, sometime in 2012, '13, every hand in the room would go up, and that's reflected these days in FDAs drug approval numbers. If you take a look at the annual drug approval course that FDA puts out, there's a column for 505(b)(2)'s, yes or no? And if you go down that list, there are a whole heck of a lot of 505(b)(2)'s. So, folks have learned, I think, already to use the 505(b)(2) mechanism for various innovative ways, because it is, again, a very malleable concept and it just needs to be more integrated into the drug repurposing world. But again, that's where the incentives come into play.

Jim Czaban:
The irony of this is that the FDA's approach to 505(b)(2) is based on a draft guidance from 1999 that has never been finalized, yet it's now apparently the predominant mode of drug approvals. And I remember, you know, in the early 2000s debating with another industry expert in a conference at Harvard as to whether FDAs (b)(2) approach was unconstitutional, and there were efforts, serious efforts, by some branded companies petitioning FDA and threatening to sue over its 505(b)(2) approach. Yet, here we are today, no final guidance --

Kurt Karst:
True.

Jim Czaban:
-- and this is the world we live in.

Kurt Karst:
Right. And what's it really at the heart, what makes an application a (b)(2)? I mean, you can have 25 phase three clinical studies in your application and still be a (b)(2). What makes you a (b)(2) is you relying on something, whether that's PharmTox, whether that's efficacy information, something for which you do not have a right of reference. And that may be published literature reports of safety efficacy studies, but it is -- that is the key to you being a 505(b)(2). You're relying on something for which you don't have a right of reference. You might be a little (b)(2), just one PharmTox study or FDA's
findings of safety for a particular drug, or you may be a big (b)(2) where you’re relying on almost everything because you’re just doing a dosage form change from table to capsule. But it is the vehicle, at the end of the day, for repurposing.

Matt Fedowitz:
So, do you think further guidance might be a cure to the [unintelligible] step here, or is that -- I mean, it seems like we need something new.

Kurt Karst:
Well, from mine -- it's not -- I think a lot of the tools are there. At least -- so, the regulatory, the legal tools are there. Again, I think it comes down to, in large part, incentives. The current statute does offer incentives, but clearly, they're not sufficient enough, or they're not well-known enough, which I can't believe. So, there has to be something well-crafted, targeted to repurposed products that provide those incentives to get people to develop those prices, whatever that incentive is. Whether it's a tax-based incentive, whether it's an exclusivity incentive, whether it's some type of a patent incentive. I don't know what the best route is there, but you need that incentive because that's what -- again, having done this for 20 years, that's what companies respond to. They respond to incentives.

Jim Czaban:
Right. I guess, let me know if you all agree, you know, why we're focused on repurposing off-patent drugs, it does not mean that there could be a new, novel use for that off-patent drug that could be patented.

Bobbie Ann Mount:
I'm sorry, we're going have to move on to the next session.

[laughter]

This has been an excellent discussion, I'm sure it could continue for quite some time.

[applause]

Matt Fedowitz:
Clearly, we all get into this a little too much, right?

[laughter]

Bobbie Ann Mount:
Our next panel will get into the series of data challenges, and Christine Colvis is the director of our office. New Therapeutic Uses is just one of them many initiatives that she works on, but she leads the drug development partnership programs, and she'll be moderating the first session on the hypothesis driven research where there's not enough data yet for the new indication to be used in humans. And I will let her introduce the two participants in this session.

[applause]

Christin Colvis:
Thank you, Bobbie Ann. And we have -- it's been such a strong start to this meeting, so that's been
really, really exciting. I think you might invite Don and Scott to join me up here. We do have a confidence screen in the front, so even if you're sitting here you'll be able to see what the slides are that are being projected, and for our person who's doing the slides, we'll be starting with Dr. Lo's slides this morning.

So, I can't tell you how exciting it is, actually, to be at this meeting and to have this meeting actually taking place. This is something that we've been thinking about for several years now, and Bobbie Ann and I with the new therapeutic uses program, we hear from a lot of investigators out there in the research world and the academic world who have ideas for repurposing drugs that are on the market that no longer are on-patent. And, you know, but we know that finding a path forward for these is actually quite challenging, and so as both Bobbie Ann and Dr. Austin have mentioned, you know, throughout the day we really want to get a sense of kind of the landscape of all different situations and the various different sectors and players that are involved in this space to really understand that, if we actually improve things over here, does it actually make it worse in some other part of the healthcare ecosystem? And so, as Bobbie Ann mentioned, the first two presentations now are going to be from Dr. Lo, one of my colleagues at NCATS, and from Dr. Weir, who's at the University of Kansas. We're particularly focusing on cases where there is no or very, very little data on the off-patent drug in humans because it isn't being used off label. And so, this may have come from screening -- using a [unintelligible] to screen the NCATS pharmaceutical collection that Chris mentioned, or it may come from literature that people recognize that the mechanism of action for a drug is actually potentially could be used for a new indication, but where we actually haven't been using the drug actually in humans. So, with that, I'm going to go ahead and hand it over to Don to get us started. So, thank you, Dr. Lo.

Don Lo:
Thank you, Christine. Morning. The last session was great, but not exactly rosy.

[laughter]

And you can usually count on me to be the sunny side guy, really kind of "rah rah". But as I was putting together the slides, I realized these are not exactly rosy slides either. But the good news is I just met Scott this morning and over the last couple weeks, he's a very positive guy.

[laughter]

So, I'm counting on Scott to kind of bring up the mood on the second side. So, let's see. Did we lose the - -

Christine Colvis:
Oh, is the clicker -- sorry.

Don Lo:
Thank you.

Christine Colvis:
And Don, I think that timer is actually for the whole session, not just for you.

Don Lo:
Oh, Christine. So, Christine just said I could have the whole time.
[laughter]

So, the first slide just shows where all the science folks among us, that it kind of starts off at the very beginning. So, not on the back end, but on the front end when you first get that notion that there might be a repurposing opportunity. And Chris already mentioned these of course, but usually it's either something like an observation in a lab, it might be, you know, a cell-based screen or assay, it might be some preclinical animal testing, or it really could be an observation in a clinic that there's efficacy in another indication, but you get the idea that it might work in a different indication. And of course, it all leads to exactly what we've been talking about all morning, which is this amazing opportunity to, essentially, redirect, you know, a known drug with clinical benefit. And the attraction, despite the last session, was that at least the premarketing, pre-IND, maybe there's an opportunity to get around what we often call the Valley of Death, which is this area, somewhere late in discovery as we get into preclinical development, into phase one, phase two clinical trials, where the failure rate is so high and so many drugs die along that path, that period, that studies become very hard to do, very hard to fund. But if you have a drug that already works in humans, maybe there's a higher chance of success because, of course, clinical benefits has been demonstrated elsewhere, and along with that some degree of safety. And it has been mentioned, there's already a track record for being able to manufacture that drug agent practically.

So, it seems like all the kind of cards are stacked in your favor, but as the little subheadings show, of course the clinical benefit and the safety really have been shown in a specific case. You know, in a particular organ, let's say, particular target, particular type of disease, and the drug product, if it does have to be reformulated, the route of administration change, there may be some surprises along the way.

And in this slide, basically, are those questions that as you contemplate redirecting the indication for a known drug, you might encounter these issues from the very beginning that you already anticipate. That you might have to reformulate the drug, change the dosage, the route, the dosage form, and then the drug exposure, you know, very often if you're a basic scientist, as I was for many, many years, you don't really think about the -- very often, the idea that different organs are in different places, the drug exposure is really different. So, your original and inspiration and great idea may really encounter some complications along the way. And of course, safety and toxicity is all tied into all of these considerations where the amount of exposure in particular organs and parts of the body may lead you to additional safety and toxicology considerations, that weren't addressed the first time around.

So, as you're contemplating, as we're contemplating these issues on the front end, not on the back end, you know, the first regulatory -- big regulatory step that you would encounter, of course, is whether or not you would need to file a new IND to start testing clinically. And just as the last few slides have outlined, the FDA has guidance -- I think this is also a draft document. But in it, there's some key requirements for having to file a new IND for the repurposed drug that are exactly along these lines. That is, first of all, of course, if it's a new indication and in the repurposing side, if there's going to have to be, ultimately, anticipated to change the label on the drug, which is the goal here, and along with that, advertising for the drug. And critically, in the repurposing idea, you need to have difference in the route of administration, the dose, is the population going to be different, and as such, there is going to be a new consideration of risk. So, for the most part, certainly in the projects that we've been involved in and IND typically is required.
So, as you go down the pre-IND path then, so the IND enabling studies path, then you might have to reexamine some of these issues. So, at one time, maybe recently but maybe decades ago, the drug substance could be practically manufactured. But is that still the case now? And if it is an old drug, let's say, even if you were able to access the drug master file, and Bob Anderson is going to talk more about that in the next talk, you know, was the original -- were the original manufacturing criteria really up to current snuff? And that can be a problem. As part of that, what used to be thought of as a pure drug substance might not be today. So, in particular, many drug molecules, obviously, could come in different forms. So, are the different [unintelligible] can be considered drug substances, or maybe one is active one is not, and so one is an impurity that would then have to be taken account of now in the current age. And of course, again, as it's been mentioned several times, in the new indication, in the new exposures that might be required, in the new routes of administrations, and doses, and scheduling, there may be new toxicology and safety considerations. And frankly, most of the time that's the case.

Okay, so, the glum part of the talk then is if you had this great idea, it's in a solid line, you're going down this path, you think it's going to be cheaper, faster, easier, but many of those checkmarks, or considerations in the last few slides turn out to be things we have to worry about. You're essentially right back into the Valley of Death. And to kind of harken back to the ROI trap side of things, the Valley of Death, in this graph, is a graph of the value of the asset, of the drug product that eventually you hope to market. And a lot of people kind of gloss through this and say, "Oh, yeah, there's a big period where there's a big challenge. The risk is very high. It costs a lot of money." But if you look at the graph, there's a negative slope in the preclinical side. So, what it really says is the more resources you poor into this project, the more money you invest into this project, the less value the project actually has in the marketplace, because you've now put much more resources and money into a product that -- but you haven't improved it's risk of failure. And so, while we very often, or almost always, talk about the Valley of Death in financial terms, you know, this kind of financial business problem then has kind of percolated over the last few decades into really a science problem. And part of that is that the dearth of resources in this period, in this Valley of Death, has progressively led to the dearth of the availability of the expertise. So, if you're in a standard, conventional academic setting let's say, if you weren't fortunate enough to have Scott's outfit running at your university, it'd be very hard to get really professional-grade, pharmaceutical firm-grade toxicology, DMPK, manufacturing. These kinds of expertise just really aren't present in most academic settings. So, most of us in an academic setting then go out, raise some venture capital, spend a little biotech company. But frankly, in the biotech company, it's you, the businesspeople, the VP of business development, but you still have to find all these experts which are expensive, they're already employed. So, it's very hard to get a biotech company, a small biotech company, to really get the preclinical team and expertise to really push something effectively into clinical testing.

So, as part of NCATS mission that Chris was talking about, on the intramural side, one of the things we've built is the so-called therapeutic development branch, and it's about 50 folks we have in Rockville, and we're designed as a multipurpose swiss army knife. So, basically a team that has among the team basically all the principal activities that you would need in the post-discovery IND enabling studies path. And as the first few slides showed, the emphasis is one whether a new drug substance or a new drug substance or a repurposed drug substance really has the right PK properties for the indication that you're talking about, will there need to be changes in the dosage, the formulation, the route of administration, and, very critically as Chris also was mentioning, manufacturing sounds so easy, especially if it's an approved drug. But actually, that's a bit of a minefield. And finally, of course, there's the safety and the toxicology.
So, the way we work is that we have this Swiss army knife, we have many projects ongoing, usually a couple dozen projects at any given time. Since the inception of NCATS, we've brought on about 70 projects, and these are all collaborations with outside parties. So, this could be an academic group, a small biotech company, a foundation. Actually, it could be a pharma company. But basically, we try to choose projects that are somehow stuck in the Valley of Death, but they're very high-value projects. That is, they could have very clinical and scientific impact, but for whatever set of reasons, whether they're financial or the lack of resources for preclinical development, we could come in as a partner and bring those projects to IND. So, so far, the track record is promising out of these 70 or so projects. As of today, we've helped clear about 35 INDs.

So, out of those projects, there have been several, you know, a number that have been repurposing projects. And because Christine actually said I couldn't have all the time; I'm just going to talk about one of them. Let's see. Well, it's this project. It's based on a very old problem of -- in the hemoglobinopathies, including sickle cell disease. So, these are all mutations in the beta-globin gene, so that all manifest post-birth, but there's a perfectly good gamma globin gene there that's been turned off at birth. And so, there's been a long time there's been an idea that if you could turn back on the gamma globin gene you could really treat a lot of these hemoglobinopathies.

So, our partner in this case, an academic that also had a small spin out company, did a hydropic screen, and indeed she found -- Susan Perrine -- found benserazide, an approved product, approved for 40 years now, that could, you see in the graph, really healthily improve the expression level of the gamma globin gene.

So, the glum part. So, it was approved 40 years ago, but really not as a single agent. So, it was only approved in a tablet form as a combination product with [unintelligible]. It -- the DMPK and tox data were really out of date, really wouldn't be up to snuff today, and as was mentioning before, benserazide comes in two forms, and it was not known whether both isomers were active. And if not, then one of them -- a new manufacturing process would have to be developed or the impurity, the inactive [unintelligible] would have to be purified out. So we're right in the middle of the Valley of Death. So, short version is, it did take a long time, took a lot of resources, but we did find that both [unintelligible] were active. That's an expensive set of experiments, but the payoff was that a new manufacturing process wouldn't have to be made. So, in fact, we could buy the new drug substance right off the shelf.

It wasn't too hard to reformulate as a single agent, but together with the efficacy, with the new DMPK that had to be done, we then were in a position to conduct all the GLP tox and safety studies, which had to be redone. And together though, that all worked out. So, the IND was submitted earlier this year and cleared, and we're hoping to enroll the first patient very soon.

So, that's kind of a happy ending, but listening the talks this morning really put me in mind, also, of an older statement. So, whether it's Moore's Law or this or that, many of you may remember a guy named Jurgen Draves [spelled phonetically], who was head of R&D at Hoffmann-La Roche. And although he was really an early champion of genomic methods, and omic methods to understand diseases mechanisms, he also wrote a manifesto, pretty much, about 20 years ago where he asserted that, if you look at the orange book, they're only about 500 drug targets. And his manifesto or his hypothesis was, well maybe there are only 500 drug targets, or maybe not many more than that. So, despite the exuberance in Chris' first slide that showed there may be 10, 20,000 new genes, and umpteen gazillion new drug targets, it could be that there are only 500 or 1,000, let's say, drug targets that are intrinsically safe and intrinsically effective. And so, all the more reason in a sunny state I meant to say that repurposing,
again, is so important because we've drug those 500 targets and perhaps there are many, many more uses despite the Valley of Death and the difficulty of getting even the first stage to IND. You know, it's going to be a great challenge and goal for us. Scott?

[applause]

Scott Weir:
I think I'm going to have to stand at the side here because I'm not tall enough to look over the podium. Let's see [inaudible], okay. So, good morning. I'm Scott Weir at the University of Kansas, and I'd like to share with you our learnings and perspectives on drug repurposing within an academic setting. And I have one foot within our NCI designated cancer center and my other foot in our CTSA. Now, we look for opportunities to repurpose drugs, FDA approved, off-patent drugs, really for three reasons. First and foremost is patients, to be able to identify new treatments for diseases in which there currently are no effective treatments. Secondly, to advance our research mission. And then third, to look for opportunities to develop products.

So, this is a snapshot really -- a kind of a snapshot of our experience in repurposing drugs in cancer settings really over the last 14 years. And I apologize, it's a busy slide, but what I wanted to highlight -- you'll see the chevrons across the top of the page that Chris described this morning. And what I wanted to highlight here is that, in several cases, we're able move directly into clinical trials. And in the lower, kind of, right hand corner of this slide are two examples where our repurposing efforts have resulted in commercial products. One, a new indication in which methods of use I.P. was generated, and in the second was employing a patented drug delivery platform technology to improve delivery of an anti-cancer agent.

So over the past 14 years or so, kind of, what have we learned? And think what we've learned is that our repurposing efforts can be lumped into kind of three buckets. One is pursuing new related indications. A second is a new completely unrelated indication to what the innovator product was originally approved for. And then the third as was discussed on the prior panel, our reformulation efforts. And our experiences are that our drug repurposing projects don't just fit necessarily into one of these buckets but may be common to a couple of those.

And what I've tried to do on this slide was kind of summarize some of the examples. And certainly in the cancer space, 49 percent of FDA approved drugs for the treatment for cancer were first approved in blood cancers prior to getting approval in solid tumors. And in the reformulation space, there's examples of where pediatric drug products were developed and approved, compounded, or extemporaneous prescriptions translated into safer and more effective commercial formulations, development of active metabolites, pro drugs, et cetera. And then new, kind of unrelated indication I'll highlight a couple of examples that we've had an opportunity to work on. Oops.

So when we look at these buckets, what I think we've experience is that the opportunity to innovate -- and along with innovation is the opportunity to be able to create an exclusivity position that would incentivize the private sector to engage with us on these projects. If you move from employing reformulations, new unrelated and related indications where you're generating methods of use I.P. et cetera; that as you kind of go down from the top to the bottom of this slide, the opportunities to innovate and again create an exclusivity position increase. But also with that are the requirements to generate pre-clinical data to be able to move these concepts into clinical proof-of-concept trials.
Now, the approach that we take at Kansas is with every cancer biology discovery that's made -- I'm not doing this, oops. Help. Oh there we go. We routinely screen libraries of proprietary compounds along with our FDA approved library of drugs. And we don't quite have the library that NCATS has but for literally every cancer target we're pursuing we're looking for opportunities to repurpose drugs. On the right-hand side of this screen we looked for opportunities whenever and wherever we can to move screening results directly into clinical proof concept trials. And then on the left-hand side of the slide is where we move through the traditional kind of preclinical evaluation phase to establish proof of principle in animal models before moving towards the clinic. And if there's product development opportunities, we then build out investigations into new drug applications. And we do that through a public-private partnership we call the Cure Bridge Collaborative.

Now in terms of establishing proof of principle we basically look at answering three questions pre-clinically. And if we can establish answers to these questions pre-clinically, then asking and answering the same questions in the clinic. And the first is simply: does the drug get to the site of action? And if it does, then does the drug engage with the target at the site of action? Then if it answered the second question, then does that drug target engagement result in a pharmacologic response that is consistent with our therapeutic hypothesis? And if we establish this pre-clinically or if there's existing data that would enable us to move directly into the clinic, then we move forward into clinical proof-of-concept trials where we answer the same questions. In cancer we've built a library of what we call window of opportunity trials where we can quickly go in with an FDA approved drug and determine: does it get to the site of action, does it modulate the target, and are we seeing a response? And if we can establish clinical proof-of-concept then at that point we look for opportunities to develop commercial products. Generate new indication information.

So I'd like to highlight a couple examples, one in which there were literally no pre-clinical data generated and a second in which we did. Chris mentioned this project here this morning. Auranofin is an old FDA approved rheumatoid arthritis agent. First approved in 1986, it's an old-world gold salt. And NCATS conducted a phenotypic screen in primary cancer cells collected from chronic lymphocytic leukemia patients. And they screened their library of FDA approved drugs; and one of the compounds that showed activity in killing cancer cells was Auranofin. That was also at a time when we had established a partnership called The Learning Collaborative with NCATS, K.U., and the Leukemia-Lymphoma Society. So we established a cooperative research and development agreement between the NIH and LLS and us to be able to translate this discovery to the clinic. We prepared an investigational new drug application and moved directly into a clinical proof-of-concept trial that was conducted at the NIH, Ohio State, and K.U. And before I leave this slide, I just want to make a comment that the model in this photo on the right-hand side looks remarkably like Chris Austin.

[laughter]

So this is an example, again, where we literally went from a screen into the clinic in 11 months including the time to negotiate a CRADA and file a IND and get clearance through FDA.

The second example I'd like to kind of close with is another opportunity we had to work with the Leukemia-Lymphoma Society initially, and a collaborator at the University of Toronto where we were repurposing an old FDA approved topical antifungal agent called Fosciclopirox. And Fosciclopirox was only available in topical forms to basically treat toenail fungus or jock itch. We worked with LLS and the University of Toronto to develop an oral formulation and move into a clinical proof-of-concept trial in AML patients up in Canada. And we conducted the trial, but what we encountered were development
obstacles, or technical issues around poor oral bioavailability; dose-limiting G.I. toxicity associated with administering this drug orally. And because the drug had lousy water solubility, we really couldn't formulate it into an injectable form. So we at K.U. invented a pro-drug and the pro-drug in the -- once it's administered in the bloodstream intravenously, it's rapidly completely converted to Fosciclopirox which has anticancer activity across a broad spectrum of solid and liquid tumors. And we were able to establish composition matter patents worldwide. We figured out how to synthesize the pro-drug, how to formulate it into an injectable. We then went on to do in vitro and veno preclinical proof-of-principle work as well as elucidate mechanisms of action. And then we partnered with our private sector partner, formed a biotech company called CidoMed, generated an IND package and we had to conduct GOP toxicology studies, GMP drug substance manufacturing and drug product. And then we conducted a first in human trial at four U.S. sites. And we're have currently moved this drug into clinical proof of concept in bladder cancer patients. The concept of this drug is we were able to overcome the delivery issues. The drug is cleared by the kidneys and eliminated in the urine and so we're selectively delivering drug to the site of action.

Summary slides are gone. Maybe I can wing it.

[laughter]

What Don and I kind of to close with are really: what are the learning's and what are the issues that really need to be addressed to be able to advance the ball in drug repurposing? And clearly, I think that for most of us in the nonprofit sector, we need access to expertise whether it's preclinical safety, formulation-develop regulatory. We also need access to information generated by the innovator firms. Whether that's access to a drug master file, access to, say for example, toxicology data what have you. And then third is we really need to be able to have a mechanism to be able to move these concepts into clinical proof-of-concept trials. So really, I think for us, and again as the panel will comment on this, to be able to advance the ball, access to expertise, creating new mechanisms to be able to fund work. What was mentioned in the prior panel: really being able to establish policy initiatives that will engage the private sector to participate in drug repurposing. Because honestly for those of us in the nonprofit section, we have to engage the private sector to be able to bring these treatments to patients. So thank you.

[applause]

Bobbie Ann Mount:
Our next panel will explore the data challenges in moving from the preclinical to clinical space at the late stage transitional science stage in the developmental pipeline. And Dr. Noel Southall he's the Informatics Leader in the NCATS Intermural Program. So I'll turn things over to him.

Noel Southall:
Thanks Bobbie Ann. So I just want to orient the audience to how we're going to run this session which might a little different than the previous sessions. It would kill me to have access to such expertise that we've already seen on display here and not have some audience opportunities to ask questions. And so I'm going to ask the speakers, try to stay to a brief period of comments. They've all prepared slides, but I'd also like them to take the opportunity to respond to some of the points that were made earlier in the discussion. This is a great opportunity to do that. So I'm a researcher in the Intramural Research Program within NCATS who's working on different strategies to identify opportunities for repurposing, both from an experimental perceptive, but also a data mining perspective.
What this panel is really going to focus on is how to develop a clinical development strategy, for lack of a better term, for taking an opportunity and actually putting into action. To generate clinical experience around the use of that medicine in a new context. And so I'm going to introduce each of the speakers in turn. They'll each make some brief comments and then I'll seed the discussion but then give the audience an opportunity to also participate in this discussion.

So the first speaker is Dr. Robert Anderson who's the Head of Regulatory Affairs at Emmes Corporation and I think he's the first bona fide regulatory affairs person that we've -- going to introduce at the meeting. And I think that from my own perspective, this is a critical type of expertise that is really unique that is difficult to access. And so he's going to help us demystify some aspects of a particular piece of data that's really critical for a lot of repurposing opportunities which is access to the drug master file. So, thank you.

Robert Anderson:
Good morning, thank you very much. Just briefly, the interest of an organization like Emmes is our work continues to go on with work with NIDA wherein we're helping them execute studies that may not otherwise be done. And the same with the NIH's funded and FTA supported programs for the Best Pharmaceutical Children's Act. So they're kind of interesting programs to maybe reflect upon on how we would do studies in a non -- a rather unorthodox approach. The objective in this discussion is really to help put some points on the map. It was an island, maybe it might be a little bit bigger than an island. And I, you know, just simply want to describe the drug master file as an information pipe, right? And it's going to be how you're going to convey proprietary information from the drug master file holder to a sponsor, or the so-called authorized party. And in this process, the information may be utilized by the sponsor but without the drug master file holder turning that information over to the IND sponsor. I will point out that the FDA, you know, people have been -- it's easy to take shots at FDA. The FDA has promulgated a new version of the drug master file and I included that reference here. It is difficult to keep up with guidance documents, and some are left, some are pulled. This one has been updated and I recommend it as you think about developing your regulatory strategy.

So just what is it? First it is a mechanism wherein the drug master file holder can describe facilities. Manufacturing processes, the articles used in manufacturing some of which are now being very interesting in that they're actually being considered part of the drug substance. If you're thinking about nuclease and guide RNAs, those are actually part of the drug substance. Processing, packaging and we'll see an interesting drug master file, we'll call it a type five. Now you can just think of it as all the other information that might include toxicology information and other information that might be relevant to your program based on an agreement with the agency about what's going to be contained in that file.

So there's type one which is discontinued, historically was used for facility information. You can still submit facility information where it's important. If you were making vials and you have a depyrogenation process and location, you'd probably want to be able to describe that without having to give all that information to an IND holder. A type two, I think you'll see a vast number of drug master files that are -- you can see the quarterly report by FDA, there's about 22,000 of them and they describe drug substance, manufacturing intermediates, production materials. Type three, there only might be about 6,000. I would say of those, probably Wes Pharmaceutical has probably let out 22,000 letters of authorization. Type four is typically for novel excipients. And type five is everything else. And I would -- this is probably the first point where I would echo the remarks earlier about discussing with the agency how you're going to handle and transmit that information. You do need to talk to the drug master file
staff about that. You need to submit a letter of intent and I encourage you to do that, wherein you're going to be communicating information through a drug master file that's not in a type two or three or four.

All right and so the utility is, in this space, I'm a largely historically been biologics person but it may be used to support NDA, ANDA, IND, BLAs. But I think that it's interesting to note that historically CBER has deemed that much of the information describing the manufacture of biologic is sufficiently complex that it should be all embodied within your BLA. So that's a consideration as you think about your communication approach. And of course devices and animal drugs. So the obvious -- my bullet here is to reiterate that this is a tool for information management. You can use it use it to communicate this information to the agency. All right and that's it

Noel Southall:
Okay that is fast and on time and I love it.

[laughter]

So transitioning a little bit from regulatory affairs expertise to, I think, perspective on the academic clinical medicine experience. I'm going to transition to Dr. Tudor Oprea who's the Chief of Translational Informatics Division at the University of New Mexico School of Medicine. And collaborated -- I've had the privilege to work on a couple of programs with. So, thank you.

Tudor Oprea:
Hello everyone. My name is Tudor.

Noel Southall:
Oops, right there.

Tudor Oprea:
Sorry. What I'm going to -- oops

Noel Southall:
There's a back-up, just go forwards.

Tudor Oprea:
Sorry. Okay.

Noel Southall:
Yep.

Tudor Oprea:
All right that's me. So what I'm going to talk to you about a little bit is an academic perspective on drug repositioning. And I thought I was allowed five slides, so one is the title, so drug discovering and repurposing rests on three pillars: drugs, targets, and diseases. So each slide kind of covers that thing in a way.

One of the questions that we've been trying to answer is: how many drugs might be available for repurposing? And in fairness, the FDA is the only agency that I'm aware of that is quite transparent
about the data that they have maintained. So the Orange Book is very easy to process. Of course there are a lot of tricks about how you process it and how do you standardize and all these things require a lot of attention. But the short story if you look on the column with colors which is the fifth column, it basically says that there are currently as of October 2019 there are 785 drugs that are on patent and about 1,454 that are off patent plus 680 which are discontinued. And the discontinued story, if you look at the original Orange Book data file has about 1,800 of those but it turns out that some are discontinued and then repurposed by a different formulation or different package or something like that. So at the end of the day the answer would be maybe up to 1,770 active ingredients might be eligible for this entire workshop, which is off-patent repurposing.

The other question that one might try to answer is how many targets are there available for repurposing? And in this particular case and earlier speaker might be just 500 drug targets out there. That's clearly not the case. We think there -- at least in the human realm, there's about 600 plus another 300 that are nonhuman. Think of antivirals. And so there's about a 1000 drug targets that we know might be already addressed by drugs. So we started with that set and then we asked the question: how many of these drugs in the indications are available? And if you look at just this set you might have up to 60,000 new protein drug disease or protein indication pairs. And we already know that each of these proteins is addressed by a drug, and each of these indications is out there available. So just the immediate set of these repurposing might be up to 60,000, so that's a really large set; but it it's probably just the tip of the iceberg. And as Bobby Ann mentioned earlier, we love icebergs.

I'm not from Minnesota, but I could be.

Oops, sorry about that, too many buttons on this. The one problem that I think -- and this is one of the biggest weaknesses in the field of computational drug repurposing is our ability -- or inability to address what's a drug. So on the left image you have Maraviroc so it has four chiral centers and most resources online deal about two chiral centers so even perception of the correct chemical structure is a problem. And there's hundreds of identifiers. If you want to navigate Drug Bank or MeSH, or RxNav, or IUPHAR, the FDA, each one comes with their own identifier. But the other problem, and this is where it gets really tricky, we do not have a computational model to address what they're therapeutic intent is when it comes to a disease indication. And there are two situations here. So Pimavanserin which is the drug I highlight. A lot of people consider it to be an anti-Parkinson's disease drug, it's not. It's intended to treat hallucinations cause by Parkinson's disease drugs. So how do you factor that in? So another one is just take calcium, calcium has an indication that it's indicated for people who have spider bites caused by a specific spider. So it's essentially a foreign agent so it's not a disease it's like spider venom, right? And it's an organism, this specific spider, so how do you encapsulate that into a MeSH code or computer system? That's not really that simple. And the other end of the spectrum, where contraindication method Methotrexate is contraindicated for women that might get pregnant if the sexual partner takes Methotrexate: how do you put that in as a contraindication? There's no MeSH code for that thing. So how to reproduce the exact therapeutic intent is not the sole problem, and if you cannot capture it you cannot model it. So it's that simple.

I was also asked to be slightly controversial and come up with a story about how do we capture this drug repositioning intelligence and of course I came up with this concept slide where you have lots of
algorithms and you can model the molecular part, whether it's your protein or your small molecule, we can do a lot with virtual screening. So we can do docking, we can do similarity-based approaches, there's a lot of stuff happening. And when it comes to mathematical approaches to mine the drug target disease association space and using it with artificial intelligent / machine learning, and all of this can be used to priority for drug repurposing. And in the end, you go to the confirmation of clinical effects. But that's not what I'm thinking about. I'm actually thinking that probably the best way to eliminate competition is to move away from this whole intellectual property protection side. Instead of competing we should actually team up. And while we make rigorous annotations for the drug indications in the off label, we should basically have like a large website where we come together as a community, we come up with --these are the fact that we know for evidence. These are the computational models that have been validated and there has to be a community-based approach for research. So that's my pitch. Thank you.

[applause]

Noel Southall:
Excellent. And then I'd like to welcome the third speaker to the stage. Dr. David Cavalla is the founder of Nüemdicus and also the author of the book on off label use. But really an expert in commercialization and I think aligning capital to get the clinical development done of the products we need to get to patients. So welcome.

David Cavalla:
Thank you, all. I think I'm the first non-U.S. speaker, so I hope to give a little bit of perspective of somebody from the other side of the pond, as it were, also from the perspective of a small company. So I've run this consultancy company, Nüemdicus, for about 10 years, but I've also been the innovator behind a bunch of products that are now in the clinic based on repurposing which I've out licensed to various other companies. So I kind of bridge the divide both being a consultant on the one hand an innovative drug entrepreneur on the other.

And along the way I've acquired a lot of information about things which have been experimentally determined to be repurposing opportunities which, similar to Tudor, I've divided into compounds, mechanisms, and targets. And in that database which is available on the sort of a freemium model there are thousands of compounds, 9,000 which are repurposable. So there's compounds which have either been launched and investigated, clinically investigated as well as about over 200 which have been repurposed in some way, shape, or form. And then over 700 mechanisms and over 400 indications, and it's quite clear from the oval things in that diagram that there are substantial numbers of links between compounds and mechanisms, mechanisms and indications, and compounds and indications.

And so the first problem we have is prioritization. There are vastly more opportunities there than we can ever develop. I'm not saying that's a comprehensive list, there are plenty of things which are yet to be explored and identified from computational techniques like artificial intelligence and genomic matching and so on. But nevertheless, my point is we need to prioritize. And prioritization can be through a variety of typical assessments of probability of efficacy, lack of adverse safety signals, the novelty, the patentability, so there's a complex array of factors that are going to drive the prioritization of those things up or down. And without that prioritization, I don't think we can sensibly allocate resources to the problem of repurposing. And two of the things that are highlighted in green on that list, I've done so because I think they're an opposite to one another. So we've heard about the problem of generic competition as something which afflicts many repurposing opportunities. And that particularly
applies to the very things which are most easy to develop. So if I had a new use for Prozac and I wanted to administer Prozac itself for ingrown toenails or something I would find it extremely difficult if not impossible to get any commercial interest behind that, even if I found a billionaire with ingrown toenails all of his life.

[laughter]

The problem is that the development ability and the commercial forecast run counters of one another. And you need to think about all of these factors before you really allocate any resources at all. Because in many cases, you're repurposing idea lies at the interface between the preclinical and the clinical, and so you're talking about constructing a plan which involves substantial amounts of investment. So you need to do that planning beforehand because you're going to have to spend a lot of money. And it's quite difficult to do that. It's different than going into the lab and doing a quick half a day experiment. You're having to do something which might cost millions of dollars. And in the absence of that holistic plan, you're not so much facing a valley of death where you might be driving a Cadillac across Southern California as driving a beat-up old C.V. across the Sahara. You're facing something that doesn't have an end point and a logical way of interacting with a set of commercial players who are going to take your half-developed product into the market and introduce it into patients. And as Chris said at the introduction, the whole point of this exercise is to make products more easily accessible for patients. For patients. Because at the moment we have a system which is too expensive and is delivering drugs which are unaffordable.

I'd like to just focus on the aspect of substitution. We've talked about generic substitution, but the whole thing really, in my view, hinges upon the prescription. So this is an example of a prescription for Tacrolimus which is a generic form of Prograf for transplant rejection. But it has a whole series of other potential uses. In the database I referred to in the previous slide, there are over 30 potential indications for mTor inhibitors which are listed. None of these alternative indications are listed in this prescription for Jane Doe. In fact, indeed we have no idea what Jane Doe is taking Tacrolimus for. It may well be she's taking it for transplant rejection, but when she presents this at the pharmacy, there is no indication at all about why she's taking it. She may have been prescribed it by a physician who is prescribing it to her off-label and may not have told her that it's off-label, and just told her to take the Tacrolimus, take this prescription to the pharmacist, and get it filled. The pharmacist has no idea of whether this is a repurposed opportunity for Tacrolimus or whether it's something which is on the label.

And I -- one of the things I feel quite strongly about is that, just from the perspective of the patient, that indication should be written on the prescription. If you're worried about privacy, then you can have it in a tear-off able form. But I think that the prescription should indicate what the disease is that is being treated, if only for the patient's benefit. But also it would also go -- that there's some way to addressing this issue of substitution. In and of itself, substitution offers a free ride for generic manufactures where an innovator behind a repurpose development is not at all compensated for their R&D investment. And so that means there is no reason for any dollars, whether or not they are pump primed by NCATS grants, or any other form of grants. There is nothing there to hang a commercial product on. And indeed, even if you have orphan drug designation that does not prevent the kind of thing I'm talking about. Where there are publicly funded projects, they may take you halfway to your destination; but they don't take you the full way. And a clear example of that is something as common as aspirin which has gone through the process of being used for pain, and then used for Thrombotic diseases, and now there is a wealth of information that aspirin has a profound delaying effect for cancer progression. And in conditions like gastrointestinal cancers there is a very sustainable risk reduction which has been meta-analysis of tens
of thousands of patients, but never taken any further. So that information is out there, it was been
published, its decades old, and it's going any further because there is no commercial incentive. Even
though I have to say, from a healthcare perspective, the pharmacoeconomical advantage of delaying
cancer is profound. Because everybody knows the late stages of cancer are extremely expensive to
treat, and if you had an opportunity as a government or any publicly funded healthcare organization to
delay patients getting into that late stages of treatment you would save yourself some money.

So is forced to look at non-substitutable products. And we have the list of things that are normally parts
of the 505(b)(2) that also happens to be the list of things which are generally non-substitutable. So we're
talking about a different route, different dose, different patients, combinations, and so on. Now I have
to say, I'm not -- although this looks like a bit trick, and there are some tricks to this whole thing, the
purpose behind this is not to generate a non-substitutable product purely for the advantage of
bypassing generic substitution. The point of it is to tailor your repurpose development specifically for
the new indication. So in the case where you might be repurposing an orally delivered drug for asthma
then conventionally inhaler route, the purpose behind changing the route is not to get around generic
substitution, the purpose behind it is to favor the use of the product in the new form for the treatment
of asthma. And I think that's an important thing to recognize. And similarly for dose, similarly for
patients and so on.

There are some issues around what happens if you have a withdrawn product. If it's a withdrawn
product that was withdrawn for safety, I'll come on to that in the next slide. But the other point I wanted
to emphasize is that we are focused here on developments for products which can be approved in the
U.S. but they world of approved drugs doesn't just include those that are approved in the U.S. and there
is an opportunity to introduce into the U.S. things that are generic but are only approved in foreign
countries as a way of delivering a non-substitutable product that can have important medical
advantages in your secondary indication.

Now my understanding for IND and I think we've heard from the previous speakers that most, if not --
well the vast majority of cases an IND is required for your repurpose development. If anybody wants to
object to that statement, please do so. But generally speaking, for an IND filing you may use the
summary basis of approval for a generic old product in your new indication development. But you would
need to add to it bridging data specifically for the new route, or the new dose, or the new patients, or
the combination, that you might need to -- what would be specific for the new indication. In the case
where a drug is withdrawn unless it's withdrawn for reasons other than safety, and if most cases I think
safety would be a prime reason for withdrawal, then addition data could not be -- would need to be
provided in the full form for the IND.

So I'll give you some examples of that. Doxepin was -- has been introduced for insomnia. It was original
an anti-depressant and the first studies to show the effect of Doxepin in sleep disorders were conducted
by a physician who was interested in the possibilities of this drug given that different doses from those
which were used as an anti-depressant. And then that was taken forward into a patent, then into phase
two and phase three trials and was finally introduces as Silenor containing lower doses of Doxepin than
were used in the generic case. And in a situation like insomnia, which is a relatively mild continuous
condition you don't really want to be subjecting yourself to higher doses of a drug which might have
adverse events. So there is an advantage, a patient advantage in the treatment of insomniacs with low
doses insomnia. Sorry, with low doses of Doxepin.

And the other example I was going to use for what was a slightly different situation is again a low dose
development of Fenfluramine. Fenfluramine was famously withdrawn. It was an anti-obesity product but found to induce high levels of pulmonary hypertension and it was a tragedy and also a scandal. And Fenfluramine, before it's withdrawal, was found in Europe to be effective for certain forms of epilepsy and long after those case reports were available those certain forms of epilepsy were reassigned as a diagnosis of Dravet which is a particular epileptogenic particular form of epilepsy. And again lower doses of Fenfluramine were developed without the risk of pulmonary hypertension. That's now in phase three and has been designated as a breakthrough therapy and is also an orphan indication because it's a rare form of this particular epilepsy. So that's all I wanted to say really.

Noel Southall:
Excellent.

David Cavalla:
Happy to answer any questions.

Noel Southall:
Exactly.

[applause]

So it -- is this on? Okay if there are questions from the audience then I'd invite you to step up to the microphone and I'm going to start off the discussion period and I think that both Tudor and David did a nice job of illustrating that there are a wide variety of opportunities that we need to investigate in this repurposing space. And so I guess my dream would be that there would be some algorithm and maybe - - we know the incentives that are currently available. It would be fantastic if those incentives changed but much in the way that I'm grateful that the National's won the World Series and I don't expect it to happen again, I don't know that the incentive structure is going to change. So given the current incentive structure and the commercialization strategies that exist, is it possible for us to sort of, algorithmically prioritize that universe of opportunities to know where we should be making our most important investments going forward?

Tudor Oprea:
The short answer is yes.

Noel Southall:
And have you published that algorithm?

[laughter]

Tudor Oprea:
I don't think there is a single algorithm that would address this, but I believe that the most difficult part is to catalogue facts and to make sure what we feed the algorithm are the correct data sets. And once we do that, I believe that it is possible to take all the drugs that are off patent and find new indications for those, algorithmically.

David Cavalla:
Can I just ask you, Tudor because obviously you've done a lot of work in this area, quite often you see the same drug coming up from multiple situations. We were talking earlier about Auranofin and
nucleoside might come up a lot. How would you know which is the best indication for that drug to be developed in? There are multiple potential indications you could develop it in, how would you assess which is the one which is likely to have the greatest efficacy and the greatest impact?

Tudor Oprea:
So that's not easy to answer because safety and efficacy are not easy to compute from molecular structure. But I will say this, I started by looking at off-labels and what I found that most of the off-labels, about 80 percent, are on the same drug target that was previously used on the original indication. So what I would prioritize is the new indications that are on a different target. Because those are more likely to find success in repurposing. So I would start from there.

Noel Southall:
There might be some good heuristics then we can use to prioritize our portfolio of opportunities. Are there particular data that you would like to have easier or better access to that would be important in computing that? And I think that the comment about exactly which indication or clinical setting to take a repurposing opportunity is -- that's a key development strategy discussion that can dramatically, you know, affect the outcome of the whole program. So.

Tudor Oprea:
I think the FDA should make the drug master files available, period.

Noel Southall:
[laughs] So, I --

[applause]

Tudor Oprea:
As an academic, I requested the drug master file for Ketorlac, and it's currently being considered for ovarian cancer which is not the original indication. And I applied for that through the Freedom of Information Act to the FDA in 2014. I have yet to receive the drug master file. I did -- the technology was licensed by my university to a start-up company in Boston, Revere Pharmaceuticals. They applied in December 2016, got it in January 2017. The same drug master file, so why does FDA not issue drug master files?

Robert Anderson:
So the FDA will give a better answer than I could, but the drug master file is the tool so FDA will give a better answer than I could.

but the drug master file is the tool to convey proprietary information. And when a decision is made, so there's a post-decisional phase wherein safety, efficacy information that is contained in a drug master file, it would be subject to the same regulation about the availability of that information. Proprietary manufacturing, for instance, would not be made publicly available post-decisional. Pre-decisionally, that is before the granting of an NDA or an ANDA. That information is in FDA's hand by law is protected. The FDA is the best organization that the law allows us to have. And so it's not FDA's decision, it's what the law compels FDA to do. All we have to do is change the law.

[laughter]
Tudor Oprea:
So if under Freedom of Information Act, I am allowed to access that information that means that information should be available by law? I'm not a legal scholar but I think that to be the case.

Robert Anderson
Pre-decisionally the Freedom of Information act does not allow you to reach into that. In a post-decisional framework that information should be made able to you, except where it's trade secret, et cetera. The FDA wants to make the information about safety and efficacy available to everyone to ensure that they're making valid decisions. They are not going to make information available about trade secrets, you know, publicly available. We have to decide what we --

Tudor Oprea:
The safety and efficacy, that would be a great start, if we can start with that component.

Robert Anderson
Right, right. So at the time of an approval, you know, we've mentioned reference to the sort of summary basis of approval. There are 40, 30 or 40 review memos that are eventually let out, including in this case the medical review should be available, clinical pharmacology should be available, as well as any other administrative and safety studies that are done.

Noel Southall:
And I just want to also comment back that you previously complimented the FDA on its forward thinking.

Tudor Oprea
Correct. Yes.

[laughter]

Noel Southall:
Its ability to get it out the door.

Tudor Oprea:
I did, yes.

Noel Southall:
And I would share that sentiment. And especially the documents they make available for the most recent NDAs, and their summary basis.

Thomas Anderson:
Yeah historical data is tough.

Noel Southall:
Exactly. So maybe we're just talking about not a change in regulatory scheme but maybe just a little facilitation for FDA to make some of the older data more accessible.

Tudor Oprea:
Correct.
Noel Southall:
In sort of a preemptive fashion, before a FOIA request.

Thomas Anderson:
Right. So if a regulatory marketing decision has been rendered, even if the SPA is not available, if you were to request that under a FOIA request, the FDA should grant that based on the availability of resources. That is not off limits, when a decision has been made. Further, by the basis of that request, the agency will now probably go ahead and make that information available through their portal. They wouldn't just give it to you, that would then become publicly available.

Tudor Oprea:
What I got was an email two years ago, you requested this, are you still interested? I responded yes. Two years later I got the similar email from a different person, and still no DMF.

Noel Southall:
So that might highlight a slightly different issue, which is access to expertise. So certainly expertise is needed in navigating FOIA process itself.

Tudor Oprea:
Yeah.

Noel Southall:
I mean perhaps the --

Tudor Oprea:
I'm fairly naïve about that.

Noel Southall:
--threat of an action facilitates a different FOIA experience from one party to the next. And so how do we facilitate access to expertise in, sort of, all aspects, not just in your case specific, you know, your case access to DMF, but, you know, indication and regulatory scheme 505(b)(2) opportunities, how do we facilitate access to people championing the specific opportunities? You know, the patient doesn't really care that there are a thousand repurposing opportunities. They care about the repurposing opportunities in their particular context. How do we facilitate their access to expertise from all different disciplines that are really necessary to put together an actionable clinical development strategy?

Aditya Das:
By creating academic groups. I insist on recognizing myself because I've been standing here a while.

Noel Southall:
Thank you. Oh sorry.

Aditya Das:
Aditya Das, Mannkind Corporation. So we've been talking about repurposing drugs, right? But we really haven't talked about one fundamental issue. The existing drugs that are out there on the market, let's say for T.B. The treatment is three antibiotics, three times a day for nine months, taking whopping doses of Rifampin and Myambutal and Isoniazid. These old drugs you
can manufacture for pennies to the ton. So that's why. That the simple reason oral therapies are currently available for TB. All right, what's the source of TB? It's a mycobacterium that sits in phagosome the in the macrophage in the lung. Are you doing anything at all by nine-month treatment? You're destroying your GI Tract, you're destroying your liver, and creating multi-drug resistant bacteria, and extremely drug resistant bacteria, and that's being spread from patient to patient without a thought. And that becomes a public health crisis. So why?

Noel Southall
So --

AdityaDas:
For example, we can deliver inhaled dry powder to the lung, right? BCD as a vaccine is completely defunct, right? We have sequenced the TB genome. Everyone talks about the human genome, but we've sequenced the TB genome. Why can't we come out with DNA dry power inhaled vaccine? Simple question. So my take on it is to look at all of the approved drugs on the market and simply route them better to clinical outcome. So what does that do? It's become unconscionable for health insurance or physicians to prescribe the generic options because it doesn't make any sense. You have a better product, a dose, a reduced safety profile. There's a drug currently which is considered for treatment of NASH, Non-alcoholic Steatohepatitis. It's a bile salt of metecolic [spelled phonetically] acid that has a volume of distribution of 618 liters, I think it's unconscionable as an industry that we're considering an oral dose of that product at 25 to 40 milligrams a day. God knows what that's doing to your tissues long term, you know? You are dosing this over multiple years, decades perhaps, because it's a chronic disease. So I worked on the first-generation inhaled insulin, Exubera. We did trials, three phase three trials and about nine phase two's. And we came out with this product in January 2006 it was approved, but it was dry powder inhaler which was that big. Because in 1989 when the product was first developed, nobody believed you could inhale dry powder off the palm of our hand, as fluffy respirable particles, because people thought of dry powder like you do table salt. And table salt, if you were to pour table salt in your palm and try to inhale, it would know nowhere. So the point is you come up with a fluffy dry powder, the concept is brilliant because when you inhale the insulin, right, P.K. profile, a sharp P.K. profile which is the same as sugar comes out in bloodstream, three times a day you have to eat, whether you're Type One or Type Two Diabetic. Mannkind Corporation who I'm currently working for, have been struggling to get this concept out there.

So thank you

AdityaDas:
What is it not it accepted?

Noel Southall:
Very passionate question, I love it.

David Cavalla:
Are you saying why is the concept of inhaled -- the use of inhaled drugs for systemic diseases not accepted?

AdityaDas:
Yes, absolutely. Inhaled and even for local lung disease. I'll get you another example, pirfenidone and
nintedanib. These are two drugs used for IPF, pulmonary fibrosis.

David Cavalla:
And they're given orally?

Aditya Das:
They have -- they are given orally. They have bioavailable fraction of five percent. So tell if that makes sense?

David Cavalla:
Well, all I'd say is that as you probably know the pre-clinical work taken required to repurpose an oral drug into an inhaled drug is quite significantly expensive. More expensive than you might think. Probably of any of the route changes, the change to inhaled route is the most expensive change that I know of.

Noel Southall:
So you -- let me re-ask the question a different way. You don't think innovation in development of drugs is hindered by any sort of lack of attention to scientific development? The calculus has been done and there's a commercial determination made, and that is really hindering the development of innovative products?

David Cavalla:
I think it's a significant component, certainly as the gentleman points out when you're dealing with drugs for TB which cost pennies, it makes it difficult to sustain a pricing argument for something which is significantly more expensive. There's just one other point I'd like to make from pre-clinical to clinical transition. Which is obviously a very important thing for repurposing. And one of the points I made in my talk was that the -- there are a lot of drugs which are approved around the world which could potentially be repurposed which are not FDA approved. In other words, drugs approved in Japan, or France or wherever. And under current regulations -- and incidentally those drugs, if they were repurposed, could be -- they could avoid generic competition, which is one of the significant problems for repurposing. However, in this country, it is not possible to start a clinical trial on a drug which has been approved, say, in Japan, absent the toxicological information which you need for your IND. In Europe, the situation is different. In Europe if you want to undertake a clinical trial for the repurposing of a drug which is approved solely in Japan, you can do that without the toxicological information because you can just submit your product information leaflet. So -- and then it may be possible having proved your repurposed idea actually works, then you have the confidence, and perhaps the investment too, to bring it back to the U.S. for phase three development. So that strategy might be quite an attractive one for bringing drugs to patients in this country which simultaneously improves efficiency of getting the drug into the clinic in the first place, and secondly gives you a commercial reason for being taken up by pharmaceutical industry players in this country.

Noel Southall:
So thinking about research agenda that NIH might invest in setting up clinical proof-of-concept as an important milestone in the product development path then would enable commercialization activities to follow on, so is the sort of supposition we need to find ways to just generate that clinical proof-of-concept any way we can and convene formal development process?

David Cavalla:
Well, I think showing something works in human context is an amazingly powerful thing to have done, and the more barriers you put in the way before that human proof-of-concept trial has been conducted, the more difficult it is. So, if say you want to repurpose a drug for inhaled use, in a certain lung disease, and then show efficacy in that, it's quite an expensive process to do that. You know, if you want to do that in the U.S. There may be alternative -- if you're willing to accept a more flexible international development environment there may be efficiencies which you can find.

Noel Southall:
Are you aware of other companies or product development strategies that have sort of taken advantage of this difference in regulatory scheme between Europe and the U.S.?

David Cavalla:
Well, we are.

[laughter]

Tudor Oprea:
So just to clarify a physician can prescribe a medication off-label without it having been approved by the FDA. So one possibility would be to do an open label trial where you select volunteers and volunteers are being told up front this is what we're doing. They sign up, and then you do a small, say, 10, 15, 20 patient trial and then go to regulatory for additional support and evidence.

Noel Southall:
So I think the original conception was talking about repurposing opportunities where there was no opportunity for exclusivity. But your comments, David, and my experience as well, is that we need to develop some sort of exclusivity commercialization.

David Cavalla:
Yeah, I mean in the strategy I just outlined you would end up with Adrix based on first the approval for drug in the U.S.

Robert Anderson
You know so I think we've generated a lot of discussion from the one speaker. We have another speaker, I don't want to step on that, Noel, but the first example we had was T.B., and it's all about incentives, right? T.B. does qualify for incentive programs that the FDA has promulgated for neglected tropical diseases. So, you know, I don't want to change the argument. I understand why we use the term, Valley of Death. I think there's just a valley of disinterest.

[laughter]

You know, that we have -- if you go to like a J.P. Morgan or a RESI, that there's lots of stakeholder -- potential stakeholder excitement with those types incentives. You know, the question is, you know, are they adequate or is there -- I think what I heard is really the need for like -- it's like a behavioral economic model. You know, there has to be a pro-social environment for drug development, and, you know, it's -- I'm probably the least provocative person but that is really I think what we're actually asking to generate.
Edric Engert
I'd like to build on that, noting the level of interest please. Hi.

Noel Southall:
Pardon?

Edric Engert:
Hi, Edric Engert from Abraxeolus. First, thank you for your presentations for this very lively discussion. I very much appreciate it. I have a general context-setting thing and a question. That is, if I understand this all correctly, our objective really here today together is to talk about how can we increase level of activity in repurposing and also together how can we overcome some challenges and obstacles that we're facing.

And if I were to focus on the first one it has to do with, okay, more focus in R&D to start with. How do we make sure that the R&D budget is not being thrown to everything else other than repurposing? But then if I think of R&D budget, I think well that's driven by portfolio strategy. And when we get to the level of corporate strategy, it has to do with: if I'm going to spend my next dollar where is it the best place to do it? And it comes down to comparative evaluations in business cases. One could be looking at small molecule, one could be looking at novel biologics, one could look at OTC or generics or biosimilars. And there are many companies that do many components of things together, sometimes even in an integrated fashion. And you can be looking at risk-return profiles, you could be looking at risk adjusted MPVs. But I want to focus one thing in particular: the probability of success. I'm personally familiar with the varying difference in probability of success from start to completion, approval, and commercialization, and what a stark difference there is between small molecule and biologics and novel biologics, and in between novel biologics and biosimilars. And that sometimes helps us to make corporate strategic decisions when we couple that with what our are hinged capabilities and this [unintelligible] all be done in a vacuum. So I think together as a team, we have to overcome these obstacles, but it's also time to build, frankly, a business case to ensure that everyone in the industry and the leadership in the industry understand there's a true business case here. And there are a lot of components. So keep it short, because I don't want to eat up all the time, does anyone on the panel or anyone in the room know what the POS is of a repurposed project from start to finish? Because I think that would be valuable information to include in this broader comprehensive business case that is needed.

David Cavalla:
I think there's no such figure. It depends on the exact project you're working to do. I mean, I pointed as I out, Doxepin is a product, I don't know what the sales are, but it is something which has been progressed as low dose form for treatment of insomnia. It's on the market.

Edric Engert:
Could we be using anything as a proxy like 505(b)(2)s? Could we look at all the times that a product has been targeted as a 505(b)(2), how many failed, how many have succeeded? We could use that perhaps as a proxy. Does something like that exist?

David Cavalla:
Maybe, but I think what you're after which is, I think, a more valuable piece of information, would be what is the quantitative difference between the sort of net present value of drug repurposing program versus, say, development of a biological or small molecule.
Edric Engert:
Yeah, I would want to build an entire business case and I see POS as being just one component of that. Because it also tells you, depending what kind of returns you need and what kind of cash flows, how many products you're going to need in the pipeline to turn it around.

Tudor Oprea:
So it's very difficult --

Noel Southall:
Actually I'm going to -- is it all right if I cut off the discussion --

Tudor Oprea:
-- sure.

Noel Southall:
-- a little bit and just recognize the next question.

Su Wong:
Hi, my name is Su Wong, currently I'm a consultant for the [unintelligible] in Taiwan, that's a company that makes Heparin, and also a consultant for the HHS in Taiwan. Okay. Before I retired from my full-time job at Portside NIH a long, long time ago working the [unintelligible] chemical company who make Excedea for the pharmaceutical company, before we were taken over by Pfizer. I had a chance to be involved in several drug development, and the reason big pharma withdraw or choose certain dosage form -- there's a market issue. Just to give an example. CCI-779 does a similar -- is a recognized derivative, at Wyeth, we made two dosage forms, one is a tablet because it is easier for patient to take at home. And that goes for breast cancer. The other one is the injection. That's for the small cell renal cancer. And after phase three clinical trial, Wyeth decided not to file the tablet form because the outcome is not much better than the other company. So how did we do this? Go for the -- your renal cell. It's had accelerated approval and also was an orphan drug and got approved within six months. But the trouble is this drug will not make much money because the patient has to go to the hospital to get the injection. But for the company, if they target how many drugs they want to go for FDA approval, this work was effective. And another reason the company will not -- or FDA will not release the DMF, the DMF has a lot of proprietary information.

Male Speaker:
Right.

Su Wong:
If it released, and if the drug like Wyeth has -- each year we put in 15 INDs -- or no [foreign language] development tracks, and eight to 12 INDs. And after 10 years, only two to four drugs got FDA approval. And all those who drugs failed, that means people who worked there, they got laid off. So that's the reason the companies protect those proprietary information. I did a lot of work before Wyeth, but I could not publish it. So just, I know for people from the academics who may think different, but in the industry they have a different philosophy. Thank you.

Noel Southall:
So may we have comments or a few last words?
Female Speaker:
We have -- if you can do it --

Noel Southall:
Thirty seconds.

Female Speaker:
-- in less than one minute.

Noel Southall:
Yes, okay. So I don't know if you want to address the question or provide any last thoughts.

David Cavalla:
Well I think what you outlined is sort of a history of the problems of the pharmaceutical industry. And that's one of the things that we think repurposing can help with. Because the metrics say that three to four repurposed drugs can be developed for the price of one NCE. And so that's one of the things I think we're all here to try and improve is productivity of pharmaceutical R&D.

Noel Southall:
Tudor, last thoughts?

Tudor Oprea:
So I want to make a comment to the gentleman with the T.B. question. The opposite has happened, and that the market success tells you an opposite trend which is when GSK was the first to launch an anti-flu drug, Zanamivir, Relenza. And when Roche launched Tamiflu in seven weeks they lost 62 percent of the market share and then they quoted this because the slowness of the U.S. to adopt inhalation therapies because the second drug from Roche was orally available, so opposite happens a lot. Oral pills are given preference. So the problem you're highlighting is, how do you take that business case and take it to a drug manufacturer and say make the inhalation one because they will take it. So you need to figure out patient compliance and the cost. The inhalator has to be cheaper than the pill, so all that has to be taken into account when you come up with your arguments.

Bobby Ann Mount:
Tudor, I have one follow-up to something you mentioned earlier about the five slides. It turns out it was a good idea to put computational scientists right close to lunch because when you say five slides you get exactly five slides.

[laughter]

So with that we're going to move on to the next session.

[applause]

So there will be three panelists, who've been tasked with the tall order of giving a synopsis of the overarching problems we heard in the morning, and also giving us potential solutions in an ideal world. So Dr. Harry Selker, the Executive Director of Institute for Clinical Research and Health Policies is
on his way up. As well as Frank Weichold from FDA, the Director of Science and Innovation. And Vikas Sukhatme, the Dean at Emory School of Medicine. So we have about 30 minutes and just because there have been frequently asked questions about whether power points will be made available this event is videocast by NIH and the videocast will be available after the event.

Harry Selker:
For those of you who are up close you'll notice that I followed Chris Austin's instructions. He asked me to talk about hitting my head up against the wall. You'll see I've been working on that. And that's exactly what I want to do. I want to -- first off all I have to get my slides up here. But, well let me do -- here we go. What I want to do in summarizing the challenges and the obstacles that we've been talking about this morning is actually give a case example, which was, in fact, how I hit my head against the wall. And this has many things we've been discussing and at the end I'm going to make couple recommendations, they've been published as recommendations, I think there's a copy of the article out at the desk. But more importantly I just want to say this is my suggestion, not any agency or even Tufts.

So, I'm going to give an example of that. And first of all, this example is off-patent treatment for the most common cause of death and that is for acute coronary syndromes. I don't have to explain to you the acute coronary syndromes including acute myocardial infarction kill more people and cause of more heart failure in infarct damage to the left ventricle, and thereby having the greatest amount of mortality morbidity in the country. In that, we ran a clinical trial sponsored by NHLBI of NIH calling the immediate trial where we use intravenous glucose insulin potassium, not patentable things, to treat acute coronary syndrome. And in so doing we reduced the composite of cardiac arrest mortality for all acute coronary syndromes by 50 percent, for S.T. elevation M.I. by 60 percent and reduces size of infarct, that is damage to the heart, but 80 percent. However, turns out there have been studies that have done before.

And this is a really great example of what can happen through a non-patented drug. This treatment has been known in animals for 50 plus years, has been used in cardiac surgery as a supplement for myocardium, but it's never been made as a product, and one of the reasons is the trials were mainly negative. Why were they negative? Well it turns out that GIK was added to drug trials already in place, and so just adding GIK to it. So it was not used the way it ideally should have been used you would look in experimental studies. And, you know, FDA appropriately, even with the first immediate trial wants another one, and it's appropriate there should be confirmatory data. And if we could get there, as you'll see that's hard, there would be potential for many billions of dollars saved, and many lives saved.

This diagram is explained, what happens when you have a drug which can't deserve its own sponsorship. You'll there this is the time from symptom onset when someone calls 9-1-1 with chest pain and that little curve that goes down is the course of cardiac arrest right after ischemia ensues. And as you know most deaths occur from heart attack in the first hour or two. You'll see those arrows there, the first is when we use in immediate trial, when we just gave GIK, in ambulances in the field, and that was within the first hour or so. But most other ones were Ramipril, other kinds of drugs, far after any there was any opportunity to save lives. The trials all looked negative. So no interest there and it doesn't have its own sponsor.

So, you know what is the path to commercialization for this? And this is a study of lack of the right incentives even though we could save lives. First of all we do have a SPA approved FDA protocol that could get us to a label. And it would be confirmatory trial for cardiac arrest, mortality, infarct size. And the idea would be also to confirm it reduces heart failure long term which we believe it could by
reducing infarct size. And then of course the next step as you all know is secure manufacturing and marketing. However -- and we also, it has to be used in ambulances, so there is that delivery issue that was just spoken of, it can't just be mixed in the pharmacy, has to be in a bag that's stable and can sit in a hot or cold ambulance for, you know, a day or two. And FDA even gave us, I think, an advantage by being able to have it be applicable to a BLA. However, there's just insufficient return on investment for any manufacturer, even under those circumstances, or pharmaceutical company to take this on. I know that's what this is for.

So, just a couple more thoughts about this example. You know, obviously if immediate to the second confirmatory trial were done, and it had the same results, it would change treatment for the most common cause of morbidity and mortality in this country and increasingly worldwide and seems important. And it also would reduce most expensive causes of health care in this country, many other places, not only for heart attack but also for heart failure. I know many have seen ICER do the calculations of what the incremental cost effectiveness for a certain drug, and you know that that threshold has gone from about $50,000 to $100,000, maybe $150,000 for quality adjusted life year, that, you know, if you want to set a drug price.

Now if you have a certain circumstance, as you well know, drug prices can be above that. This drug costs about $10. And, you know, maybe you could charge $150,000 for life you safe but seems unreasonable and also brings up the social cost of not having these drugs available, and benefits if we did. It turns out also if you reduce heart failure hospitalization, the most expensive cause of hospitalization, there would be billions of dollars would be saved as well. But there's still no interest in sponsoring the drug, either from NHLBI -- and actually Chris, you know commented I think insightfully about level of interest for kind for, kind of, straight-ahead phase three trials at NIH for non-patented drugs, it's not there, it's not that exciting. And there's certainly not enough incentive financially. So in the current ecosystem, there's no path to market for this drug.

So, here's a couple suggestions, recommendations that we're supposed to have. Obviously, what we need to do is align the benefits to patients with those of the other stakeholders. Here is three possible suggestions. One of course is one that's been basically discussed already this morning, which is, you know, have regulatory and policy reform such as happened, for example, with so called orphan drugs. Another approach would be to figure out a better value ecosystem for these drugs that is beyond just having the drug companies incented, how about if we make clear that payers, both governmental and private ones, should be at the table, and patients, oh my, and employees in the public should be there too. So how do we align all those interests? that is really the social calling. And the third thing would be to, you know, to go to public health benefit organizations such as governmental agencies and foundations to see if they will fund it. The point of this is there's a huge reward for patients if we could solve this problem, and that's what we're here to do today, right? Thanks.

[applause]

Frank Weichold:
Hi good morning. I make it easy for your eyes. I don't have slides.

[laughter]

But I would like to share some thoughts, particularly with this daunting task to kind of bring out the overarching opportunities and challenges. And of course representing the FDA I would also like to thank
my colleagues for all the discussions and hard work that they do every day. And yet I'd like to remind us that the role of the FDA is evolving. And as we were in the past a kind of policing and enforcing agency, much more so than we are now, it is also clear that we have to become a source of expertise, reference, and guidance in order to meet our goals and responsibilities namely to promote and protect public health, not just public health but also individual health. And I think that's a significant challenge because what we have done in the past didn't necessarily reflect the individual as much. Now, the previous panel discussion clearly pointed out to everyone that we probably cannot solve all the problems today.

So, I would suggest that we perhaps see it as an opportunity to establish perhaps a taskforce or framework that could deal with some, I would suggest maybe at least four, major questions. Often at the agency we start where our process and think around the process, how can we fit our needs through the process and make it work. But I think perhaps we should start with the needs. We should start with the economy around the things and how we assess impact of public health measures or what we develop and that what's not there.

So I think instead of making it the economic question, the last question as it often ends up, I think we have to start with it and in a way define how commercialization and how a process or probability of the success is influencing our decisions. But that needs to be driven by the needs. How do we assess the needs? Who are the stakeholders? And for whom do we want to incentivize? Public goods, medical products, we are evaluating medical products right now very similar as if they were consumer products. In the overall context of impact to society that may not be the only way to look at it so I would propose we think in a way about the impact. And the impact as number two, perhaps, would lead us to how do we deal with data, the evidence. Real world evidence is often used, as opposed to perhaps non-real world evident, but it's defined as such. We need to figure out how to leverage it. So data also leads us to the question of ownership. Who owns the data? How do we protect the data? What is our data governance approach? In my mind it cannot be up to the individual or the individual organization to protect from abuse. So let me elaborate a little bit further on the four issues: economy, governance, data, and process.

I think at the center point there is the question of transparency in what we do. If you want to apply scientific process, I think we have to follow scientific rules. For that we need to understand the quality of the data. We should use standardized and structured processes, need to have in mind interoperability of data, those are all things we've been talking about but haven't done that yet. Patients in different health systems have different identifiers and as such we actually use software to link the information from a person with relative probability in order to understand what actually the problem of the issue is. That's unnecessary, and we complicated situation. And we also know that we need ontologies that are meaningful and that are evolving systems, learning systems, data provenance. I often call it the birth certificate that certifies authenticity of the data point and carries that information on so it can be reused. Just like with the next generation sequencing, that's very obvious that technology is changing so fast that the risk of using an old dataset is different for a particular analysis than it is when you use, say, let's say, the instrumentation from last week. So the biocompute object that was defined for using sequencing data is very useful in that context. We also know that we have to have access and address the question of ownership, why? Because we need to be able to exchange and we need to be able to reuse data, and as such I call it data liberation. We need to keep in mind we have existing data standards such as in the Odyssey System, we have registries, platform trials, and it also makes it clear what we currently do is not good enough and I believe we should discuss how we bring patients, all of us, into the equation as co-
owners of the data when we define how to liberate data and make them available, accessible, interoperable. Of course, the previous panel touched on many questions I don't have to get into, and we won't solve them today. But at least I think those four groups probably are important issues that we should keep in mind if we define a perhaps task force to discuss that, and standardized data bases, and open platforms such as the Global Substance Registry for Clinical and Preclinical Data that assigns a code to a UNICODE to a particular product and carries it through its lifecycle; probably are good ideas that we need to leverage in order to understand how to make this work.

I touched on data protection. It cannot be up to the individual to protect oneself from data abuse and going all the way in the other direction to say, okay, we're going to make data we use impossible or we define it or restrict it very strongly perhaps more so than the GDPR has proposed, is probably moving the wrong direction because that will inhibit innovation. Those are considerations that I believe have significant impact on the discussion of repurposing of drug products because the central point of having data and evidence that needs to lead us into prioritization and assessing the value of what needs to get done is critical also to make resources available to direct them in a good way. So valuation, I touched upon the drug pricing is certainly not the responsibility of the food and drug administration, yet it influences many things that we're dealing with. A societal value assessment and a scientific discussion about the economy of health and healthcare, future wellness, and disease prevention, I believe are very critical questions. And then we think of current business model I think there's room for improvement. I think we need to focus on prevention and I think we need to focus on making investment into future wellness just like a commodity where we invest a discount rate now to have significant impact later, that's perhaps a better way to do it. So when we think of economic incentives and where to get resources from, we also have to think of the impact, the impact for whom and then understand who do we set incentives for. So with that I would hope we can, by the end of tomorrow, be sure that we continue the dialogue perhaps include the consideration for forming a taskforce that includes all of the stakeholders, into the dialogue and inform that -- or keep the public formed and do that in great transparency in a highly scientific way. Thank you.

[applause]

Vikas Sukhatme:
Just waiting for the slides. Oh, okay. Here we go. All right. Thank you very much. Thank you for this invitation. It's a pleasure to be here today and to provide perhaps a slightly different perspective on the problem that we're considering. I have two other disclosures to make relevant to today's presentation. I'm co-founder of a non-profit called Global Cures, also sit on the scientific advisory board of another non-profit, Anti-Cancer Fund. Both of these entities are devoted to problem of repurposing of drugs. So I think the big picture is fairly straightforward. The problem is we have lots of diseases for which we are - for which therapies are not adequate. They're re either very expensive, sometimes quite toxic, and sometimes only modestly effective. So the opportunity, and this is only an opportunity, that I'd like to highlight today is there are entities we have labeled, and the we in this case is a blog that Professor Lowe -- who's sitting back there, I just spotted -- and several of us wrote a few years ago calling out the name financial orphans, that is, ideas that are promising scientifically for new treatments which are not being developed because of a lack of sufficient financial incentive. And there are several buckets of these. The single largest one in our view is repurposing of drugs. The others are nutraceuticals. There could be lifestyle interventions and so on.

Now I want to emphasis that it's only some repurposed drugs that we're talking about here. In other words, if the drug is already existing, and if it has the right biological products, pk/pd, toxicities, certain
element of efficacy for the new indication, if the mechanism of action is appropriate, then those drugs can be moved immediately into clinical testing for the new indication. In other words, we’re not talking about many of the issues we talked about earlier today, that is, taking those drugs, reformulating them, et cetera. For business or for biological reasons. So that that subset of repurposed drugs is what we’re calling out today. So the goal of this opportunity, take advantage of this, to provide enough evidence to change practice guidelines, and to obtain insurance coverage. So I’d like to suggest here that FDA approval for the new indication would be desirable. I don’t think there’s any debate about that. But I don’t think it’s necessary. And I say that humbly, I would respect your opinions on that. I will however say that for the testing of -- for the new indication it may well require the appropriate approval or exemption for an IND. That, no question about. And that will largely be determined by the risk or additional risk that that new indication, excuse me, use of that drug in the doses scheduled, et cetera, poses for new indication. That I fully respect and that is where engagement may well be required with the FDA.

So we’ve established a center at Emory fairly recently the Morningside Center in honor of the foundation that endowed has this center very generously, who’s co-founder is also here in the audience, Gerald Chen. And we’ve labeled this as a center for innovative and affordable medicine. And I’ve put out sort of what our initial manifesto is, why we exist: to develop practice changing reimbursable treatments that are effective, affordable, and non-toxic. How will we do it? We will adopt these quote-unquote financial orphans. In other words, we will pursue for clinical development scientifically promised ideas that are lying fallow because of lack of financial incentive. Our initial focus we have decided will be on cancer. And we will engage a number of efforts across the university and outside to do the things mentioned there. Try to identify and prioritize what these interventions might be, again with focus on cancer, design studies, fund some critical preclinical experiments here, studies, experiments, publish some data on this, ideally develop novel study designs -- I want to come back to that -- and engage in advocacy and education efforts.

And again what I want to emphasize what we value is a laser sharp focus on patient benefits and safety. Let me emphasize that again, an openness of mind to evaluate any financial orphans, and some ideas that we’ve been looking at are pretty outside of the box. So I think Shira [spelled phonetically] will be proud of us if we ever tell you some of these, however unusual they may be, if they have potential for helping patients. So advantages we’ve talked about at this meeting quite a bit already, affordability, potentially toxicity that is typically better known or well known, and wide availability of the drug. Impact therefore could be rapid and worldwide. Challenges, many of them listed here. Let me take two or three of these and enlarge upon those. I won’t talk about prioritization, a topic we can talk about -- we’ve discussed briefly, but I’ll be happy to tell you more. I want to spend time on the other challenges.

So this is a rather busy slide. But I’ve put it up there so we can start thinking about this. Conventional trials, no question about it. We want to think of phase one and two’s, proof-of-concept trials, heavily biomarker end-point dependent trials, and this will be largely for interventions in which the existing drugs especially ones not in common use or with potential overlapping toxicities are considered. So we have to do that. We have to establish that degree of safety feasibility, no question about it. Ideally, we want to be able to get a human signal out of these studies. But I’d like to draw attention to the second or third column here, and that is distributable, I’m referral as distributed studies for want of better word. There are other protocols of this type that the FDA in fact and others have talked about so-called master protocols, point-of-care studies that the V.A. has going on. Participatory studies and others. And I think this is the sweet spot that was alluded to a few minutes ago, that is particularly appropriate for what we’re talking about today. In other words, if the drug safety feasibility and some endpoint has
been ascertained, it would be very interesting to take these drugs out into the community, 80, 85 percent of oncology is in the community. So if for example we wanted to do a study of adding a series of drugs. Could be beta blockers, ARBs, metformin, all have data with checkpoint inhibitors, retrospective data, and animal data. This could be done in a multi-faceted way, in a rapid way out in the community.

So again, I can spend a lot of time on this. There are lots of issues with this, it's not all straightforward. But the concept would be to have a coordinating center, it could be an academic center it could be out here. Such a center would require IRB approval, get IRB approval, investigators at that center would be listed on that study. But in addition, there would be treatments that would be given in the community without necessarily requiring IRB approval for those. The little nuance in this, and an important one is that patients would then ask that their data be transmitted back to headquarters, so to speak. That's the coordinating center. That's the sort of concept I'm throwing out as a sort of straw man proposal. It will take a village to adopt financial orphans, no question about it.

At the center I would like to audaciously suggest humbly also suggest a public fund for patient benefit. We've heard words this morning from Chris Austin, patient benefit. We've heard them over and over again; it is time for us in the United States of America to take some action and put forward such a public fund. I am proposing $1 billion for 10 years to take care of the backlog of these financial orphans. One thought is possibly as FFRDC. These are federally funded research and development centers, I'm sure many are acquainted with these, there are 40 of them. There are different sponsors that come in, there are different ways of administrating these centers, NCATS could clearly play a very major role in this, as could many other agencies, and that relay at the center. All other entities have to play a role. And I've adopted this from a mini version of a slide I had seen in fact on your website a little while ago. And you can see on the right there are lots of activities. And they need very careful coordination.

So let me just give you one example. There are about 30 trials going on with Metformin, with chemotherapy, with radiation therapy, a bunch of things of things. And there's some published data. There's some prospective data that is coming out, some is contradictory. Bottom line: nobody has taken the time to coordinate this. So you're going to get back a fragmentary sort of view of whether a drug like Metformin can be added to chemotherapy in cancer treatments that makes sense or not makes sense. And we're not going to know. The purpose of an agency like this, a coordinating body, will set standards for the kind of studies that are done, how they're done, what will be measured, in other words, bring the rigor of for-profit sector into these kind of studies. I think that's the last slide, thank you.

[applause]

Bobby Ann Mount:
It's my pleasure to introduce Heather Stone from the FDA office of Medical Policy. Miss Stone will be emceeing the afternoon session as we move into the clinical experience spectrum. So I just wanted to pass the ball to her so she can take over the afternoon.

Heather Stone:
Thank you so much, Bobbie Ann. Well I want to start off by thanking the staff from NCATS especially and Reagan-Udall Foundation and my colleagues at FDA This has been a tireless effort, and they have done an extraordinary job to put this meeting together, so if we can just give them all a quick round of applause, please.
So thank you to them. It's my great privilege to start the afternoon by introducing Dr. David Fajgenbaum -- come on up [laughs]. Dr. Fajgenbaum is both a patient and physician. He has an extraordinary story to tell about a repurposed drug saving his life, and hopefully continuing to do so. And I think we have a great deal to learn from him about this space. So with that, Dr. Fajgenbaum.

David Fajgenbaum:
Thank you so much for that introduction Heather. Welcome back, what an awesome start to the day. It's such a pleasure and honor to be with all of you guys today, and to think through solutions for the many problems that we face in rare disease drug development. So let's see. All the formatting is off on these, can you go back to the original version of this document? I think you might have copied them into the doc. Sorry, guys we've got technical difficulties. Gives some people more time to come back in after lunch. Nice, okay we're cooking, guys.

As I said before, special thanks to FDA and of course to Heather for the work they are doing along with NIH and NCATS to make this possible. So I'm going to give a perspective as a patient, but also as a physician-scientist. I titled my talk personalized, personalized medicine because I'm a physician-scientist trying to practice personalized medicine and I'm also a patient battling the same disease I'm studying as a physician-scientist. The picture on the left is me as a healthy third year medical student training to become an oncologist in memory of my mom who passed away just a few years before. And the photograph on the right side of the screen is from just a few weeks later when I was dying in the intensive care unit at the hospital of the University of Pennsylvania. I was experiencing multi-organ failure. My liver, my kidneys, my bone marrow had all shut down. I was on dialysis, feeding tubes, daily transfusions to keep me alive. All with no diagnosis. I've considered this time from the time where you can see the photo which is when I had my last rites read to me by a priest because doctors didn't think I would survive. I've considered that moment to be the start of my overtime, time when every second truly has to count.

So today I'm going to share a bit more about my personal journey. My odyssey with this disease trying to identify a drug for myself, share the challenges I faced along the way, and hopefully close with some solutions and lessons learned. Over the course of 11 weeks, as I mentioned earlier, I was in the intensive care unit with multi-organ failure and was sick my doctors didn't think I would survive. I eventually had a lymph node biopsy done, this is a picture of my lymph node actually where a pathologist said we don't think this patient may have lymphoma, what everyone was concerned about, we think this patient has Idiopathic Multicentric Castleman Disease. IMCD is a rare immune system disorder where the immune system because hyperactivated, attacks and then shuts down the bodies vital organs. About 5,000 patients are diagnosed each year with Castleman Disease.

My subtype is most deadly, about a third of us will die within five years of diagnosis, and another third within 10 years of diagnosis. But with a diagnosis came an attempted treatment. There were no FDA approved drugs at the time, but chemotherapy was used off label in patients with IMCD, and I was given a first dose of chemotherapy. Unfortunately I didn't respond right away but thankfully it saved my life and I was able to improve, and about a month later leave the hospital. Unfortunately, I went to relapse shortly thereafter. Again multi-organ failure, dialysis, needing daily transfusions, very, very ill, but this time I was so sick I was given multi-agents. Seven different chemotherapies, VDTA so a combination of
the most toxic and ablative therapies known to man but fortunately that combination of chemotherapies saved my life. So after spending almost five months hospitalized, you can see this the picture of my dad and I sitting up and I'm feeling better. I've lost my hair from chemotherapy but I'm just so thankful to be alive. This picture here you can see my dad and I going for a walk on the Hematology-Oncology floor. And you can see I have a large belly because my liver and my kidneys had completely shut down so I had a tremendous amount of ascites, I was getting between seven and nine liters of fluid taken out of my belly every other day due to the organ failure.

But this is New Year's Eve 2010 and my dad and I are so thankful and feeling better so we decided to take a walk on the hematology-oncology floor and passed the family waiting area we noticed there was a gentleman looked like he was drinking on New Year's Eve. He was kind of, like, swaying in his chair. And on our next lap around the floor, we saw had he fallen onto the ground. And so my dad helped him back into his chair. He looked at my dad and said thanks so much, good luck to you and your wife. We were like, wife what is he talking about? Then I looked at my belly and I realized he thought I was my dad's pregnant wife.

[laughter]

Which was a low point for both of us. But I turned to my dad I said, man you've got an ugly wife and we laughed really, really hard about that. So here's a picture from a few weeks later and you kind of appreciate how someone maybe could have confused me as a pregnant woman. And this is a picture from a couple years before. I played college football at Georgetown just down the street. You guys may not have known that Georgetown has a football team, we do.

[laughter]

And you can see, this is the worst before and after picture you could ever imagine. But if we could reverse the order, I feel like I could be a great advertisement for Peloton or for Muscle Milk but, unfortunately, it's in the wrong order.

So I got out of the hospital and took a picture every week for the next eight weeks. And you can see the chemotherapy was doing its job. My fluid was going away, I was feeling much better, my hair started to grow back, and by the end I looked less like my dad's pregnant wife. So I was able to return to Penn Medical School and complete another six months of rotations. And while I was doing those rotations, I was on an experimental drug called Siltuximab. It targets interleukin six. Unfortunately while on that drug I had another life-threatening relapse. So the only drug in development for my disease I had now failed to respond to. And I required [unintelligible] chemotherapy again.

So in this photo you can see my bald head from the seven-agent chemotherapy that I had received and fortunately that combination of chemotherapy saved my life. But right around the time that I started getting the chemo, I had a conversation with my doctor. I said, okay, Siltuximab's not working but what other drugs are coming down the pipeline? And he said there are no more drugs in development. I said okay what promising leads are there out there? There must be cell types or signal pathways or cytokines that we can target. And he said there aren't any. And I said well there must be researchers out there that are, you know, looking for targets on its case. And he said he said, no, there aren't any. And so within a matter of minutes I went from being this optimistic hopeful Penn Med student believing that there were researchers out there solving problems and finding drugs to realizing for many diseases, in fact most diseases, there are no FDA approved drugs.
And unfortunately for many, there's no work being done. So I turned to my dad, my sisters and my girlfriend, and told them, I'm going to dedicate the rest of my life however long that may be to try and identify treatments and maybe even a cure for this disease. So when I returned to Penn Med, I kind of followed three paths. The first is that I began conducting laboratory research at Penn. There were no laboratory researchers at Penn but a colleague of mine gave me some space in her lab and I provided all the samples that I could need from myself. And I started a foundation called the Castleman Disease Collaborative Network with the idea being we wanted to accelerate research and drug development for Castleman Disease. And we wanted to take a unique approach to drug development. I don't have time to go through that approach today with you all, but basically to try to get away from the randomness that occurs typically in drug development where you hope the right researcher applies for the right project at the right time and they happen to have the right skill set. To get away from randomness to actually create a community of physicians, researchers and patients, crowd source from within that community the most important research questions and go out and recruit the best people in the world for those particular studies, whether they know anything about Castleman Disease or not. And that approach has resulted in major breakthroughs for Castleman Disease. Again, I don't have time to go through the details of those, but really this new approach has been quite revolutionary for us.

And right around that time a major gift was given to Penn to start the Penn Orphan Disease Center. And so I went to the interim director and I said I have an orphan disease, I'm on this orphan drug, can I be part of this center? And I was part of the center part helping out with ODC and also continuing to drive forward the science for Castleman Disease. And in this picture, you can see my graduation day from medical school with my girlfriend, Caitlin, and we were so hopeful. At the time I was on three chemotherapy drugs that I took weekly, and we were very hopeful that that was going to keep me in remission, again these are off-label drugs, they were not approved or ever even studied clinically. But we hoped they would keep me in remission. But unfortunately just a few months after graduating from medical school, I had another life-threatening relapse, and spent a month in the hospital in critical condition. This time was engaged to my wife, to Caitlin, and I so badly wanted to make it to our wedding day, May 24th, 2014. And with my rate of relapses, it was unlikely that I would make it to our wedding date without another relapse, and whether I would frankly survive to our wedding date. So, when I survived, thanks to multi-agent chemotherapy, those even chemotherapy agents, I returned to Philadelphia, and I got to work. And I started performing experiments on samples I had been collecting on myself in the months leading to the relapse with the hope I could identify some drugs, something that was approved for another indication that could maybe help me.

So what do you do when you run out of options? All the drugs that had ever been tried for Castleman's had been tried on me. And so went back to samples, ran some -- what are called cytokine panels, found a couple cytokines began to rise in the months leading up to my relapse. One being VEGF, another one a marker of T-cell activation, went back to separate samples, I confirmed VEGF was up, confirmed that t cells were activated, and then thinking about my clinical picture that was certainly consistent with a role for VEGF. So very vascularized lymph nodes, hemangiomas popping up, and certainly the fluid accumulation. So the clinical picture was consistent with what I was finding in the laboratory. And just to kind of simplify it in a diagram. In IMCD, the immune system becomes hyper activated and then attacks and shuts down vital organs, but we don't know why or frankly, how to stop it. For about a third of patients we know interleukin 6 is the key cytokine. This is a picture -- [coughs] -- excuse me -- of Kazuyuki Yoshizaki who identified interleukin six to be elevated in Castleman Disease. He went on to develop Tocilizumab which blocks interleukin six
receptor. And I had heard a rumor that he had given Tocilizumab to himself to prove it was safe as the first human. And so I went to Kazu, he's a good friend of mine, and I said Kazu he's a good friend of mine, I heard you gave Tocilizumab to yourself as the first patient to prove it was safe. He said no, I didn't give it to myself, the nurse, she gave it to me.

[laughter]

Said exactly Kazu. So those of you who have followed the Cart Therapy Story, CRS, will know that Tocilizumab is what saved Emily Whitehead's life when she was dying of CRS and it saved the entire Cart Therapy program. I think this is an important example of a drug that is developed for a rare disease, for Castleman Disease, in Japan, and went on to save the entire Cart Therapy Program. Because if Emily Whitehead had died as the first pediatric patient, it certainly would have changed the trajectory of Cart Therapy. Unfortunately for two-thirds of us we don't improve with Siltuximab or Tocilizumab so interleukin six is not the problem for two-thirds of us with Castleman Disease.

So what do you do when interleukin six blockade doesn't work, nothing else is working? I mentioned cytokine panels earlier. We ran serum proteomics on my samples, flow cytometry on my samples and then we connected it with the clinical picture. And so we asked the question: do we target t cells with anti-thymoglobulin, do we target VEGF with Bevacizumab? These are drugs that are FDA approved for other indications, they have pretty nasty side effects, they are very expensive. So we asked is there something common to T-cell activation and to VEGF? Could we hit two birds with one stone? And so we ran the proteomics data through our pathway analysis software through three databases, and all identified the PI3K/AKT/mTOR signaling pathway as a candidate signaling pathway. Well, mTORs is actually critical to T-cell activation, and also to VEGF expression.

So we were pretty excited about this. Well maybe if we could target the mTOR pathway, we can hit the T-cells and also VEGF. But I wanted to do one final experiment and unfortunately during my last re-relapse had a lymph node biopsy performed. And so this was a normal lymph node, we wanted to an experiment looking for mTOR activation. So in this lymph node you can see that there's a lot blue. Blue stains positive for nuclei and brown is positive for mTOR activation, this particular communication line. And you can see there's some brown in the lymph node, some mTOR activation in a normal lymph node. And then this is my lymph node. And you can just see it's striking, the amount of mTOR activation. So as you know in research and drug development, we find positive things all the time that turn out to be false positive. So this was no guarantee that inhibiting mTOR was going to be the solution, but at least it meant we had a candidate. We know that the thing we that want to target is through the roof, let's see what happens if we do target it.

So we started me on Sirolimus based on this data and today marks 70.97 months since my relapse. And I say 70.97 months because I realize that I can't round up. I don't know when I'll be back in the hospital, I don't know if today I'll be back in the ICU. I know I'm thankful for every moment, but I know I can't round up. But I also won't round down because this has been so much effort from so many incredible colleagues and friends of mine working with me to drive forward this science, for me, but also for other Castleman Disease patients. So I won't round down. The New York Times wrote a story describing this as "Doctor, Cure Thyself" which I think is a bit of an overstatement. I think it should be doctor helping himself a little bit right now, and hopefully for a lot longer.

[laughter]
but I don't think they could have fit that as the headline. But most importantly, I was able to make it to May 24, 2014.

[applause]

Thank you. I was able to make it to our wedding day. You can actually see in the picture my hair grew back just in time.

[laughter]

That is never before been cut hair that you're seeing in that picture after the chemotherapy came back. You would think that wouldn't be that important, but that actually was pretty important to me to have hair on my wedding day, because I just didn't want the external reminder to Caitlin of all that I have going on internally, and all that, you know, that I'm dealing with health wise. So that meant a lot to me. And then most importantly, 15 months ago my wife and I went on to have a daughter, Amelia. And this is our sweet girl who makes us so happy and brings us so much joy. And of course the thought that without this drug, this repurposed drug saving my life, keeping me alive, certainly Amelia would not be here. So we've gone on to give this drug to other patients, this is a patient, Joey who presented a year ago to the Children's Hospital of Philadelphia right next door, failed first line and second line therapy, we gave him Sirolimus, he had a really beautiful response. And this is a patient, Katie a couple years ago, had been refractory to a number of different drugs and has a really positive response to Sirolimus.

So importantly as we think about off-label drug use, I'm a huge proponent that if we're going to use drugs off-label, we need to systematically track whether it works or whether it doesn't work or electric we're going to continuously repeat the same problems over and over again. I run a natural history registry out of Penn. Patients enroll from all over the world, we get their medical records, we systematically extract data into the database and from the first 56 patients we were shocked that 33 different drugs have been used off-label in our first 56 patients. There's only one drug FDA approved. And we've now looked at about 150 patients, and we're over 40 drugs being used off-label. So drugs are being tried, especially in these deadly diseases like Castleman Disease. They're tried but they're never systematically tracked. So we never learn what works and what doesn't work, so patients just keep getting random things thrown at them. So I think it's really critical that we do this.

We ended up publishing data describing use of mTor a couple months ago, and then we've gone on to shown mTOR activation in about 26 patients now with IMCD. And we've opened up a clinical trial out of Penn. The manufacturer of Sirolimus is not interested in pursuing a label change, it's a generic drug. I'm not [unintelligible] the label change with the FDA but we were able to get NIH funding to fund the trial and we just recently enrolled our first patient.

Unfortunately though this drug we know off-label has helped some patients, somewhere around, about third to one-half of the patients that I'm aware of have benefited from it. The other patients who haven't benefited from Sirolimus, there were and are no other options. So these are a couple young patients, Lisa and Sergio who passed away in the last year, where Sirolimus was kind of the final hope and we all hoped so badly that this drug was going to work for them and, unfortunately, it didn't. So it reminds us that we have to keep working, we have to keep looking for those other drugs that are already out there that can help patients like Sergio and Lisa. So thinking through the challenges that we face, the first step is candidate drug identification. You can get a lot of false positives when you do bioinformatic analysis like I did. I don't know if you guys saw, right above mTOR was malaria, we don't
think malaria is involved in Castleman disease, but these sort of tools have a lot of random things and noise that come out of them. And so it’s really critical, in my opinion, that if you do these sort of things that you then follow them up with some sort of in vitro or in vivo validation, where you can show kind of in black and white that what you think is there is truly there.

Getting access to drugs off-label is often challenging, fortunately a drug like Sirolimus because it’s generic it’s very cheap, so I had zero problem whatsoever with an insurance company. They were thrilled Sirolimus cost 10 percent of all the other drugs that I get. So they were thrilled to pay for Sirolimus. Even though I was the first use ever with Castleman disease of Sirolimus they gave no problems whatsoever. And I think as I said earlier it’s really critical when drugs are used off label that we track them systematically.

Of course, when we perform clinical trials when possible, submit data to the FDA when it makes sense and then also disseminate information to providers and patients. So I’m going to close with some solutions that I think we can -- hopefully address some of these problems. The first this is a graphic, trying to represent all of the diseases out there. And I think that we’ve heard a couple different numbers today, somewhere between 1,500 and maybe 3,000 compounds that are FDA approved for at least one indication. And we think somewhere around maybe a quarter of all diseases are covered by those compounds.

So what can we do to think about expanding use? I think this cartoon is nice, think about an old dog reading about new tricks. How many of these old drugs could be repurposed in new ways to help diseases that don’t currently have any.

I want to close with this last slide talking about lessons learned. And I actually recently wrote a book that came out in September called, "Chasing my Cure." One of the main reasons I wrote this book is to share this story, this example of having a deadly disease where there was no hope whatsoever. My doctor told me there was no hope, there really was no hope. But thanks to this drug that was developed 30 years ago, I’m here today. I think it’s really important to highlight these stories for patients out there who also don’t have hope, that with the right team and the right people working together we can certainly identify drugs that are going to help patients.

So the first is within candidate drug identification, it’s critical to collect the samples, to be able to do the things that we did. If I hadn’t been collecting blood on myself and lymph node tissue, we wouldn’t have had materials to do the experiments that led to this. I mentioned earlier you have to do target validation, just because it comes up in a bioinformatic database does not mean that it’s going to effective in humans. The next is that when possible, if it makes sense, if it’s safe, and it can be given to a human, make sure that you’re tracking systematically whether it works or whether it doesn’t work. Seek funding from places like Cures within Reach, NIH oftentimes, the manufacturer will not provide money but maybe they will provide drugs. So in our case Pfizer provided Sirolimus for free to us for the trial. That cuts out a large portion of the budget. Work closely with FDA. I’ve been so impressed with all of our FDA colleagues that we’ve worked with during this time. And then it’s really critical to start to disseminate information because you actually may be able to change practice without -- you can change practice with solid trial even without a label change.

And then I’m just going to close with three lessons that I think are important. I mentioned at the beginning of the talk that I’ve considered that moment when I had my last rites read to me in 2010 to be the start of my overtime. A time when every second counts. I really want to encourage you all to think
about how we’re all in overtime. None of us know how much time we have. We really do need to live with that sense of urgency.

The second is that I really was so hopeful, and I prayed, and I hoped that someone somewhere would find a drug for me. And then at a certain point I realized if it was worthy of my prayers and worthy of my hope, than it was worthy of my action and that I needed to turn my hope for solutions for myself and for other patients into action. I think you guys being here today is the first step but as you heard earlier from Chris Austin, just talking about it is not enough. Let’s turn our hope for progress into action.

Lastly, solutions may be hiding in plain sight. This drug that has me on the stage in front of you guys and alive was at my neighborhood CVS for those years when I was in and out of the ICU, but no one had ever thought to try it. How many drugs are there out there that are just waiting to be repurposed. Thanks you guys so much.

[applause]

Female Speaker:
Thank you so much, David. What a great and inspirational talk. I really hope that sets the stage for this afternoon’s discussions and for tomorrow’s conversations as well. Turning hope into action. That’s what this is really about is how can we generate effective -- safe and effective therapies for patients and make sure that they are available.

With that I’d like to invite the clinical experience spectrum participants onto the stage. This will be moderated by Kenneth Gersing, who is the informatics director at NCATS. And I’m happy to have Jacqueline Corrigan-Curay, office director from office of medical policy at the FDA and CDER, Claire Thibideaux, who is the director of scientific affairs with Cures within Reach, Patroula -- and I’m going to mispronounce it -- Smpokou -- sorry -- from the rare and genetic disease group at FDA, Joseph Ross, professor of medicine and public health at Yale, and Matt Might, director of Hugh Paul precision medicine initiative.

And the purpose of this session is really to just discuss the situations in which there is clinical experience. There are case reports, perhaps there are even clinical trials or extensive real-world evidence, and what can we do to move the space forward when we’re in that situation. So with that, Ken? Oh, sorry, too many people.

Kenneth Gersing:
Thank you all for being here. What an amazing panel to work with today. I thought that I would talk about -- we’ve been talking about drug repurposing, but I think maybe our panel should be labeled data repurposing. As you saw in the last talk, the data was actually essential, but it also had a lot of false positives. So it offers both the wonderful opportunity and a problem for -- or a potential problem.

I thought I would start out by just talking a little bit about some of my personal experiences. I used to run an electronic medical record company, and I’m a psychiatrist by training. In my field, which is closer to crystals and metaphysical field than a scientific field, my field has been changed by accident. Lithium, which was really used in bats to cure gout, became the first drug to help for people who had bipolar disorder, and then Thorazine, a drug that was really invented for people with anti-emetics and nausea, turned out to be an antipsychotic. And these drugs have changed the world for me, in my field, for the patients in my field, other drugs like Depakote for bipolar also were really seizure drugs. So to not use
these drugs off-label, at least in psychiatry would be a terrible, terrible shame.

But there's a flip side to data too. Very much following in the last talk is I used to follow the residents in the clinic where I worked, and they started using Seroquel for sleep, and Seroquel is an antipsychotic. I just thought I'd write down some of the things that Seroquel can do: weight gain, endocrine problems, sedation, anticholinergic, hypertension, seizures, EPS, which is kind of Parkinson's like, blood dyscrasia -- can stop you producing blood cells, cardiotoxic, sudden death, and neuroleptic malignant syndrome. So why were these residents using Seroquel, a very dangerous drug, in kids? Well it turned out that the drug rep said, hey you know, there's another reason you can use this drug. And so I had to run over there and say what's going on here? And so I think data cuts both ways.

I want to reinforce the need to look at data and it's easy to beat up on the FDA sometimes but I think thank goodness they are there because they are the ones saying, hey, we really got to reach a higher bar. But there's another side to this, which is repurposing these drugs, and so I think finding that balance and what is good enough data for fit for purpose, meaning that we use data for different reasons, sometimes it's for safety, and sometimes it's for a new drug indication, and I think if we can have some clarity on what the data can be used for and the quality we need at every levels, then it can go on to help us for different things and it won't be just this black box. S with that, I thought I'd pass on to our panels today and they have already been introduced, but Jacqueline, why don't you start out for us.

Jacqueline Corrigan-Curay:
Is that better? There we go. Okay, so, thank you to the organizers. It's been a great conference so far. We were asked to talk about, as we said, sort of real-world data and sort of repurposing data. I think as you heard from the previous talk some success was how well everything was documented and done by a physician-scientist. And even speaking about the type of data that you want to capture on every patient. That's a little different than real world data, it's data that, you know, physicians may be doing in the course of clinical care and they're gathering that data to serve their purpose not necessarily to serve the research purpose. But so what can we get from that data?

I think first and foremost I know we want to talk about evidence generation. We do certainly real-world data is fit for purpose for hypothesis generation right off the bat, right? But we heard some of the issues with off label use is actually knowing what the drug was used for. I mean, it may be obvious if it's a cancer drug and the patient doesn't have cancer that it's not being used for cancer, but the reverse may not be true. So this continues to be somewhat of a challenge.

The other thing we need to really think about is when we're starting to think well we're going to launch some sort of evidence generation or clinical trial not to underestimate how much this data can be used for just figuring out what kind of trial you should do, what kind of patients, where they are in enrolling because although that's not the sort of ultimate goal, we want to use this other evidence generation, you know, the cost of under enrolling, the cost of having a protocol that can enroll and that you have to amend several time just can't be underestimated. But then you want to think about what can I use as data to get something in a label, an FDA label, and be that effectiveness or safety, but I think largely folks are thinking we won't effectiveness, we want an indication.

And I think we do need to remember that the extent evidentiary standard doesn't necessarily change, right? It is substantial evidence and, you know, we have been asked to really look at real-world data, and real-world evidence, and how it can inform regulatory decisions, but one of thing things that Congress clearly said was our evidentiary standard doesn't change. Real world evidence won't be the answer to
everything. You really have to think about what's the question first that you want to answer and then can you answer it with real-world evidence.

So you start first really with what's that study design that you need and then what's the data you need, and is that data even available? So let's say you want to start with a prospective collection of data, and maybe you're a pragmatic clinical trial because often, you know randomization is something that really helps us understand whether there is an effect. So you're not going to -- you can confirm the diagnosis because you're going to talk to the patients, you're going to get that data, you're going to be able to look at administration. But let's say you want to sort of capture endpoints and safety data, that's what you're going to use to make your trial more efficient and more pragmatic.

So you have to think about let's say in the safety area, so if you're looking at a drug -- so it's been on the market, and we're going to change the indication, largely if we don't expect any new significant safety issues to rise in this population compared to the population that it's been used, that may give you the opportunity to what we call, sort of, streamline the safety collection; so rather than collecting every adverse event that might happen you might be able to do all the serious adverse events. And those that are medically attended, again, those are the types of things that are more likely to pick up in real world data than sort of everything that happens to a patient along the course of the way.

And then you start thinking about endpoints, and what is your endpoint because your outcome, and that's what you need to think. And so if an outcome is measuring a change in disease severity, that's a particularly challenging thing in real world data, unless there's a very common way that physicians, you know, assess their patients and they do it, but in our sort of drug world we often use these very elaborate sort of tools and scales that allow us to really discern whether it's effective but they are not very practical sometimes in the real world.

How do we bridge that? What's being done in the real world in terms of assessing whether patients are getting better or not and how does that relate to what we're used to looking at. Now one solution potentially is starting to look at mobile technologies and sensors. We talk about real world data being data that's routinely collected to inform on health. And routinely some people think well that's only repurposed.

I would argue you give a patient a sensor and they are walking around in their daily activities, that's what we really want to get out of real world data is how are patients performing, you know, the 24 hours that they are really not in a healthcare setting. Now of course, you're going to use a sensor, you're going to have to sort of be able to do some of the background and what's the validation of that endpoint and how does it relate to a clinical endpoint that we know. It may be also that your endpoint is something that we can pick up in real world data, maybe things that end up in the hospital, you know, an M.I., or a blood clot or something like that. And so that may be a little bit less challenging to use real world data to generate real world evidence.

But again you're still going to have to be able to validate that what you're taking from the data represents that true underlying clinical activity. It may be a lab test, you know, maybe you say you just need a couple lab tests. Again, that also seems like data that should be easy to get and sometimes it is. But when is it being collected? Is it being done at regular intervals so that we can start looking across populations and looking at effectiveness? Is it collected in the same way so you can harmonize across multiple systems?
When we started doing some work with labs, in sentinel it turns out that, you know, there were 70 different ways to represent a single, very simple platelet count across. And so you need to have the data folks who can bring that data into systems and integrate. And of course, it may be that it's not only understanding what the data elements you need but how are you going to get that data from the source and into an analytic dataset and all the processes and that there's a quality and that we can follow that data from the source all the way to what you're submitting to FDA. So it's things like that that need to be thought through and you need to have the right people on your team to start doing that kind of work.

Maybe you're not going to do a randomized trial. Maybe this is a rare and life-threatening disease with no treatments and predictable course and people are not going to be randomized, and so you're thinking I'm going to do a single arm trial and I need to look back and see what's the natural course of the disease. Can I use the real-world data that way? Can I use an external control for patients?

And that's certainly possible. Again, you still have to be able -- can you identify the correct patients in the dataset? Do they have the current diagnosis? Are you going to get the same endpoints that you're getting in your clinical trial and are they sort of matched at some level? I mean, no matter what, even in rare diseases, we may see differences in populations that end up in a clinical trial versus those that we see in real world data that have to be taken into account.

But certainly, that's where we've seen real world data used at FDA to some extent when we're thinking about effectiveness. You think of Glucarpidase, which was for -- to treat methotrexate toxicity. I mean that was approved on a series of NIH compassionate use cases, which is really sort of clinical treatment. And if you look at something like Myozon [spelled phonetically] for Pompe disease, it was based on a review of historical records. What happened to patients before they were treated? And more recently the accelerated approval for leukemia drug, [unintelligible] they went through 2,000 records of patients with that same leukemia in Europe and U.S., and then they got down to the patients who sort of matched who was in the clinical trial and they did some propensity score matching and that was used as a reference for what they saw in the accelerated approval, and then of course that drug went on to do a confirmatory trial in that clinical benefit that was recognized.

No again, we also -- when you're thinking about rare diseases and you're thinking about how do we use real world data, I think we need to think about registries because registries at least give you a really -- a ready source of real world data that you've already thought through, what do you need to capture, and some of the work that FDA is doing actually is supporting some work with c-path [spelled phonetically], our critical path initiative institute and [unintelligible] to think about what are the platforms for the registries. And I'm sure my colleague can speak a little bit more about the importance of having a good registry and thinking about that at the start.

Now we also talked about maybe you have some -- a little bit of clinical trial data but this is a drug that you're going to use chronically and what you're thinking about, what FDA is looking for is more safety data, and certainly we're very used to using real world data for safety. We use it all the time. We have a sentinel system; and so that's another area where you could start think about using these data. Finally maybe you have a small clinical trial but you're seeking some additional confirmatory data.

The question to us is sometimes what can we do with just a non-interventional design to provide further evidence of effectiveness, what about these observational studies? I admit that this is still an area that we are exploring and you have you all the data issues that you would have when you're even thinking of [unintelligible] but even more because now you need precise data about your diagnosis your exposures...
and you don't have a chance to go back -- and confounders because we often are looking across
different groups, right? We're looking at whoever got that drug and whoever did not get that drug. We
often are -- we're doing a large project to really understand observational studies versus RCT's. In that
project we design it such that we look at patients who are getting one drug or another, sort of what we
call the new user design as a way to get at bias.

Well if you're talking about an off-label use and no one else -- that's the only drug, people are using it,
it's very difficult to figure out are the patients who are getting that drug off-label fundamentally very
different than the people who are not and how do you control for all that confounding? So these are all
sort of considerations as we think about how does real world evidence become an answer for some of
these issues.

And I think the bottom line is, you know, what's your question? And then determine what's the best way
to answer it. It may not be worth using real world evidence if it doesn't have the good data and it is not
the right design for you, but if it is then there's a lot of different things that you have to, you know, sort
of work through in a very methodologic way to make sure you've got the evidence that can sort of
convince that this should go into a label. I'll stop there and maybe turn it over to my colleague.

Patroula Smpokou:
Can you hear me? Okay, so, this was a great introduction for me. My role at FDA, I'm in the division of GI
and inborn errors products. I'm one of the team leaders in the clinical team. And what we do is we
review application and regulate products that are intended for chemical genetic disorders. Those are
called inborn errors of metabolism. By so by and large those are single enzyme defects with very, you
know, well delineated chemical pathways. Sometimes with some natural history, most times not.

So the use of drugs kind of in the context that we're discussing comes up quite frequently in our division,
our applications, and our context. So, and mainly the way that it applies is through blood chemistry. Of
course, in approved drugs, or drugs that are marketed, there's good understanding of what the drug's
mechanism of action is. So now we are in the era, of course, with tremendous increases in
understanding of what are the biochemical pathways, the molecular pathways of many rare diseases
but of course more common diseases.

So with this understanding comes, of course, more ideas of how to use therapeutic ways to treat those
diseases. So from the context of rare genetic disease, targeting a chemical pathway of course makes a
lot of sense. But that assumes that you actually know that pathway and the natural history of the
disease very well. You know, that's one piece. It was previously discussed about natural history and
registry.

A lot of times, of course, in rare diseases you might have an idea or have a good understanding of
biochemical marker pathway, but because you're limited by the patient numbers, right, and patient
availability, many times if not most times the natural history of the disease is not well known. I can't
think of a single disease where we have a really good understanding of what happens, except in some
very severe diseases for example infantile Pompe disease kids tend to not survive past 2 years of age,
and that you have a pretty hard endpoint of survival, and that's really the clear understanding. In most
other cases we really don't.

The way that I guess this context applies to rare diseases is when you have some clinical experience,
right? So what does a clinical experience look like? So what we see oftentimes is drugs used off-label
which we talk about a lot, and so how are those drugs used, why would people even think about using it off-label? It's because they know a particular drug works in a particular biochemical pathway and it just makes a lot of sense scientifically that you would try that, right?

We see that quite a bit. Many examples of drugs that have actually been used for decades to treat specific diseases that have actually become standard of care, so one disease that I can think of is Cerebrotendinous xanthomatosis, or CTX. So that's a disease where you have a defect in the bile synthesis, bile acids in the body. And so it would make a lot of sense that if you were not able to produce bile acids, you just give the bile acids, right, to the patient. Well, there is an approved drug that is a bile acid, it's not approved for this condition but it's available. It's approved for a different indication.

So many, many decades ago some bright physicians thought that they would try this drug in their patients. So, many years passed and there's really no other drugs available, right, or approved for their disease which is the case for most rare diseases. Then after many years and many uses, this has now become the standard of care when patients get diagnosed with the disease, they are automatically put on this drug which is used off-label, right? So, all of a sudden, you know, a developer comes to talk to us and say, "well, we have this drug that looks like it works, but we want to actually have a label for it and have an informed use which makes also a lot of sense."

But how do you actually do that? Now you are in a circumstance when you have a drug who is not approved, for an indication, who is technically the standard of care, no patient will, of course, want to get off of the drug to be able to do a trial of any kind. So you're faced with a dilemma of, well, you know, it's been used for so long, it's clinical practice, it's not labeled for that indication, what kind of data do we need?

That brings us into, you know, what data do we have available, right? The quantity, the quality of that. What type of data? So, you know, getting back to the evidentiary standard, which is providing really the substantial evidence of effectiveness, that's true for common disease, true for rare diseases. There's actually no difference in that standard, right? This is under which we operate when you review applications to decide whether to approve a drug or not. So that's not different in rare diseases but it becomes more complicated because you just don't have a lot of data to base your decision on.

So, the considerations that one might think about is what type of data do we have, is it on the dosing, is it on the pd biomarker, pharmacodynamics, a lot of times we don't have pharmacokinetics because nobody does that as part of clinical care and then what kind of efficacy data are out there, in what context, in what methodology, how is that collected, right?

So, examples of those that we've seen a lot is where you have a drug that's been used off label for many, many years, and people have published on it. So you have single case reports of that. You have case series, even some retrospective studies. So it might be that a developer comes in and says, you know, this is what the literature says, the physicians are using it and so now we want to put together an NDA for it. Of course this is a very, very challenging endeavor, but one that we are very in close contact with sponsors to really say what do you have and how do you fill in the gaps there.

You know, of course, when it comes to using literature, or published data, there's a lot of difficulties in really being able to distinguish whether some clinical assessments were done in a certain way, systematically in standardized way, how often, what is your population that you're looking at, if it is a population that was diagnosed 20 years ago where there was -- there wasn't the rigor that we have now
in the molecular genetic technologies, then you may not even be certain that's the right population that you have. So putting together kind of the advocacy piece, in and of itself, based on literature or published studies or single case reports become extremely challenging as you can imagine.

Of course the safety piece is unless something was really -- really, really went wrong in terms of serious effects, you may or may not see it, right, published. So of course the safety piece, which is really central piece of the application, if that's missing, you really get nowhere. So if you can't really fill in those gaps, you're still stuck. And how do you get to the next level is if you need some additional information, you need to conduct a clinical trial to fill in those gaps of potentially what should the dosing be? What is optimal dose for safety or efficacy? How does the drug behave in the population as opposed to maybe a population that's very different, that's been approved? What are the safety signals in that population, which may also be very different than what’s been approved and how do you fill in the gaps? If you are to do a clinical trial, you have to consider visibility. And that's a real big challenge in the rare diseases. So, of course you have small numbers, but on top of that you have very severe diseases.

We've heard about this from the previous speaker, those are very debilitating diseases. And so if there's a drug that's been used for many, many years, you can't expect a patient or family to consent to having them withdraw from a drug, right, to show an effect. There's just kind of -- the practicality of it and a bit of the ethical aspects of that. So, you know, how do you kind of find creative ways to get the data that you need from the population with a small number of available patients and, of course, a great uncertainty about the outcome. So that becomes a big challenge. And that's certainly something that we discuss a lot with industry sponsors about what kind of data are we actually missing, what do you have and what form? And what part of the application do you need to fill and how?

And of course the devil is always in the details. And so it might be that a summary of the literature review from someone may actually give a different impression than if somebody else conducts the same literature review. So we may actually read the same sentence differently. If you don't have access to the raw data which a lot of times is not the case, how do you even make sense out of it? So it becomes challenging. And then other examples that I can speak to is, for example, vitamins are cofactors, right? So those are commercially available, anybody can buy them.

Some of the biochemical genetic diseases are based on single enzyme defect. And, of course, there's a lot of cofactors that go into those. One prime example of that is Phenylketonuria, or PKU. And there's kind of a sister disease that's called atypical PKU that's very, very rare, more rare than PKU, where you're missing a cofactor called tetrahydrobiopterin; so you cannot synthesize it. That's an important cofactor in the [unintelligible] but also in two central enzymes in the central nervous system. Those are responsible for generating neurotransmitters, and so if you're not able to make neurotransmitters, so that's serotonin and dopamine, you have a severe devastating disease in kids and adults. So there we see that there's supplementation with cofactors; those are widely available, but those are not approved for this indication.

So now you have widely available drugs, not approved, not labeled, again their standard of care. It would be exceedingly difficult to do a trial and collect data. And, of course, there is no data systematically collected in this instance. And so when something is truly standard of care especially in population where you have very severe manifestations, if you don't think ahead like the previous speaker mentioned, which I think is really important of how you can collect systematic data over time, really proactively, doing it retroactively and retrospectively, which is what we typically do a lot of times is really not good enough for the standards that, of course, we operate under.
So the last piece is a little bit about relating to expanded access; I think it was talked about a little bit. So we have some experience with what we call n-of-1 trials or expanded access use for treatment, in rare diseases, and we see that increasingly in our area.

The challenge there becomes that maybe you see this snowball effect. So of course you would want to treat a patient with a very rare and serious disease with an investigational product, for treatment purposes, right? There's nothing else out there. It's a serious disease. There's an unmet need, and there's no drugs under development. So then one patient after another gets on the drug under expanded access.

Of course, the expanded access pathway is not -- is not meant to collect any efficacy data in any systematic way; it's for treatment. So once many patients get on expanded access treatment protocol, so to speak, looking back it may be there's some signal, right? That something's actually working in the population. And we've actually seen that in some instances. But when you try to make sense of the evidence, it's just not there because it's not systematically collected.

So the big challenge there is how do you put together data that's not systematically collected and it's not meant to be used for regulatory use in a serious disease, rare disease, where now it's too late to do a trial. We've had plenty of instances like that where it becomes very challenging to really get the evidence we need, and we have to really go back to the drawing board and be creative again of how do you put this all together.

So I'll stop there. I think that's probably more than enough to talk about rare diseases, I could talk all day, but I'll leave it up to the next speaker.

Kenneth Gersing:
Claire, why don't you -- we'll go from high regulatory down through the middle [inaudible] and kind of down to [inaudible]. So why don't we kind of get you to speak form your perspective?

Claire Thibideaux:
Sure. Well hello, everybody. Again, my name is Claire Thibideaux. I'm with Cures Within Reach, and I'm really excited to be here today. I'm excited for a couple different reasons. First of all, it's super exciting to see so many people here in the room who are interested in repurposing. The number of people who have been interested in repurposing over the years continues to grow. So along those lines I see a lot of familiar faces but what's more exciting is the unfamiliar faces I see here. So not only is it more people, it's new people. So that's exciting too.

The third thing, although at first I was angry, but I'm like everybody is taking my points, when I was in the audience, but then I think how great is that, that people are starting to think the same way and get aligned around these issues. So I'm glad to hear some of the things that I've been thinking about talked about as well as new ideas as well.

With that let me give you a little bit of background about Cures Within Reach. Thank you to David for the shout out today. We're a non-profit based in Chicago. We exclusively fund repurposing research. So when we talk about repurposing research, we talk about drugs, devices, nutraceuticals that are already approved by some regulatory body, usually the FDA, but we're open to EMA, Health Canada, Japan's regulatory agency. Those kind of drugs to test them to see if they are going to be safe and effective in
different indications. So it's not repositioning where it's a drug that has failed at some point along the pathway, it's been shelved for a while. These are things that are already approved.

And one of the really great things that I think about Cures Within Reach is that we're disease agnostic. So again, to us it can be a rare disease, it be oncology, it can be diabetes. What we care about is repurposing because we really do believe that that's the fastest way to get treatments to patients in need to get more treatments to more patients, more quickly. And that's -- we've been talking about the patient perspective here and there throughout the conversation but again at the end of the day that's what we're all looking for is how can we get these treatments to patients.

So, with that in mind, we funded probably almost 50 different repurposing trials over the years. Some projects have been, you know, we've seen great results from that. Other projects have been -- have found roadblocks along the way. Where we come in with our funding is we do a proof of concept clinical trial. So these are ideas that we like to say are the comeback win ideas. So these are researchers who say you know what, I have this really interesting idea, and then they run to the NIH and say hey what do you guys think? And they say that sounds great. Come back when you have some data. Come back when you have some sort of evidence that this may work. So we are the funders that come in at that point and provide that sort of catalyst to get it going.

What that means is that many times our projects are small. We have 22 ongoing trials right now, and the sample sizes range from five to 150. So they're small but they are enough to get data that's critical, data that's publishable, and can hopefully allow the researcher to take the next step. And when our researchers apply for funding, they are much more effective to get it. And so, you know, we've invested $6 million in repurposing research over the past years, and our leverage to that is $49 million; so our researchers have been able to raise additional follow-on funding of $49 million. So I think that really talks to the power of just even what a little bit of clinical data can do to get the ball rolling. However, it's not enough. You know, from what we've heard there are many studies that will get to proof of concept, phase 1, phase 2, and then kind of get stuck. You know, not only are we indifferent to the disease that is being looked at, we're also indifferent to commercial value.

So, many of the projects we fund are what we call philanthropic projects; they don't have commercial value or may be very little commercial value. These are projects that may not catch the interest of industry or others, but they have a lot of patient impact, which is really, again, at the heart of what we do. So when I was asked to join this panel and start to think about challenges and issues and obstacles and things we need to think about to move forward, one of the main stakeholders that I work with are the researchers who are doing this work on a daily basis, and it's not a shortage of ideas on their part that's preventing more repurposing from being done, but they face a lot of issues.

First and foremost is that they feel disconnected. They say things like I have this idea but nobody's going to care about it. I'll put it away and focus on something that's deemed innovative by other funding agencies. Where we say that sounds really innovative to us, let's see what we can do with that. So I think that I'm not only having a centralization of the data that we've talked about here but also kind of building a community, and today I think is a great step in that direction, but a community of repurposing where universities we have departments of oncology and department of cardiology, but wouldn't it be great if someday we could say I'm part of the department of repurposing. And really make it a central part of what is happening at the research level.

And part of that too would be bringing in patients. You know, patients are really important when it
comes to this. You know, one question I get asked a lot is, where do these repurposing ideas come from? Sometimes they come from natural history. They come from data. They come from individual case studies. But a lot of times the patients, especially in rare diseases, are very savvy.

We heard David talk about his situation. You know, they research, and they learn, and they talk to each other and say, hey, what did your doctor use? How did that work for you? And they start to come up with ideas as well. So they are a very important part of this process. Not only to think about how can we find treatments, how can we be the data, how can I give you my data to help you do what you’re doing, but also what’s important to them when it comes to what we’re looking at with the research. Patients don’t care about mechanism [unintelligible]. They care about results. And so what’s that impact? How can we factor patient impact? How can we factor in, you know, outcomes when it comes to evaluating these projects at a funding level?

That's one thing that I think about a lot. It goes back to what we heard earlier in the morning about how sometimes repurposing research is considered not innovative, which always gets me, but maybe if we started to think about, okay, is there a way to factor in those criteria when it comes to evaluating these projects that would help them succeed more in larger funding. And even though our PIs have had success in getting follow-on funding, it's simply not enough. It really does depend from disease to disease what kind of opportunities are out there. We recently funded a couple projects, repurposing projects in Meniere's disease. If you don't know what that is, it's an inner ear disease that messes with your vestibular system, patients have terrible vertigo, they have anxiety, they eventually lose their hearing. It can be very debilitating.

And I was talking to researchers, saying hey we've got this funding for repurposing research, bring us your ideas. I had researcher say to me well, you know, that's all fine and well, but nobody's going to fund the next study so why should I apply? Why should I bother? And I think, you know, that's one thing that we need to think about as well.

So, again, maybe this isn't exactly what you do when you have clinical data but if we have an opportunity to start down the path of collecting clinical data then we really need to start to think about, okay, what's going to be the step after that and the step after that and the step after that to bring it to patients? Not necessarily bring it to market. You know, I think we need to have options. Maybe there needs to be different tracks. One that can be available when there is commercialization, interest in changing the label, and one where there's no interest in changing the label. You know, we can't just think one size fits all when it comes to how do we get repurposed treatments to patients. It's really important for those kind of opportunities.

So, you know, again, I think that having these sorts of considerations, thinking about, okay, once we have a small proof of concept clinical trial, what's going to be the next step, is it enough in a rare disease to start to think about changing clinical practice?

And we have an example of that. It's in a disease called ALPS, autoimmune lymphoproliferative syndrome, which gets me when I'm talking in front of a crowd, I'll call it ALPS for short. This is a disease that's a pediatric autoimmune disease, these kids have an overgrowth of their white blood cells, they are very sick. They end up in the hospital. Blood transfusions. They don't have a good prognosis. And Cures Within Reach funded a clinical trial, first a small animal trial, and then a clinical trial, that had six patients. It's a very rare disease; so there were six patients. In these six patients there was complete or partial response in all of them, which was great.
The results got published in a medical journal, the researcher who conducted the study was contacted by other researchers to ask about this. How he dosed the study, what he did, that sort of thing. After additional studies were published, one or two other studies, it became adopted, clinical practice was changed to help these patients. Now these patients are living their lives. They have a better prognosis. They are not as sick as they were. They have to take two pills a day. The drug was Sirolimus, same as David's drug. So there is an example where it was a rare disease population, these small studies were enough to publish and get some traction going to change clinical practice without having to think is a label change appropriate for this or not. Doctors were able to read about it and make their own decisions.

There's another example of a project that we funded, and that's in type 1 diabetes. Again, that's a little bit different than a rare disease. So it's taking a generic tuberculosis vaccine, the BCG vaccine, and testing that in type 1 diabetes.

We came in early when it was proof of concept, again the clinical trial was small, I believe that one was 7 or 8 patients. That initial data was published. The researcher who is out of ass General Hospital, was able to get follow-on funding, now she's doing a fully enrolled phase 2 trial which is 150 patients. So, again, different diseases are going to need different situations when it comes to what do we do with that little bit of clinical data that we have. Is it enough to think about off label usage? Is it enough to gain the interest of other funders who are going to come in and help and allow a larger trial?

So, I would encourage all of us as we move forward to think about everything. Let's put it all on the table and look at all the options and not think, okay, what we really need is a label change or what we really need is off-label usage. I think we need everything, because just as our patients are diverse, the diseases are diverse, and the research approaches to treat these diseases are all very diverse.

So with that I'll turn it back.

Kenneth Gersing:
[inaudible] one of the things I'm hearing is the value of -- [inaudible] how do we optimize that value and make sure that we can operationalize that to other [inaudible].

Joseph Ross:
Well, let me see what I can do to address that. Thank you for inviting me. My name is Joe Ross. I’m a primary care internist on the faculty at Yale, School of Medicine, School of Public Health. And when I was first asked to come and present today, I said why am I being asked to talk at a drug repurposing conference? I primarily do large database research, I work with existing claims, electronic health record data, do a lot of work in the medical product evaluation space working with FDA and others. But I don't do any work in the repurposing world.

And although when David was talking -- it was a very inspiring talk and actually it reminded me of how aligned the goals are. As he talked about using data to better understand his experience, and to search for a cure, it echoes a lot of the way I think about the way our healthcare system needs to move, right? We need to be learning from every patient, learning from every prescription, how can we be engaging, pulling data together, aggregating that information so that we are moving forward with more understanding behind us and not just continuing to move further into the dark.
So, in that way I think what I have to say is very [unintelligible]. So I'm going to talk about a couple initiatives that I'm involved with at Yale that I think sort of at least will be of interest to folks in the audience. One hat I wear is I direct a data sharing project at Yale, called Yoda project -- it's a clever name, don't get us sued -- the Yale open data access initiative where we're working with large pharmaceutical companies to share clinical trial data. And while the existing clinical trial data has a lot of value, particularly to investigators out in the world, to understand subgroup effects, rare effects, outcomes that are rarely seen in large populations as you aggregate information together, in particular to meta analytic community. Also there's a lot of value to repurposing community; it offers control arm data, which can be both used when you're thinking about placebo arm data to try to better understand the historical course of disease, but also the drug data can provide a useful comparison to understand safety. It's not exactly perfect but it is a resource that's available.

So ours is one of a number of initiatives, there's been a relative sea change in data sharing initiatives over the past five years. Some companies will share directly, others use platforms like ours or clinicalstudydatarequest.com, and it's just something I think that the community should be aware of. I also want to talk -- you know, I'm often asked to talk about how to identify a data that's sort of fit for purpose. Dr. Corrigan-Curay talks a lot about that. I don't want to repeat points in sort of thinking about is the data clinically rich enough, you know, if we were going to study an off-label use of the drug. You know, could you identify if it's a new use, is the population representative, do you have enough sufficient longitudinal information to better understand outcomes and what are the outcome data. And, you know, that's really -- it's hard research to do.

Often, I like to think that it's a triangulation problem. You know, because you want data that can account for the confounding, about the clinical decision about whether to treat, account for confounding around health system, the differences in quality that you might see within -- why is one health system providing therapy off-label and another one not, or why is one physician providing a therapy off label and another one is not. And also you have to account for temporal differences in the patterns of care and what you're seeing. So it's challenging. We have come a long way in terms of methods, using propensity scores and instrumental [unintelligible] analysis. There's a lot we can do. But I think the key is also, you know, are you able to observe the same associations in multiple datasets. And so if you're seeing something in the true vin-data [spelled phonetically], do you see it also in the Medicare data? Do you also see it in the VA data and the Kaiser data, and like putting -- you're essentially putting a jigsaw puzzle together? You also want to account for other prognostic differences when you're thinking about the testing of off label uses.

I like to recommend the use of negative controls. Somebody early this morning talked about treating a hang nail disorder. Well if you use hang natures as a negative control are you seeing differences in outcomes or incidence of hang nails when you're comparing two groups. And if you are there's probably something that's the matter in your comparison. So the use of negative controls is quite useful. Along with thinking about treatment effect, heterogeneity, and the challenge of always finding sort of the differences between outcomes in patient groups are generally small, we power clinical trials for a reason. And you don't want to attribute a difference to a therapy when it's just a difference in a prognostic or clinical profile of the patient. And this is really critical -- Dr. Gersing talked about, you know, all drugs off-label, they carry some potential benefit, but they also carry potential risk and so we have to be thinking about that.

Our team -- so the other thing I'll just talk about, our team has done a lot of work in thinking about, well, since there are challenges to using existing claims data are there ways we can better embed clinical
trials within health system data, using existing claims, you know, the existing experience of a patient to better understand medical products.

And I think this really gets at some of the trials that people have talked about here. We've been testing with some funding from FDA, but also some funding from NEST, the National Evaluation System for Health Technology. Essentially a patient-centered data sharing platform called Hugo PHR, or the Hugo Personal Health Record, which essentially puts patients at the center of their own medical record and allows them to aggregate their health information in the same way that people use mint.com to aggregate their financial data. It allows them to link together their various my charts across different health records. So if you're getting care at Yale New Haven Health System, but also at the Hartford Hospital; you can link those two and it smooths it out and aggregates it. It allows you to embed your pharmacy data like CVS or Walgreen's, anything that uses the same my chart services that are actually required by law through the High Tech Act, that health care facilities are supposed to be using.

We've been testing merging that data along with patient-reported outcome measures, or PROMs, pushing out information to better understand functional status, symptom status, and linking to other wearable digital device data to get to -- you know, Fitbits or, you know, we did a trial where we were following patients after they were had an atrial fibrillation ablation procedure and irregular rhythm of the heart and we gave everyone a two-lead EKG that connects directly to their phone and that we're able to pull in that information to look, you know, could we have identified irregular rhythms over time.

So we have a number of different studies that are doing this. What I like the most about is it is using real world data. We're embedding patients, you know, we're pulling data from their health care experience, their routine care. We're at a point of care enrolling them and we're able to follow them going forward but patients they're taking their records, their making the decision to share it out with the research team. And then with the research team we can then use that information to better understand their experience of care, medical products, medical devices, whatever it is. And I think this is actually a brilliant model when you're thinking about rare disease studies and thinking about repurposing because you are still creating those kind of inception cohort, randomizing patients to receive one thing or another, but it minimizes the other cost of clinical trial.

So I'll stop there and hopefully there will be time for discussion. So thank you for having me.

Kenneth Gersing: Matt, why don't you --

Matt Might: Sure.

Kenneth Gersing [inaudible] very unique experience. And I think at the other end of the spectrum of bringing in --

Female Speaker: Dr. Gersing, the audio isn't coming through very well. Do you mind repeating the question in the podium mic? When you speak, Dr. Gersing, we can't hear you very well in the audience.

Male Speaker: Use a mic when you speak.
Kenneth Gersing:
I was just saying that Matt is going to speak next, totally different experience from the engineering data in, but also [unintelligible] the clinical world. So I think -- thank you.

Matt Might:
Thank you. So I guess the slides got converted at the last second. There's supposed to be repurposing with big data at the end there.

[laughter]

The irony of this is actually that I am a computer scientist by training, I spent much of my career working with big data but when it comes to repurposing, I'm generally working with almost no data. So I got to imagine what that was like for the purposes of this five-minute pitch. I wasn't going to use slides. I saw this morning, I think I do have a way of visualizing, sort of, the central problem here when it comes to why we're sometimes not able to repurpose, even if we have lots of data that's available.

I think the central problem here, if you think about drug approval in general, is that there's this fundamental tension between certainty and value if it's a direct conflict. In fact, you cannot maximize both at the same time. Here is why. The issue is that the value of intervention has an opportunity cost to it over time. That cost really goes up, but the value goes down as you wait to intervene on behalf of a patient that is desperately in need. At the same time you can spend lots of time generating more and more data to get ever more certain about the utility of that intervention, so if you take these two curves and you multiply them out to get the expected value of the intervention, it actually has a maximum at some point. I think we're often erring on the side of maximizing certainty, which is way over here, well outside what Dr. Gersing is, I think, was referring to as the good enough point. When is it good enough to actually intervene?

The challenge here is really to move over here, and I then I was hearing points from the other panelists saying, well it's actually challenging to do that. There's congressional mandates in place that say how you can actually do these things, how you can make these approvals in the first place, so it almost forces you out too far under this curve. So I think fundamentally the issue here is that what we're trying to do is come up with a confidence that the drug works for some definition of works, whether that's efficacy and safety together or just efficacy alone.

But we're trying to estimate the value of the probability here. The way we often are forced to do it is to say well with respect to this RCT data what do we believe the value or probability of this drug actually works is, and what we want to do is be more expansive and consider all the available evidence that we can get our hands on, all the real world evidence, the clinical evidence, and use that to compute this approximated probability that is actually works in practice. And I think what we're seeing is to some extent our hands are a little bit tied. The RCT is so trustworthy and easy to do that we often rely on that. But if we're creative with our data science and I think we come up with other ways where we can better approximate the value.

So to give you my perspective on why I'm here and why I think a lot about drug repurposing, and also how I've done some of it, I'll tell just brief fragments of my personal story. I'm not medically trained at all. So you should take any medical advice I give you with a grain of salt, unless you also consider that medical advice, in which case don't take the salt either. I'm in academic medicine now after most of my
life in academic computer science because of my son Bertrand [spelled phonetically], he's one and a-half here, but he turns 12 next week and to egregiously over-summarize the story, he spent the first four years of his life on this diagnostic odyssey, only to find out through XM sequencing that he was, literally, the first patient ever discovered with this new disorder called NGLY1 deficiency. That led to a bunch of other stuff happening. It led to natural history studies at NIH, as we started to find other patients, it led to a lot of basic science being done on behalf of this disorder.

When you put that together, I was actually able to -- about two years after discovery of the disease make a prediction that there was something out here that was potentially therapeutic for this disorder and that was, in fact, a missing metabolite. You know, we could reasonably predict that there was a deficiency involved with this disease. In this case, it happens to be [unintelligible] cosamin; it's a natural product that you can buy on amazon.com. And so it was really easy as parents to actually try this this out. And just to give you the snapshot here, this is the disorder where patients have seizures, severe developmental delay, movement disorder, and a lack of tears. And so we had no idea in advance of knowing what, if anything, this would impact in terms of his disorder but the thing it impacted for him was actually his tears. He was able to cry real tears for the first time in his life after giving him this compound. And that's quite significant because at the time he was on the verge of going blind from cornea erosion. They wanted to do a [unintelligible] sew his eyes shut. And it was just awful the stuff we were going through at that time. So, you know, it would have been nice to also impact things like seizures, but we got was tears. And then, you know, continued to do this science, just oceans of -- those few small tears really swelled into an ocean of science for the disorder as a whole. And, you know, whenever I pose this question or tell this story to biologists, they always say, well it's great that it worked in a person but we're biologists and what we want to know is does it work in flies?

[laughter]

And so we built a fly model. Turns out it's pretty severe for flies too if you take out the gene. But if you raise the flies on this compound and you keep them on this compound, their survival shoots up to around 80, 90 percent. There's evidence, not clinical evidence yet that this worked, but some evidence still. Finally last year we were able to publish this four years after some of the patients started taking this compound. I use this to illustrate this point right here, that if go back to these curves of certainty versus value, you can look at the point where we intervened, where we had some confidence but not a lot of certainty yet that this might do something good. You can judge that against where we finally published a paper last year. And, honestly, it's still not perfect certainty.

We just finally, through NCATS, I got this consortium grant funded to do a real clinical trial of this compound. So it might be eight years after the first hypothesis that is my work that we finally have a paper published that says yes, it actually does. If you consider what this means in terms of the patient when we intervened Bertrand still had vision intact. If we waited until now, he would be blind like many of the patients that we find this age from corneal erosion. But he has vision today because we intervened without perfect certainty.

This led to a grant getting funded to do bigger drug development, to sort of over-summarize this too, we played around with planarian worms, we found a drug target, we did computational and lab screens against the target and we actually found that Prevacid was something that hit this target. So Prevacid is n-gase [spelled phonetically] inhibitor; it's also -- well on label it's a proton pump inhibitor, but n-gase inhibitors are exactly what you need for Bertrand's disease.
So if you fast forward a bit more, I end up becoming the director of Huh Kaul Precision Medicine Institute, a full career shift for me where just do this kind of stuff all day every day for the patients that reach out to us looking for this drug repurposing research as a service. That's really what we provide now. We do it through a number of different ways. I spend most of my time actually do it using big data and AI. This is actually through a project also funded under NCATS; this is part of the translator project. And to summarize this, the tool we built, what it's really doing is it's using old school logic, combined with high speed automated reasoning, to achieve superhuman-like deduction, with clinical insight.

[laughter]

So that's the goal of this tool. And, in fact, I think many of the teams within this consortium project, and so the question for how we did this is actually -- it really is through this consortium project that these teams have been working in a sort of hyper-collaborative fashion to structure essentially all of biomedical knowledge that's out there. What's amazing, it's actually working. We have access to these enormous datasets now that are in a structured fashion that allow us to do automated reasoning across them and to make predictions about what could be therapeutic down to the level of an individual patient or an entire disease.

So we've embodied this as a research consultation service, UAB, where again, people just reach out saying, you know, I want to do research and drug repurposing for my disorder. How do we even start this process? And the goal for us is always to find the next step on their therapeutic odyssey and oftentimes we will deploy these AI tools on their behalf. If you're interested in seeing it, you can come down to Alabama on any given Monday where we're holding these case reviews and debating the science around repurposing for each of the disorders that we're working on. If you're wondering, the tools also made predictions for Bertrand, and that's over-summarized here. What it basically said is he needs to eat a ton of broccoli, on the order of 60 pounds a day to get enough sulforaphane to up-regulate nerve 2 to compensate for the inactivity in nerve 1 that comes along with his disorder. Luckily, you can get this stuff in pill form, so he doesn't have to eat 60 points of broccoli a day.

And just one parting thought here, you know parting [unintelligible] Bertrand is that he's advanced enough after severe developmental delays for many years to using an eye gaze computer in the last year and a half. And when I came home last month, he was actually speaking this out as I walked in the door. So he's gaining some communicative capacity after being stuck at nine months developmentally for most of his life. And he also likes, as it turns out, yogurt and fish.

[laughter]

So the take-home here is that while uncertainty can definitely be problematic in the context of drug approval, so can certainty. Like if you wait for too much certainty, certainty itself will also be a killer because we'll wait too long to intervene on behalf of patients. In my view as a parent at this point, when it comes these ultra-rare diseases, toxicity is really the line that I aim for in deciding whether or not an intervention may be appropriate for my son or for other patients. So, thank you.

[applause]

Kenneth Gersing:
How much time do we have? Fifteen minutes. So, Matt, one of the things that I thought was brought up is that there's a new-fangled thing you keep talking about called artificial intelligence. It's just a black
box to me. I mean how do I know I can trust it?

Matt Might:
That's a great question, actually. So for the newer forms of artificial intelligence, you can't. To over summarize. So there's really two camps here. There's statistical AI, where it looks for deep correlations and patterns out there and says a is correlated with b, so maybe try a to treat b. It will say things like that. I'm actually a big fan of old school artificial intelligence, the stuff we used to do back in the 1980s where everything was logic driven. So back then you had to construct proofs, essentially, around anything that the system could find. These were called things like expert systems back in the day. So when our tool actually gives you an answer back, it actually emits, essentially, a mathematical proof. It says this is why I believe that this is useful. So it doesn't just say try this and I hope it works. It says try this because and gives you an explanation for that.

Kenneth Gersing:
From the FDA's point of view, and someone gives you all these black box answers, and they say, you see it says it works right here, this black box, you know, it comes from this big company. They advertise on TV. Can we trust that black box? Will FDA be okay with that?

[laughter]

Jacqueline Corrigan-Curay:
Well, we always believe everything we see on TV. So, you know, in artificial intelligence I think we're just starting to see it. Obviously, our folks in devices have seen it. I think they have approved, sort of, two products that we're using but it's not the kind of artificial intelligence that I believe keeps iterating; it's more of an algorithm that's, perhaps, locked. We're reading about how this is being employed earlier in drug development, and sort of, you know target identification, other things like this. I don't think we've seen it yet in the clinical trial, and it's something we'll have to think about. I know that our colleagues in CRH just published, sort of, a white paper on this to sort of start the conversation. There's certainly a lot of interest what does this mean and what it will mean from a regulatory perspective. You know, and I'll defer to my colleague here, I mean, what typically is done -- I appreciate your thing about certainty and that can be too much, although I would say in the rare diseases, although we have substantial evidence we also have considerable flexibility in how we interpret substantial evidence.

But the bottom line is we tend to really look under the hood and look at what that patient level data is and what it means and, sort of, a lot of times medical officers are repeating the analysis, it's not that we, you know, you send us an analysis and we say that looks good. I mean, so, you know, how we'll do that with artificial intelligence and when it will be done, but there's probably a lot of places that it can be used along the development to sort of speed that and help bring things, you know, figure out what should be tested and how it should be tested that may not be that it's giving us the one answer.

Kenneth Gersing:
Well, Dr. Ross, I have a question for you. You're trying to --

Male Speaker:
[inaudible] premature.

Kenneth Gersing:
So you're telling me I should trust this EHR thing. I was reminded that when I was working at an
institution that will remain nameless, big [unintelligible]North Carolina blue --

[laughter]

And they were -- we were looking at the medical record, and we were just looking how many EHR primary visits even had vitals. It was only 50 percent even recorded vitals. So why would I trust any conclusion you're getting from claims data which has then been even changed more by the coders who are trying to look for maximum profit, not maximum accuracy?

Joseph Ross:
Yeah, yeah, that's a very good point. And the -- I don't know if I ever said to trust the electronic health record data. What I'm saying is that we can make use it to better understand patient experience, patient outcomes. I think that it's an underused resource. And it's imperfect. I have no qualms about saying it's imperfect, it's, you know, designed for data; it's data that's designed for billing; it's not designed for clinical care.

There's challenges with copy-forward, and paste, and as any clinician in the room knows there's tremendous inaccuracies. But that doesn't mean it's unusable. And in some ways it's just as usable as clinical trial data, which, you know, where you're having somebody come in and they're answering questions when there's other forms of bias that play in sort of how the questions are answered. And they often actually go back to the medical records to validate it. So they're using the same problematic source. For us as we think about how to use electronic health record data there's clear needs for advancement, but I think what I talked about in terms of aggregating various real world data sources one of the key values of that is that you're also getting information directly from patients, and that's the patient-reported outcome measures. Which they can also be not telling the whole truth, nothing but the truth so help them god, but it does allow you to, sort of, triangulate various sources of data around the individual.

I just want to say one thing about the concept of artificial intelligence. I am not data scientist; I am not an expert. But we've been using algorithms in medicine all the time, right? Clinical prediction rules are in algorithm, right, to identify somebody who is more likely to benefit from treatment or less likely to benefit from treatment, and every single of one of them has a sensitivity or specificity, or positive predicted value. And just calling something AI does not mean it's perfect, right? All of them have the same challenges, and so that has to be kept in mind as we're thinking about how to apply those in medicine today.

Bobbie Ann Mount:
Matt, do you mind telling the audience, who hadn't heard the story how before you were an academic scientist you did the toxicity testing on the Amazon [inaudible] safe enough for your son.

Matt Might:
Yeah, I did a pretty rigorous trial. I got on Amazon, and thanks to Prime it showed up two days later on my doorstep. I sat there with a spoon and ate the entire bag in one sitting. I woke up alive the next day. That for me was FDA phase 1 safety testing.

[laughter]

Male Speaker:
reverse order. The first one was about the accuracy of medical data. One of my hats is as a
guest professor at the University of Copenhagen in Denmark. And the lead scientist there is
[unintelligible]. He published a paper, I believe, and majored in communications. He even got
interviewed in "People" magazine and other places, where he essentially showed that when you
separate the medical record data, so [inaudible] Danish population registry. He's done that separately
for the male and female population, and what he finds is that there are different misdiagnosed aspects
that are consistently, you can use machine learning to highlight these differences between men and
women, and it's quite fascinating, I encourage you to look it up.

The other one on artificial intelligence, so I also wear a hat applying machine learning quite a lot. It's just
another name for pattern recognition and machine learning. So AI is just a buzzword that's been caught
on to attract investors in the last three years. On the plus side there are two cases where I know that
artificial intelligence might exist.

One is Go [spelled phonetically]. So there is a strategy to win at Go that was invented by one of the
alpha Go machines that was designed by Dick Might [spelled phonetically] to the point that one of the
top professional players in Go has publicly announced he quits because he can no longer beat machines.
Clearly there is machine intelligence. The other one is a paper that came from Alex [unintelligible] in
Nature Biotechnology in September, where he came up -- they used generative chemistry to design new
chemicals, a lot of people who are not on that paper argued that it's similar to drugs that are already on
the market, the truth is it is innovative enough. So it was new chemistry generated.

Male Speaker:
Thank you for the discussion. I wanted to ask, I guess I'll make it a question, is there going to be a
session that can help us think about the timing and how we're using different regulatory study designs?
So is an emergency IND more applicable in a scenario where you have this timing issue, and what's the
tradeoff when you do something under an emergency IND how does that help us think about maybe the
-- you know, future expanded access studies, where in I am answering a particular problem but not
necessarily addressing a situation which I'll have adequate information to say I can now offer this to a
larger group of patients.

Patroula Smpokou:
So this is a good question. I talked a little bit about that earlier when it comes to expanded access. So,
expanded access use of drugs are -- it's one way to provide treatment to patients who have serious or
life-threatening diseases, and where there's obviously an unmet need and many times no treatment is
available. So that pathway is very specific to treatment use of investigational drugs. You know, one
critical point to think about is that this is not a way to study a drug or provide evidence of effectiveness.
That's a really important point to make.

So what I was talking about earlier is how sometimes you see the snowball effect. We've certainly
started seeing that increasingly for rare diseases where there may be one investigational product that
looks promising, it could be that it just fits the biochemical pathway, and as I said previously just
scientifically makes a lot of sense. And a physician or researcher thinks to try it, and so once you start
using it under expanded access -- this is for treatment purposes of a single patient or a small group of
patients; this is not for evidence generation by any means. So the challenge then becomes once you
have patients treated under that paradigm where you truly do not have systematic way of collecting
data, it's just exceedingly difficult if not impossible to provide any evidence except safety because this is
really the only requirement under expanded access is to provide, of course, periodic safety reports for
purposes of monitoring.

When you talk about emergency IND, that's one type of expanded access use. This is truly for emergency situations, right? So we sometimes get requests for emergency INDs, and when I actually look at it, it's really not an emergency, right? So an emergency is a patient who is in the hospital in critical condition. We sometimes do see that in inborn errors of metabolism, right, where you have a child who is critically ill in the hospital and is dying. So that's a true emergency situation.

There's certainly very legitimate and very reasonable uses of investigational products in that context and we've certainly gone through that. But that's of course not a way to generate data; it's just not a way to do that because the whole purpose of that is to provide a potentially lifesaving drug in a critical situation, in which the expectation is that you would provide it for treatment, right?

So I don't know if that answers your question but I think the point here being that the whole point of expanded access is not generating substantial evidence, and what we have actually seen it that it becomes an obstacle many times to providing the evidence needed for either labeling or other purposes for a drug. And what I've seen is that this increasingly is being used and then it becomes truly a disruption of really providing the evidence that we need, and of course we accept that in rare diseases that are, of course, a higher degree of uncertainty.

We don't typically -- we really never require that you have your two [unintelligible] well-controlled studies; that's just not feasible. It just doesn't make sense. We are used to that. We're used to the regulatory flexibility; we use that all the time. We acknowledge there's a higher degree of uncertainty. However there still needs to be substantial evidence, and if you are relying on just non-systematically collected data it just becomes a true obstacle.

Jacqueline Corrigan-Curay:
I agree completely with that, that you really need the, sort of, systematic collection. On the other hand there's nothing to prevent someone -- we don't want collection of data to interfere with access because that's what expanded access is about. On the other hand you don't want to waste any data if you can. So there is a requirement under expanded access of filing sort of a summary of what happened, and so the more that that can be complete, it certainly is unlikely to be the total picture in the most rare cases as I talked about in methotrexate toxicity or something, but it may, you know, add some more if you've got a patient population of a rare disease and it's under 50 patients, and we've got a small clinical trial set, and yet we have three or four very well documented expanded access, that may at least help add to that package and give us a more totality of evidence.

Kenneth Sterling:
We have one last question.

Female Speaker:
Thank you. This has been wonderful. Thank you. I'm actually a veterinarian, and a comparative medicine specialist. I just wanted to put a plug in there for tools. One of the things that we really work with natural animal models of spontaneous disease, often enough these rare diseases, and as a tertiary care specialist I'm actually at North Carolina State University College of Veterinary Medicine, the other North Carolina university, and we are used to working with managing cases without approved drugs. So for us I think we could really -- we serve as a step between trying something in a rodent model and then trying it in a natural animal model of the disease, and there are very many -- there are a lot of similarities, and
many of our natural animal models are worked up from the genetic mutation all the way to the pathological findings and studying the comparative aspects between animals and humans.

So I think at this conference when you're looking for tools and solutions, I would just put a plug in for thinking a little about some of the natural animal models and how that might provide a fairly inexpensive step, and many pet owners are very involved, our college runs about 30 clinical trials simultaneously, and has a clinical studies core. So there may be some opportunities to get some inexpensive data in some cases that could provide a step up. Thank you. This has been great.

Claire Thibideaux:
Actually I would say that we completely agree with that. I have a funding opportunity for that so we should talk later.

Female Speaker:
Thank you. I'll e-mail you. Thank you.

Female Speaker:
So on that note thank you so much.

[applause]

Female Speaker:
Thank you so much to our panelists and moderator. What a great session. I think that this laid out a really good way of thinking about it. So we've been having a lot of discussions about how to frame the question and how to think about ways to move the discussion forward. And if I could ask the slide person, there should be a slide with five pre-clinical and then four clinical scenarios, just one -- nope, not that one. It's the very first one, she says.

So I think it may be helpful, and I will say this with context that this is how we may encourage you to speak tomorrow in the breakout sessions. We thought it would be helpful to think about -- that the challenges involved in drug repurposing really vary depending upon level of data that you already have. And so just as the agenda is organized from where you have only pe-clinical information in this new therapeutic area to where you have extensive clinical trials and EHRs, that there is a spectrum of information that is required and challenges that ensue.

So we framed it as -- which hopefully the slide will come up -- as five different areas. There we go. Thank you. So in the first scenario you really only have pre-clinical data. And we heard in our earliest talk about -- or panel about the challenges in that particular space and when it's appropriate to move into humans or what other data might be required in the interim.

But then as we think about the different clinical scenarios, I think it's useful to think about it in terms of these four different segments, where you have varying levels of information. So in the first you potentially only have case reports. A few anecdotal cases, but no extensive real-world evidence, no substantial clinical trials. Oftentimes, the goal in that space is to move it into either more case series or observational studies or ideally into a small proof of concept trial or large phase 3 trial.

In the second scenario, there may be quite a lot of real-world evidence. There may be sort of widespread use within the clinical community, potentially information in electronic health records or
other observational studies in other areas but there are no randomized trials. So the ability to discern safety and efficacy to the level that would be ultimately desired may be lacking due to amounts of confounding and bias, in those sources of data. So but then you have potentially a lot more confidence in the information with which to inform a clinical trial.

And so there are different opportunities that exist in that space. The third clinical scenario is where you have multiple phase 3 clinical trials. That are -- actually that's wrong. It's where you have a single phase 3 clinical trial, that is regulatory grade but may not be sufficient depending upon the disease context, more study may still be required, particularly if one is seeking regulatory approval. And then the last scenario is where you have multiple phase 3 regulatory grade clinical trials as well as extensive real world evidence, and the question is really how do you bring all of that data together when a sponsor, for example, may not be interested in expanding the label or where it's not clear who owns the information, but in order to benefit patients there's a need for data aggregation.

So I just want to put that out there as a way to help frame the conversation and tomorrow as we begin the discussions in the breakouts which I’ll explain a little bit more in just a second, I think it may be useful to pick one of those areas, and this is not mandatory, but as a way of thinking about it, to pick one of the spaces for the discussion of the problems and solutions because as I said I believe the potential -- the challenges as well as potential solutions really vary depending on which space you're operating in.

So I know there's been some confusion about tomorrow's breakout sessions, so I just wanted to try to clarify because as enlightening and exciting as this day has been, and I think it really has been quite tremendous, tomorrow is the day for action. So as we move from trying to landscape the situation and understand the challenges to really trying to identify and prioritize problems that preferably have actionable solutions, and then what those solutions are and who might be responsible and how we can coordinate our efforts towards achieving those solutions is what we hope to accomplish tomorrow.

So there are three breakout sessions, one is -- two in the morning, one in the afternoon. And it's principally the first breakout is where we will be trying to identify and prioritize the problems. So what are the biggest challenges, what are the icebergs? In the second session, there will be a discussion of what the solutions to those challenges might be and the ownership of the challenges. And in the third there will be a prioritization of the solutions as well as understanding of the collaborative framework and who owns what problems and I might be messing this up. Nope, okay [laughs].

So the extent of it is that we want to identify the problems, we want to identify the potential solutions, and really have conversations about who can take ownership of the solutions and where we need to work together and what framework we might operate under for that kind of collaboration. So with that being said, let's see if there's anything else.

No, okay, so with that I would like to take this opportunity to announce a very exciting collaboration between FDA and NCATS. This is a space that both agencies have been interested in for some time. It's an area that we see as ripe for public health benefit, and where there is a lot of work that could be done. So just as we've talked about, the situation where there's limited clinical experience, we've also heard a great deal about where there is a need to capture that clinical experience. And to have a way to systematically gather that information so that it can be utilized to, in general, inform further drug studies or generate additional hypotheses. And so we have actually -- well that didn't work -- we have actually jointly developed a website and mobile application called CURE ID, which if we could have that
Did I do something? There we go. So I'm excited to share with you this application we've developed called CURE ID About trying to identify repurposed drugs that could be used for, in this case, specifically infectious diseases that lack adequate approved therapies, but the potential of this platform to be used beyond that is quite significant. And we look forward to conversations about how to expand it. So I encourage you to follow along. I'm just going to give a brief overview to sort of hopefully whet your appetites for interest in this application, and the possibilities.

So please consider downloading the app by searching for CURE ID In the app or Play Store or you can go to the cure.ncats.io -- they told me that's the new sexy thing to do -- I don't know. Ending versus .gov. CURE ID is -- so what is it? It's an internet-based repository that gives the global clinical community the opportunity to report novel uses of existing drugs for patients with difficult to treat infectious diseases. And they can do through a website, a smartphone, or other mobile device. The platform includes a couple of major features: the explore functionality allows you to view reported cases, discussions and clinical trials, create your own case report or discussion post, comment and participate in ongoing conversations with other thought leaders, and a news feed to stay up to date on most recent infectious disease news as well as submissions to CURE.

So with Explore, you can see all of the drugs that have been repurposed for a particular infectious disease with case reports both from the published literature and from today forward, from clinician reports. You can then see the cases in order of the number of cases that have been submitted by drug to get a sense of the number of times a particular drug has been used in that disease. And you can continue to drill down increasingly to greater level of specificity to see outcomes associated with that particular drug as either monotherapy or combination therapy and then the details of the specific case report form.

You can also view clinical trials. Where there is additional data beyond case reports we want that to be available and accessible. And so we have -- we pull the data from clinicaltrials.gov, then importantly we've manually curated the information. If any of you have tried to search clinicaltrials.gov you may know that it's not the easiest thing to do. So this is specific to drugs that have been used in clinical trials for these infectious diseases. The discussion forum is one of the most exciting features where clinicians can engage with experts and other community members from around the world and get rapid responses to their treatment questions or other discussion items.

And we've had some in our initial user testing, we've had some really very engaging conversations. So I encourage you to check those out. You can create using an easy to use case report form that we have developed. One of the challenges was to try to identify a way to collect information from clinicians in a standardized way in which the data could be aggregated, so that it could be used for potential additional analyses and further study, and so we've created a very easy to use case report form at its most simplest. It's really just four questions: what was the disease, what was the drug you used, why did you use it in a new way, and what was the treatment outcome. But you can extend that, considerably, to add as much additional detail as you would like to really provide the context of the case and details that the clinician feels are important and then that is viewed by the fellow users.

So this is just an example of sort of fully iterated case report form to get a sense of the information that's available and it provides a nice summary of the patient's treatment. In addition the discussion forum is less regimented, more open forum for asking questions. You just enter the body of your text
and ask a treatment question and then can get responses from others.

We have recently added a news feed functionality, which I think will be great for sharing information about upcoming events, about articles that have been posted in this space, as well as to stay up to date on the latest and greatest that has been submitted to CURE. And you can have a daily digest [laughs].

I should mention that there are limitations to this data. We’re not trying to suggest that this information would be intended to be used by pharmaceutical companies or manufacturers, to advertise or promote unapproved uses of drugs. There’s a really critical distinction between off-label use and off-label promotion that we’d like to emphasize. Anecdotal evidence is not going to be sufficient to establish the safety or effectiveness of a new use of existing product in a regulatory context. But we think it has an important role to play in being hypothesis generating and then helping to push the conversation and the science towards the generation of better information. And of course it really is just a repository of information, so we don’t validate.

I think there are a couple potential uses of CURE that I’d like to share with you. It’s really an opportunity to share information on potential therapies for diseases which lack adequate approved treatments. And like I said we’re beginning with infectious diseases because that’s the space we work in but the opportunities for rare diseases, for oncology, I think are tremendous, and I look forward to ongoing conversations about how we can expand to those other spaces where there’s a high unmet need. Importantly, it allows for the exchange of opinions between global communities of experts. We’re often in our silos and in geographically limited situations.

So if I am seeing a patient with a particular disease, I often call the local expert, right? But for many of the diseases we’re talking about in particular the expert may not be local. They may be across the world somewhere, and in a network that I’m not connected to. But this is a way to engage with those individuals. Just as important as to identify potentially new and effective uses of existing drugs, it's also important to identify ineffective or harmful uses and the to, ideally, limit those uses.

I think David pointed it out very nicely, and Shira has also mentioned, there is so much potential benefit from using drugs in new ways for patients with high unmet needs, but there's also a great deal of harm that can happen. And by not collecting that information, we are continuing a system which fails to benefit patients to the greatest extent possible and fails to benefit science.

And so this is hopefully a way to help generate some of those signals. And it has important opportunities for disease and treatment surveillance which I think we’re only beginning to see. This is a really important collaboration between FDA and NIH, and NCATS specifically. I want to thank Dr. Chris Austin and Dr. Janet Woodcock and Amy Abernathy and Jacqueline Corrigan-Curay, and the other leadership at FDA and NCATS for their ongoing support of this project. This is something that we’ve been working on for several years and has been really an incredible initiative with the two agencies working together, so thank you. And I think the opportunities to, as Dr. Abernathy said, to get effective -- safe and effective treatments to patients faster using a platform of this kind are tremendous. So please download the app, submit your cases and discussions.

We have a booth outlined if you would like more information. And with that, we will take a short break. Please return by 3:37 p.m.

[laughter]
Thank you so much.

[applause]

Thank you so much. Let's go ahead and move to our late afternoon session. We'll begin with a session on the economics of off-patent repurposing. I think this is an issue that we have heard spattering's about throughout the day. You know, obviously, the ability to commercialize or the lack of opportunity and the potential need for innovative partners and mechanisms in the space is quite great. So I will hand it off to Andrew Lo from MIT who will be moderating this discussion. Thank you.

Andrew Lo:
So, I'd like to thank Chris Austin, Christine Colvis, NIH, NCATS, FDA, and the Reagan-Udall Foundation for organizing this meeting, inviting me to participate with such distinguished panelists. Really thrilled to be here talking about repurposing, particularly in this context of all of the things that have been going on in the space over the course of the last few years.

By way of background, I should provide the following disclaimer that I'm an economist by training and trade, not a biomedical expert by any means. And I'm not even a health care economist. I'm a financial economist. So my focus is on investments, financing, risk-reward tradeoffs, portfolio theory and so on. I got interested in health care really for personal reasons, friends and family dealing with various kinds of cancer, and it became very clear to me that there are all sorts of important economic issues that are at the heart of drug development and getting drugs to patients faster, better, and cheaper.

So this issue of repurposing for off-patent drugs is a particularly acute one that I first learned from talking with Vikas Sukhatme, who is at Beth Israel at the time and his wife Vigila [spelled phonetically] Sukhatme. You've heard from Vikas earlier today and you'll hear more tomorrow. And also from talking with Kevin Grimes at the Stanford SPARK Center that's been doing some amazing work on repurposing. I want to start with some motivation. The motivation I think you've already heard from a number of speakers including Dr. Fajgenbaum, a really remarkable story.

It's a motivation that I first learned from Vikas about the fact that there are generic drugs out there that have miraculous properties for diseases that most people would argue is hopeless, one of which is pancreatic cancer. Just recently a patient and also doctor named Stephen Beagleson came up with his own cocktail treatment for pancreatic cancer that put the disease in complete remission. Now, I don't know much about the underlying biology of the disease, but I've spoken to a number of pancreatic cancer specialists who tell me they feel more like morticians than doctors because there's nothing that can be done.

And here's an n-of-1 example, using generic drugs, that seems to have saved a patient's life. And this is more and more the case now with examples that we've seen. There are some really extraordinary results that are possible. And they are within our reach, which means that if we know we can cure a patient, and we don't, then that's just an absolute outrage. So this idea of repurposing has moral and ethical dimensions that we haven't really gotten into yet, but I hope we will tomorrow.

Let me tell you about the flip side it though. The flipside is that there's a danger if we don't take into account repurposing in more systematic ways. I see this more and more at MIT, as well as other universities, and the term "Biohacker" is something that I think you may have come across. There are a
number of individuals who are now wanting to do this at home, obviously nobody in this audience would be as foolhardy. You all understand the importance of conducting clinical trials and having proper supervision. But like it or not, there are desperate patients out there that are looking for therapies, and they will try this at home if we don’t help them in some manner. So the question is what do we do about it?

As a financial economist, I generally think of things in terms of risk and reward. I'd like to start by providing a little bit of context that will set the stage for what our two other panelists are going to be talking about. To do this, I'm going to take you out of the biomedical context and bring you into my domain, which is investments. And for those of you who have seen this, I apologize for the repeat, but I think it captures very succinctly how economists think about various issues including drug repurposing.

I'm going to give you an example of four financial assets. I'm not going to tell you what they are or over what time period they span. I'm simply going to show you what the investment return is for putting a dollar in each of these four investments over this unspecified time period. A dollar placed in the green asset turns into $2. Not a lot of return. But not a lot of risk. A dollar in the red asset becomes $5, after the unspecified time period. Much more return, but more risky. The blue line turns $1 into $8, way more profitable, but way more volatile. And the black line is somewhere in the middle of the pack.

So if you could have only one of the investments for your retirement, for your kids' college education fund, for your parent's or grandparent's 'life savings, which one of these four would you pick? Show of hands, how many people would pick the green line? Nobody? Okay. How about the -- well, one person. All right. Black line, anybody? Okay. Red line? No, no takers? One? Blue line? Okay, a few hedge fund managers.

[laughter]

Entrepreneurs. By far the most popular choice is the black line because it's got the best tradeoff between risk and reward, right? It's not the most profitable but also seems to have pretty steady returns. Well, what you all did is what most everybody has done in audiences that I've tried this out on including my MBA students. Let me tell you what you picked. First of all, the time period goes from 1990 to 2008. Quite a few years. The green line is U.S. Treasury bills, the safest asset in the world, at least for the next few weeks. We'll see what happens --

[laughter]

-- after budget talks. Not very rewarding, though. So if you put your money in T-bills in 2008 you would've earned pretty much nothing since then. But you wouldn't have lost anything. So for those who are concerned about risk, it's a good choice.

The red line that very few of you picked, most of you already have that. That's the S&P 500, the U.S. stock market. And if you put your money in that in 2008, congratulations, you would have done just fine. The blue line is the single pharmaceutical company Pfizer, largest pharmaceutical company in the world. Way more volatile though but also more rewarding and if you put your money in Pfizer, congratulations, you would have done even better. Now what about the black line, the most popular asset in this audience and in most? Black line is return to the Fairfield Century Fund, which is the feeder fund for the Bernie Madoff Ponzi scheme.
And that's why I had to stop it in 2008. It's human nature, like a moth to a flame, we're all attracted to high yielding/low risk assets. And in finance we have a term for that. The term has to do with measure called the Sharpe ratio. After Bill Sharpe, the Stanford finance professor who won a Nobel prize for some of these ideas. The Sharpe ratio is the expected return of an investment above the risk-free rate, about T-bills, divided by the risk or volatility. So you could think of it as the return per unit risk that you're taking. And we all want high sharp ratio investments. So Pfizer and S&P 500, they've got Sharpe ratios of around a third. The Madoff Ponzi scheme before it blew up had a Sharpe ratio, a factor of 10, higher, which is how he sucked in all of these unsuspecting investors.

So the idea behind the private sector perspective for repurposing is what's the Sharpe ratio? Is it a good deal from the perspective of investors, drug manufacturers, and the other stakeholders in the system? Now it turns out that from a scientific perspective, actually it's a very good deal, in the sense that repurposed drugs by definition have already gone through safety trials and so we know that they are generally going to be pretty safe. They may not have efficacy, but safety is a big deal.

And for those of you who are in the drug development business, and for those of you who are investing in drug development, you know that the most expensive, the most dangerous, the most difficult challenge to get to raise money is in pre-clinical and phase 1. The big money that pharma spends is in phase 3 because of the size of the trial but by the time of phase 3 a lot of the risk has been reduced, has been de-risked. So if we could actually de-risk our phase 1 trials, that's great, right?

So, from a repurposing perspective, the risk is actually pretty low. So why doesn't everybody do it? Well, it must mean because while the numerator is the problem, there's not enough return, and that's what I want to talk about briefly, and then turn it over to the panelists to describe to you their unique perspectives on how to deal with it. So, in terms of private sector challenges, there's a really interesting article that was published last year by a law professor named Erika Lietzan. And the title of the article is "Paper Promises for Drug Innovation," and it's all about repurposing of off-patent drugs.

It turns out that there is actually a mechanism, a well-developed legal mechanism for encouraging innovators to repurpose drugs. It's called the U.S. patent system. It turns out that even an off-patent drug, if it has a new indication, you can patent it. The problem is that patenting it doesn't necessarily mean you're going to be able to profit from it.

And let me give you a quick example. This article gives much more detail than I'm going to. I want to talk about Alzheimer's. That's a pretty a horrible disease. Affects 5 million patients in the United States. Does anybody know when the last drug was approved for Alzheimer's? Any guess? Last year? Two years ago?

Male Speaker:
In China, two weeks ago.

Andrew Lo:
Well, in China, maybe, we'll see. There's some controversy about that one. But 2003, in the United States. And the drug is Namenda. It doesn't even deal with the actual disease; it deals with some of the symptoms. So since 2003 that was the last time we had a drug in Alzheimer's. So suppose I have an Alzheimer's drug, right now, and suppose that this drug actually prevents the disease. And let's suppose
that I get it approved today, and let's suppose that, you know, we're going to sell it for $10,000 a year. How many people feel that is a good deal for society, a drug for Alzheimer's, $10,000 a year? You know what other drugs cost, cancer drugs? $100,000, $200,000? $10,000, okay?

Well, for any drug company that would be a huge home run. Five million patients, $10,000, that's a lot of money and investors would be all over this. Suppose the drug is 50 milligrams of aspirin taken every other day? That's a possibility. How many of you here are doctors that prescribe for patients? Okay, keep your hands up. Of those who are prescribing for patients, how many of you would be willing to prescribe a $10,000 drug for Alzheimer's and avoid giving them an off-label use for baby aspirin, how many of you would be willing to do that?

Yeah, that's the problem. We could have a drug today that treats 5 million patients, that Medicare and Medicaid spent $200 million last year -- $200 billion last year treating the symptoms of this disease. We could have a cure for it right now. But there's no money in it because doctors won't prescribe the branded version. The FDA won't necessarily distinguish between therapeutic equivalence in different cases, they'll just describe as equivalent. They won't distinguish between branded versus off label. And the system, itself, is geared towards basically not allowing the economic incentives to be there. Looks through the entire set of stakeholders, the incentives, the economic incentives are simply not there to be able to allow the private sector to take some of these amazing therapies and bring them to market.

And the article by Professor Lietzan describes some of the legal challenges for this. And without pointing fingers it's not any one person's fault. It's the system that we constructed that makes it very, very difficult for a private sector solutions to work. By the way, this is not just something that affects repurposing. I can give an example of an off-patent drug that saves lives, for the particular indication and there's a shortage of it right now today. I'm talking about Vincristine. Vincristine is a drug that saves lives for children with acute lymphoblastic leukemia and Teva pharmaceuticals decided to stop producing it just recently because it just didn't make economic sense. And so now there's a shortage. Pfizer is trying to ramp up production. But I suspect there will be patients that will be affected by this.

So the economics are a serious issue that we need to grapple with and complexities. So what do we do about it? Well, I think that's why we're here today, and the panelists that we have are are tremendously well qualified to talk about some of their solutions. So I listed a few here. We've already heard from some about the things that could be done.

But what I'd like to do now is to turn it over to the panelists and then have them describe to us some of their unique perspectives. So first we'll hear from Sung Hee Choe from Milken Institute, [unintelligible] and then we're going to hear from Barbara Handelin from Audacity Therapeutics. So please join me in welcoming Sung Choe.

[applause]

Sung Choe:
It's always reassuring to come up here and make a presentation after you've kind of failed the basic test that Andrew Lo presented with the four assets. I chose the black line. The Bernie Madoff line. And it really questions your confidence and your ability to provide some expertise on this topic. And you'll notice, I stopped volunteering as you continued to ask questions because I felt like I was going to be tricked. So I'm going to echo what Claire from Cures Within Reach mentioned in her remarks, which is that, you know, I think one of the things that you experience when you also present at the end of the
day is that all of the points that you were planning to make have already been made.

And so a lot of the remarks that I had prepared at least as of this morning have evolved, and I think the opportunity for me now is to really synthesize what we've heard throughout the day and really punctuate the points that I think are really important. So what we have established today is that there is a lot of promising science that is not being pursued or advanced for reasons that don't relate to their scientific basis or for clinical reasons. And they are not being pursued for business and commercial reasons.

The current pharmaceutical model is not set up to accommodate the development of drugs for which commercial prospects are low. So while we focused on research and regulatory challenges to drug repurposing, for much of the day, I think we're going to talk about the economic challenges and thank you Andrew for presenting the risk/reward trade off. And when we think about these solutions to the economic challenges we really have to think about the drivers of economic return, which is fairly simple. It's the cost of the trials to develop the drugs, relative to the revenue potential of that drug. And so, indeed, while costs associated with developing a repurposed drug are lower they are still high, and I think that we heard from somebody this morning that the costs are still in the range of $300 million and certainly it carries risk as well.

And then on the revenue side, when we think about reimbursement, it is a really difficult conversation for a developer to have with a payer that they deserve a higher price for their drug when there is a perception of a cheaper generic drug available on the market. And so with the high cost of doing trials, inadequate -- potential for inadequate reimbursement, the economic potential of repurposed drugs are lower, and therefore we don't see the investments that we would like to see in this space.

So as we kind of think about solutions, I mean I think we have to think about how to influence the cost and the revenue levers that go into the calculation of a return on investment for an investor. But as we also go into tomorrow and think about what near-term actions are that NCATS could take as of Monday, is one, how can we support and enable the non-profit actors that are really doing the important work around repurposing today, and I think Scott Weir from the University of Kansas really articulated those needs very well, and it's not always about funding. It's about access to the expertise, and its access to the data that have been generated by the innovative companies.

The second is I think we need to expand our view of what stakeholders should be involved in this conversation. Specifically, where are the employers, where are the payers, where are the health systems? And I'd encourage us -- and I think, Vikas, you had a really great framework for what the stakeholder universe could be, but I would also say where are the impact investors that think about, as part of their return expectations, what's the social benefit to their investments? And then the third thing I would encourage us to think about going into tomorrow is how can we leverage the work that is going on in other spaces that are also tackling this issue of lack of commercial incentive. And so specifically there I'd call out the work around AMR as well as the work around pediatric oncology. So, let's try to create synergies with the thinking that's happening there and, you know, use that consolidated expertise to really think about what new models could go forward. Thank you.

[applause]

Barbara Handelin:
Do you want your notes back?
Sung Choe:
Oh, thanks.

Barbara Handelin:
Okay. Hi, I'm Barbara Handelin. When I left my first job, which was at Integrated Genetics, which later became Gemzyme Genetics, people started filing into my office when I announced that I was going to be moving out of the area and taking a different position, and saying, "Well, you can't leave." And I said, "Yeah, you know, the walls aren't going to fall down or anything." They said, "No, no, you can't leave because you're the only one who will say the things that need to be said that nobody wants to say."

[laughter]

And that has turned out to be the, kind of, one of the defining characteristics of my career. And so, I'm going to take you up, Dr. Austen [spelled phonetically] on perhaps saying some things today that feed directly off of my fellow panelists here. And from things that we have heard, I think repeatedly today, which is there just isn't enough money. And that's actually not true. So, let me take you through this. Let's see. There we go.

So, I spent my whole career on the innovation side of science and technology, all of it, up until the last five years. And through the -- and so did the cofounders of our current enterprise, which is a public benefit corporation called Audacity Therapeutics. The basis of Audacity, which is an audacious idea, I guess, that we're experimenting with, is that we maybe already have the vast majority of the innovation that we need, and that's why we're all here in this room today. Maybe we've created a lot of the value that we need. We just need to be smarter in our industry, like other industries, at maximizing the value out of inventions or resources that we have already developed to become more efficient, to become more productive, using what we've already put up on the table.

And so, we said, well, okay, that's great, I guess we're getting out of the science innovation part and we're -- that means that we're going to need to innovate on the business model. And you don't have a business in our industry without investment. So, we then said, well, I guess that means that we need a new investment model. And if we're going to take advantage of what has already been developed with this concept of repurposing, and I actually like to think about revisiting. We heard earlier today from other speakers about going back into -- people going back into the literature, people going back into looking across the panoply of compense that we already have to revisit, to look at those old studies that end of one, and of 10, and of 20 where a study was done by a creative, maybe desperate clinician, trying to treat some very hard to treat patients. And that study, you know, got published, you know, 20 years ago when, you know, nothing really came of it, but they're revisiting our willingness to use old-fashioned intelligence and our ability to reread and reconsider now with today's lens, I think is a great source of opportunities. So revisiting, reconsidering, reformulating is a way that we may be able to create new intellectual property. A little bit of innovation to give us some of these protections that we need in order to generate a protected pathway to patients. And repurposing or repositioning.

So, I -- since we're here to talk about the repurposing of off-patent compounds in particular, I'm going to focus on that. So, we have said at Audacity, well, what if the goal is really, as Dr. Austen sat out this morning, what if the goal really is to make as many medicines as possible for as many truly unmet medical needs, and to deliver them to patients -- actually, to our system, at affordable pricing. And I don't mean affordable to individuals. We mean affordable to the system. So, if that's your goal then, you
know, come on, we’re scientists and engineers. You design to what the objectives -- what the actual objectives are. So, if that is really your goal, then what is the business model and the financing model that you would set up? And what would be the characteristics of companies of an industry sector that had that as its mission? As its sole or primary mission? So, just hang in here with me.

Well, you would be incentivized to reuse what we already have. You would be incentivized to maximize the value of compense that we already have and especially as we've just said, especially to use those compounds that are known to be safe. Because let's face it, making drugs is really, really hard. It's always really, really hard. And because we don't actually know that much, so we have two uses -- or two actions, you know, those that we know about and those that we don't know about. So, let's make use of those things that have at least gotten past, you know, the most egregious hurdle, which is safety.

And if you want to deliver as many drugs as possible at reasonable pricing, then you better be sure that you have a very efficient development, manufacturing, and distribution system. We could probably learn from some other industries. Our industry has had the luxury of being able to drive our own prices to a customer-base that actually doesn't get to choose. We’re not choosy mothers choosing Jiff. We’re patients who need the product. So, we've been in an industry where we got to say, look, we're delivering like the most important products ever for patients, and so we don't need to be super lean about how we get there because the value to society of good medicine is always so, so, so high.

So, we say, okay, but if we want to do that more often, and across a broader spectrum of patients, we probably ought to get to be a lot more lean and mean about it. All on the way.

And so now, instead of value being generated by, you know, are we really treating people? Which is how we're supposed to be valuing medicine, I don't know that we are, but if -- but now affordability would also be incentivized because we want to, again, make as many products as we can. And we can't afford million dollar -- we can't afford another 6,500, you know, treatments at $100,000 a year per patient. I mean, the system can't afford it. So, we've got to engineer our way to being able to deliver much more affordable.

And so, that means we would also say, well look, we're not going to bother ourselves with making incremental improvements, you know, minor changes in color of the pill or maybe even, you know, how many times you have to take it per week or per day. We’re really going to focus on meeting the things that have not been met in any way or woefully inadequately. And now our decisions about what we're going to work on get driven primarily by are we going to impact patient's lives?

And in this way, I think what I've described starts to look like -- and I just thought of this as I made this slide last night, but it starts to look a little bit more like a public utility, a public benefit. So, if we want to do this, we need a different industry, and we need a different financing mechanism. And so, that is what we are pursuing in this experiment that we call Audacity. And it has to start with a different investment thesis. It's true that we're saying we're going to start with things that have been greatly de-risked. So, that's good.

But we also need to say we need investors to help us to build this new industry. And I like to think of us at the threshold of a new industry, just as the biotech industry was in the late 70s. A bunch of really smart people started to say, gosh, you know, we could redefine disease, we've genetics, we've got molecular biology, you know, this could be a whole new way to approach medicine, medical problems. And investors, who had been investing in other things that looked very similar, very high risk, really high
reward if you're successful at it, venture capital came along and said, you know what, we could probably
make a nickel investing in life sciences, let's do it. We'll have this model where we make really huge
returns on some things and not much on others. And that is how we have built a whole new industry,
which has produced some really, really important innovation.

But now, I think what we need is a new class of investors and they're out there. This is a class of
investors who can be found in the trillion-dollars’ worth of private wealth that is about to change hands
generation to generation, just here in America. Wealth that is looking to do something of value in
addition to creating more wealth. And this is -- we would have called impact investment. I’m all about
making up new terms for things that suit my purpose, so I more inclined to call it compassionate
investors, social-medical impact investors, who are really putting medical value here. And if I get my
money back, and I make bond-like returns, or maybe -- hopefully more than Treasury bonds.

[laughter]

But if I get my money back, and I make a little bit of money, that's okay because the value to me and
everybody else in society is so high if we're successful at bringing a lot more of these products out to
patients who really need them, that's for me. And it's going to require that scale of capital, isn't it? So,
we're going to have to have a business model that work at scale.

So, what I -- let me, I see that we're probably running out of time. Let me just say that we've got a
tremendous opportunity. We need to redefine how we do manufacturing and distribution. There are
companies that are working on new kinds of manufacturing that can be done just in time, highly
distributed, so-called continuous cycle chemical synthesis. These are things we need to invest in and we
also need to invest in some much more direct-to-patients so that ways of distributing and educating
patients and physicians about our products because we can't spend 50 to 70 cents on every dollar on
sales and marketing anymore. We won't make it if we have to continue to do that.

So, Audacity, as I said, is being stood up. It's a B corporation. We're also standing up a fund because we
will need scale investment in such a new industry space. I would be happy to talk with anybody about
that. The investors in this fund would be these kinds of making program-related investments with their
foundations, other kinds of similar vehicles as social impact investors in the fund looking for those kinds
of returns. So, the questions is where are we going to find those investors? Because we really do have
an opportunity to start a whole new industry here.

[applause]

Andrew Lo:
In the interest of time, let's open it up for questions or comments from the audience. Yes.

Male Speaker:
I've got a question. So, even though I voted for the blue line, I thought could we explore the space under
the green line? That is, you know, a lot of the discussion today from the ROI trap conversation this
morning until now, you know, much of the conversation has been, I think, based on the idea that there
needs to be a return model that's viable from soup to nuts, where ever you start at the soup. But in fact,
there's a number of groups that have zero return expectations, so it could be the government, could be
a foundation. Are there proactive ways we can say that it's just not convenient non-diluting funding you
can get along the way, but can we think about building that in structurally into the entire process so that
we have blended ROI models where ultimately, for example, a neglected disease, or a rare disease you could come out on the backend at a cost plus model, I'd say, because that enterprise did not have to integrate all the development costs coming up there.

Andrew Lo:
So, I think what you're talking about is already starting to happen but maybe there's a way to super charge that. For example, philanthropist have played a role for many, many years and they are not expecting any return. So, the Morningside Center at Emory that we talked about earlier, Cures Within Reach, thank god for all these organizations that provide basically all of the funding without any expectation for return. The question is whether there is a profitable way for us to combine by -- I mean, financially profitable, but is there a successful way to combine those investors that don't expect a return with those that do.

Male Speaker:
You know, indeed, and a pre-structured one so it isn't a surprise but all the players, the zero return and the modest return, have already agreed --

Andrew Lo:
Right.

Male Speaker:
-- on a path from the very beginning.

Barbara Handelin:
Yeah.

Andrew Lo:
Yeah.

Barbara Handelin:
And I think that, I mean, Andrew is the one who published on having a stratified bond kind of model. There are ways to incorporate different investors who are looking from anywhere from zero return, philanthropist or the government, who can sort of serve as a -- even as a guarantor to investors who would invest for this kind of return and some who would invest for this kind of return. So, integrating multiple sources of capital to enable more capital to come into this space. But I think we do have to -- from my perspective, I'm not talking about dismantling our current system, just by the way, not that much of a revolutionary, even though I did go to Berkeley.

[laughter]

But because we need it, but I think we need a parallel path that is based on a different set of expectations.

Andrew Lo:
Over there.

Female Speaker:
You're running [inaudible], so you can have one more question now and then if you guys could come in
Megan Golden:
Hi, I'm Megan Golden from Mission Cure, and that's actually what we're doing is combining the different types of capital. I think at the root of a lot of the incentive problems that people have been talking about all day today is that nobody in the current system is incentivized to improve patient outcomes. There's no financial incentive to anybody to do that, and that's why these rare disease organizations that are really driven by the passion of the individuals are the ones pushing things ahead really quickly. However, there's a lot of movement in other areas to really incentivize outcomes. I've been involved in something called Pay for Success, or social impact bonds. And Congress -- there's a $100 million that Congress appropriated to encourage that in health and other areas. And there's some progress around gene therapy and thinking about that. Nobody yet, besides my colleagues and I, some of them are here, are thinking about applying that outcome-based, patient-outcome funding to developing therapies, but we really think it's doable, and hope that we can work with some of the people here to do that.

Andrew Lo:
So there's a -- since we're out of time I can't get into it, but there is a proposal that Vicosoondi [spelled phonetically] and I came up with a few years ago called The Last Resort Clinic where it would actually provide a kind of reward-based system for NO1 outcomes. But you're absolutely right, that is really what is necessary and hopefully will be developed over the next few years. Thank you.

[applause]

Female Speaker:
I'm sorry to cut the discussion short. I know it's such an interesting topic and needed discussion. So, let me just tell you all that we are going to have a networking and meet and greet from 5:30 p.m. to 6:30 p.m. basically just after this, after our last session in the Eisenhower Room. So that will be an opportunity hopefully for everyone to continue these engaging discussions.

So, our last session is on the use of payment data to potentially identify repurposing candidates. So, I'd like to invite the speakers for that to come up. We have Shari Ling, who's the deputy chief medical officer of CMS, Ed Pezalla, who is a subject matter expert from Aetna, and Francesca Cunningham, who's the director for Center for Medication Safety at the Department of Veterans Affairs.

And this panel is a little bit different. It's an unmoderated session, so I will hand it off to each of you to give your talks, I guess, starting with Shari.

Shari Ling:
Okay.

Female Speaker:
Do you guys want to present from here, or you don't care?

Female Speaker:
I don't have slides.

Female Speaker:
I have slides.
Female Speaker:
You do?

Female Speaker:
I have slides.

Female Speaker:
Okay. All right.

Shari Ling:
Okay, so good afternoon and thank you for the kind invitation to be part of this panel. So, I just -- I have no slides. I've actually shared some slides with Chris [spelled phonetically] and Christine [spelled phonetically] and Chris. But I just want to get a chance to actually speak through some of our thinking and as Chris mentioned at the start of the day, these are my own opinions, my own perspective, but I think hoping that I can really illustrate how we approach not just the data, but the actual context that the data comes from and represents.

So, just by way of background. So, CMS remains the largest payer of healthcare services, including for drugs of whatever ideology globally, and we touch upon the lives of one in every three Americans. So, our charge is to provide for care and services for our beneficiaries, but the context of payment has really been changing over the last few years, so that this is not just paying for volume, or just that a treatment or service is delivered, that we're actually increasingly focusing on the outcomes. And ideally focusing on the outcomes that matter to the people who we serve.

So, this becomes exceedingly necessary, to focus on outcomes. And given the context of the complexity, the population of our beneficiaries, that complexity is actually increasing over time. And, you know, if you were to think about any single disease that you may be creating and repurposing drugs to manage, hopefully cure. And the Medicare population, it's probably that one disease is probably represented by a very small percentage of the Medicare population. So as an example, if you have -- Dr. Lowe [spelled phonetically] was speaking of Alzheimer's disease, if you're interested in creating solutions for Alzheimer's disease, the population in fee-for-service Medicare that has just Alzheimer's disease, is probably less than 5 percent.

What is prevalent at greater than 55 percent, is the number or the proportion of the beneficiary population that has five or more other conditions. So, the consideration of outcomes, and meaningful outcomes, for the people who we're serving, not just for the disease, becomes even more critical. So that is also a trend that we have seen in the Medicaid population. Many of you may be interested in rare diseases and pediatric populations but remember that Medicaid that may be a primary payer for pediatrics conditions, not -- it doesn't just only service children, but also people with disabilities who also have financial constraints.

So, we have a growing percentage of the beneficiary population that actually is eligible for both Medicare and Medicaid. And then, you know, Medicare is the primary payer, but what is being paid for? And just to put it into context, you know, the numbers that are being discussed as far as what the cost is, $10,000 per year, let's say $50,000 per year, you would think that that's a fairly reasonable cost. Right? That would be about the estimated cost for healthcare service delivery or in-home help, right, and that would be reasonable. What would be staggering, though, is to think about the population and
the population needs for something like Alzheimer's disease where an individual is likely paying $8,000 a month, right. And what does that cost? That is the cost of not developing effective therapeutic or finding additional solutions. And that is the cost of your average assisted living facility, per month. Nursing homes ratchet it up, and that's for a shared room. So, I think the business case is to find real solutions for the population of beneficiaries and for patients but really this is challenging for us, and by way of context, the expectations of the data and the evidence, we require evidence that FDA requires, but also evidence that a specific treatment or service actually works and the beneficiary population in which its going to be applied. So, with Medicare, as an example, if we're thinking about treating Alzheimer's disease, then there may be a tradeoff between managing Alzheimer's disease effectively that may be limited by congestive heart failure, or diabetes, or any of the other conditions.

Now, how we actually understand the context actually comes from the data. So, we have many, many data sources that are becoming increasingly available for public use and if you wanted to get a good handle on the scope of the problem, let's say by way of an indirect measure of a disease by way of part D Medicare claims, so just to -- for those of you who are not accustomed to thinking in terms of, you know, A, B, C, D. So, A is the payer category that we provide payment for hospitals, skilled nursing facilities; B, for physician services; C is payment by way of healthcare plans, such as Medicare Advantage; D is for drugs, and each of those benefit categories have data, administrative data, that can be used to ascertain the scope of a problem.

However, because they are administrative claims, there's a lot of information that is not on the claim. So, it doesn't provide you with a complete or deep picture but does give you some clues. Optimally, if you wanted to know what disease conditions pair together, so if might be a two-for in a given treatment or drug, that could be -- you could understand the potential there by way of some of the claims.

So, the data sources that we have include parts A, B, and C from Medicare. But we also know have data from Medicaid, which, you know, as of 2015, are becoming publicly available, too. And there are three different ways one can acquire the data. One is -- and if you actually Google search ResDAC, R-E-S-D-A-C, is probably the one vehicle that you can learn about how to acquire the date, what purposes the data can be used, and what the conditions are that one would have to agree to in order to use the data.

The three vehicles are a virtual research data center, which is run by the ResDAC, which gives you -- one could purchase a seat or two, and you can actually go in and conduct some preliminary data analyses, get a sense of what it is you really want data on, and that can be a percent sampling of the entire beneficiary population, whether it's Medicare or Medicaid.

One could also make a data use request and have that data shipped to you. But, you know, you could save time by understanding what exactly what data you want and for what purpose would you like to use those data. And the third is something called Blue Button 2.0, which is a vehicle that beneficiaries can now agree to who they share their data with, each beneficiary, and what are the conditions that that data sharing can transpire.

We also have a CMS Innovators' Guide, so that you can understand not only the data, but all of the other vehicles that can be utilized to demystify the process and the evidentiary requirements for each of the purposes and programs. It is circa 2015, so it is being revised currently. We actually can't keep up with the pace of what it is that you need to know, so you know, if there's something that you need to know that is not addressed in the Innovators' Guide that is -- that would be really helpful feedback for us.
We also have the ability to help support enrichment of clinical trials by way of the Clinical Trials Policy. So, CMS can pay for what is reasonable and necessary in the care and keeping of Medicare beneficiaries. So routine care and services as long as a clinical trial is approved, and documented, there’s a vehicle to provide that type of payment as well as a IDE, or investigational device exemption, and also coverage with evidence development. These are all different vehicles that CMS can help support -- the routine care and services as important questions are being answered.

Now, I will also say that, you know, that it's often asked of us so who decides how much evidence is sufficient, right? And for Medicare, that is based on the preponderance of evidence that applies to the Medicare population. And I will say that probably the most common reason a treatment of service is -- a national coverage determination is actually deemed non-coverage, as opposed to coverage by way of local contractor discretion, or coverage by way of evidence development, is because the evidence is insufficient as it applies to the Medicare population. And if you think about who it is that actually enriches clinical trials for the first purpose for FDA, which is safety and efficacy, the Medicare population is much more complex. And for Medicaid, it is a question of is it not only necessary, but is this routine care and services, is it really, truly reasonable, in the best interest of each and every state. So, there are processes there for both, but they're all -- and we are able to track and utilize the data for purposes of scope of uptake, including prescribing practices across the country.

So, with that, I will stop and turn it over to my colleagues here who actually have slides.

[applause]

Edmund Pezalla:
Great. Good afternoon. Thank you for the opportunity to be here and speak about this. I'm Ed Pezalla. I'm a consultant in payer strategy and market access, and I work principally for pharmaceutical and biotech firms. For many years I've worked for managed care organizations, retiring from Aetna in 2016 as vice president for pharmaceutical policy and strategy.

So, what role do payers play in anything, really, okay? So, we don't treat patients, although we get this all the time. It's like, yeah, how do you treat patients -- no, we don't treat patients. We pay for stuff. We don't conduct clinical trials, you know, but what do we really do? We do transactions, lots and lots of them. You know, you can kind of think of it as this is basically a big Mastercard operation for health care, right. I mean, this is really what most health plans do. When you look at it from, you know, say a Blue Cross Blue Shield, large regional plan, for a national plan, you know, we're not directly caring for patients. Yes, we have impact on direct care of patients because we pay for some things and not other things, and we have rules. But we don't actually do all of that actual care of patients. But what really do is that we pay bills.

And so, we know who got what drug, what diagnostic codes are associated with that patient, what procedures they've had when they were in the hospital, when they were in the doctor's office, and what did all of that actually cost. Now remember, this is the cost of direct cost. This is the cost of health care, not the cost to the patient, not the cost generally to society for something.

So, we've spoken a couple of times today about Alzheimer's Disease. Alzheimer's Disease has some pretty big direct costs. Alzheimer's Disease has enormous societal and individual patient costs, and if we can treat it, then that would be absolutely amazing in terms of the impact on the U.S. economy.
So. But how can payers help if we don't actually treat patients, right? Well, you know, we do have data. Now, as mentioned a couple of times today, the data's limited. We don't know a whole lot about exactly what happened to the patient after we pay for something, right, so we don't know, you know, are they walking better after their hip replacement? You know, did their pain get better after they took some morphine sulphate? You know, what happened? We don't know all of that, but we can hypothesize about some of it. You know, if they take a medication and their taking it for a little while, and they stop and taking something else, well, we can make some assumptions. They stopped for a reason, you know. It didn't work, they couldn't tolerate the side effects, somebody told them something else was better, but we got an idea that they moved on, right.

So, there's some things we can do, and we can help to develop some hypothesizes or perhaps test a few assumptions, but certainly we can help to estimate the size of particular populations, you know. How many people are using a drug currently? And if we can associate that with some other data, like other procedure codes, and other things, diagnostic codes they might have. You know, then we can estimate the size of a population, and we can also estimate their cost. So, there's some value in all of this, but we have to be sure that we understand that we can't really tell how patients are doing clinically. That is something that we would just guess at.

However, we're good at reimbursing, right. You know, there's formularies, preferred drug lists, there's pharmacy claims, there's all sorts of other things that we know, where that money is going and who it's going to. And so perhaps we can help by solving one of the other problems that we've talked about today, which is how do people get paid for ideas that are not protected in some way, legally. Right? So, let's propose a solution to that.

We don't really know why a generic medication is being used. It's a generic medicine, we don't ask questions, we just pay for it. It's a few dollars, right, here and there. And so generally we don't really know. But we do know who's getting the drug, we know how much of it is being given out. So, we could estimate the number of times a patient is getting the drug for a certain particular indication. Now, we don't know for certain, you know, because we don't know. There are actually codes in the code lines in NCPDP version 2, which is the software that runs behind every retail pharmacy in the country, and how we all pay claims. And there's 10 places in there for each script to have a diagnostic code, but no one fills them out. That's because the pharmacist has no idea what the diagnostic code is supposed to be. He doesn't get it on the prescription, she doesn't -- she's not able to see what the doctor said, and so we don't really have accurate diagnostic codes there.

But we do have other diagnostic codes. We know when a doctor writes a prescription, they've usually written a code somewhere to justify that prescription, you know. So even if it's incidental to the reason for the visit, it'll be on the second or third line in the visit somewhere, or the second line in the hospitalization. So, we'll have some idea of that.

Well, what can we do with that? Well, we what we could do with that is that we could estimate the size of the royalty that somebody's paid for their idea. So, in this case, we could totally uncouple the idea of manufacturing a pharmaceutical and selling it from being reimbursed for its use. So, if we establish, for example, a fund that you use a word that I won't say out, but it starts with a t and with an x, on each generic prescription. Then we can add to that fund, and then we pay people for the use of their idea out of the fund by estimating how many patients are receiving the drug because of that particular indication that they received.
Clearly, there's an enormous number of huge guardrails we're going to need to put into place for this sort of thing. What's a trivial use that we're not going to pay for or worry about at all, right? Because there'll be plenty of those. What are things that can't be reimbursed by insurance? What are things that can't be reimbursed by CMS? Well, that's a good start. We could actually say, well, at least everything has to meet part D rules, so we're not paying for cosmesis, and we're not paying for erectile dysfunction, and there's a number of other things we're not paying for, but that's okay. We're not looking for innovation in those areas. We're looking for innovation something else. Right?

So, my suggestion here is that we could take advantage of the opportunity to have information from part D, information from commercial plans, and use that to get an estimate when a new purpose comes up for a drug of how much of that drug is being used for that purpose. And some tiny fraction of a penny for each time that drug is used can go into a fund to help reimburse people for the idea. So, you could theoretically create a pharmaceutical company that never touches a pharmaceutical because you don't have to manufacture it because somebody else is making it, right, but we don't want to disadvantage them.

So, I'll leave you with those ideas that there's plenty of data. The best use of the data is probably to find out what things cost and how many people have something. There's probably some other things you can do with that interesting data, but more importantly, we can then use the data to get to the idea of how we reimburse appropriately for ideas as opposed to just reimbursing for a thing. Thanks.

[applause]

Francesca Cunningham:
I'm the last speaker, so I'm happy I still see a room full of people. So, thank you for inviting me. And my name is Fran Cunningham. I'm going to take a slightly different approach on presenting our data.

First, let me do full disclosure. In my position, I'm responsible for overseeing drug safety surveillance and effectiveness inside of VA for our operational side. So, what does that mean? That means that we make decisions with the data in relatively close to real time, so that our decisions can be made for our patients. And so, everything we do from the VA side, as a comprehensive healthcare system, we do for the patient. And so, I'm very patient-focused, especially for our veterans, those that bore the battle. So, everything I talk about, I don't really want to say VA perspective, right, because it's my perspective from the VA. Full disclosure there on that side, but I will talk a little bit about our healthcare system so that you can see the data that we have, and pretty much how you can utilize these type of data inside of a given system, and ultimately how it can be used. At the end of the presentation, I'll talk about how this - - the same concept can be used for repurposing.

So that being said, for those of you that don't know about the VA system, I know you know about the VA, you see it on the news all the time, anybody watches World News Tonight sees something about the VA. But I'm going to give you an overview of the system in a little bit more detail for those of you that may not be aware. It is the largest integrated healthcare system in the United States, okay. When you look at the total number of patients, from a healthcare system, it's small. You know, it's not like the larger healthcare -- the largest payors, so to speak. It's a smaller system. We are a comprehensive healthcare system. What does that mean? That means that our providers work for the VA, okay, so they are employees of the VA. And also, our prescription benefit is inside the VA. So, is that a good thing? Yeah, it is because it allows our systems to constantly speak to one another, but it allows us to talk to
one another, too. It's not just computers talking. And so, even though we're a national system, we're very interactive as a national system -- both from a technological standpoint but also from a personal standpoint.

We have over 9 million enrollees, 6 million use the VA healthcare system consistently, and over 5 million get their prescriptions, meaning they're sick enough to have prescriptions. What about our patient population? What makes it so unique? They have multiple comorbid conditions. They choose to use this system. Those patients that come into this system and use it frequently choose to use the VA system. They're very sick patients, and we have set up good information systems, so that's another thing to think about when you're looking at our system.

So, why is a VA system good for safety surveillance, effectiveness surveillance? Of course, that's my plug as well as [unintelligible]. Well, because we have high medication use. I said we had multiple comorbid condition patients, multiple -- very high medication use. We're a generic-based system. So, we use generic drugs -- not that we don't use new drugs that come into the system, we do. But when you look at our drugs over time, you're going to see there's a lot of generic drug use.

Small turnover in beneficiaries. So, I talked about it being a smaller healthcare system. When a patient comes in the system, they stay. So, from a longitudinal standpoint, if you're interested in studying something longitudinally, it's a very good system in which to do that, okay, just because our patients come and they stay. Not that they can't use other systems, but we always have contact with them, which makes that very good for evaluations.

We have an integrated database and corporate data warehouse. So, we have all the data you could think of, and we love it. I love data. I'm a big geek. I live inside the data. You ask me about a drug, I'll tell you. I love it. And so, we're able to utilize that database system for a lot of things, for surveillance, of course. We monitor our outcomes for our patients, we look at the safety and effectiveness of certain drugs as we place them on the formulary, or as they come into the system. Or maybe something as simple as a subject matter expert may say, hey, can you give me all of the antipsychotics and let me look at -- show me all the ones that are used on-label and all the ones that are on off-label. I'm like, okay, and they're like, hey, that's such a good project. We have a lot of trainees. We have postdocs, we have residents, we have pharmacy residents. It became a project, something that we look at every year now. So, for our antipsychotics we can look at utilization across time, and we can begin to see certain disease states in which those medications are used that were underused beforehand, say for antiepileptics eight or nine years ago. Talking to one of my colleagues, I was like, this deperemede [spelled phonetically] is just like skyrocketed in use. And we went and we looked, and it's used for migraines, so.

Other things. So, we can look at that data very easily and then we can conduct studies, observational studies, and also utilize that data for clinical trials. We have an awesome research program. VA has its own internal research program. We have the clinical trials program through the cooperative studies. We also have health services research where a lot of pharmacoepidemiologic studies are conducted and other health services research. So, it ends up being an optimal system for real world evidence, point of care studies, and pragmatic clinical trials.

So, I am very VA focused. So, this is a cool system. It's a good system.

So, repurposing of off-patent drugs, an ideal solution. Well of course I had to talk about the VA. So why is this a good system to look at these agents? Well because we do have a clinical trial system inside of
our -- inside VA. So, we already have imbedded in there the possibility to develop these trials. Our patient populations receive many generic agents for multiple conditions, as I stated. The data are available, and we have accomplished researchers in place that can conduct studies, and do the analysis, and team up with whomever. Very important is that we'll allow our veterans to participate in clinical trials more readily. So, as we can conduct these types of trials in our healthcare system, it'll give our veterans a chance to participate in these type of trials. We have excellent collaboration between our Office of Research and Operations and Office of Research and Pharmacy. That's important because as we see things and have questions, we can ask our researchers to do certain things, and circle the other way, as clinical trials are complete, or even as surveillance is completed, we can begin to build guidance from that. And we do, we do. That's the advantage of having the type of system that we do have.

So, what are some of the barriers, limitations, and possible solutions? I'm going to skip the first two because everyone's talked about that. I'm going to talk a little bit more about something that may be internal to a healthcare system that you may not think about. They're policies that exist inside of healthcare systems, so they may be an off-label use, drug use policy that may limit the utilization of drugs where the evidence isn't available, which was just said earlier. So, you may want to do certain projects using these data in certain patient populations, or in certain systems, but there may not be enough use.

And so how do you get around that? Well, you can't, but you can do and our system -- what we did is we developed something called pharmaceutical use outside of approved indication, a guidance on off-label prescribing. And so, what it does is it takes us through -- what's the best off-label prescribing? Well, it's that which has evidence, right? So, we can go with the evidence-based medicine, which we are evidence-based medicine system. But we take it all the way down to where the level of evidence is not as great. And who do we have in our system? We have some of the greatest providers, physicians. They're just the -- they're doing the work. I have to give the shameless plug because every time you see things on TV it looks negative and it's not. We have a lot of great providers. And so, what we try to do is we try to give them guidance on what they do, and we try to make sure that pharmacy is available to support them, so it's not working against them. So, with the Pharmacy and Therapeutics Committee, we try to say if there is some semblance of mechanism of action, you know how a drug works, support this provider, track the safety.

More recently, my department has developed a way to look at real time data collection for a medication, so as the medication's being given, we are data collection sheet, filling out the information, taking the data back, doing real time analysis, feeding that back to our subject matter experts. Guys, that's a whole another data set of structured data that can be used ultimately for analysis in the future. So, thinking outside of the box, not just that which can be extracted, but there may be medication you see evaluations that are going on in different healthcare systems. Ask for that data, especially for drugs that are off patent. So, when you look at off-label use, we try to do a little bit more. But think about that, sometimes it's not always possible in other healthcare systems.

Industry influences on potential treatment. It's really an indirect industry influence on potential treatment. Well, why the heck is that a barrier? What if you have an old drug, off-patent, really doing good. You have a lot of patients now enrolled in a clinical trial, or you're tracking it from a medication use evaluation, then here comes a new drug on the market. Don't know if it works better than the other drug that you're looking at, but all of a sudden everybody's going to use the new drug. And what happens to the trials? Or what happens to the patients that were using the older drug that may be effective? What do you do then? Well, you talk to the providers, and we try to tell them you can still use
that drug. It may be an intravenous drug. It may not be as easy to use, but we still need to look at it to see what will ultimately be come of that drug.

So, what are some potential solutions? Utilizing systems. I gave you an example of a system, ours. You could utilize other systems to conduct these trials. Increased funding, public-private -- private-public partnerships, in our instance, we would be the public systems, so we would need a little bit more support from the private system to conduct more trials. Involving payers all the way through the process. That’s important. No matter who the payer is, that’s going to be important at every level.

And then, I think just leaving you with the summary. Patients, I know for us our veterans are most important. So, at the end of the day when we’re thinking about this, even from our side, our patient is our most important. So, delaying the removal of barriers, or not coming up with solutions in an optimal time period, impedes potential treatment, and hurts our patients. So, having this workshop these two days I think is awesome, and I’m excited to be here, and look forward to see what happens tomorrow.

Thank you.

[applause]

Female Speaker:
Thank you so much. Maybe we could take just two questions.

Amy Rick:
Hi. Amy Rick, Food and Drug Law Institute. My comment really goes more towards the end of the day, and as we move into tomorrow, rather than specifically to this panel, but a speaker earlier today did reference parenthetically that FDA approval is not necessarily required. I am not proposing that FDA approval is not a good thing, but I think when we move to the solutions portion tomorrow, it’s important to focus on what the goal is. If we want the comfort and imprimatur of assurance of safety and efficacy, and completely following the Food, Drug and Cosmetic Act, FDA approval is very important, and certainly may help with payers.

But we all know that the recent statistic I read is 40 percent of prescribed drugs are actually off-label, and FDA has recently issued some guidance on what drug manufacturers can communicate to payers about off-label use and what they know. But if our goal is FDA approval, that’s one thing.

But if our goal is actually to encourage more research on repurposing, and encouraging the knowledge about what potential repurposed drugs, and sharing, making that information available, that is actually a very different thing that we’re trying to incentivize. It’s a step towards FDA approval, but it kind of -- the road forks at some point. And so I would just, from my perspective, again, legal and policy perspective, I think it’s important as we think about solutions to think about what behavior that will incentivize, very specifically in terms of FDA approval or not, and what incentives will not -- what behavior incentives will not result in. And I’m curious about the payer perspective on that.

Edmund Pezalla:
Sure. So, we’re going to assume that the drugs have been approved by the FDA for something, so they have market authorization. And that's fine. No, but we've talked about a whole range of things today, and nutraceuticals have come up, and all sorts of other interesting things. And they're all important, but we'll talk about drugs that have already market authority. And it's not absolutely necessary to have an
FDA approval for a particular indication in order for a drug to be reimbursed. As I mentioned before, a lot of drugs are reimbursed, and we have no idea why they're being reimbursed because we just don't control them in that way.

But if it's a more expensive drug in a more complicated area of treatment for patients, and that sort of thing, then we may know. And in that case, we would want to have good data to show that it's worthwhile to use it in that way, but it doesn't have to be a FDA approved indication, right. It doesn't have to be added to the label. There are really complicated processes to do this in cancer where we have the National Comprehensive Cancer Network, and they go through a lot of stuff, they spend a lot of time, and energy, and money on, you know, looking at uses, not all of which are there in the label, but that guides what payers will pay for. And payers have various rules, some of them are dictated by the state, and some of them they just have incorporated about, you know, if there's peer reviewed literature that's well done, and you know, it specifically shows that this is a good use for the medication, then they'll allow it.

And I think that's important because we do have to note that part D Medicare, specifically in the law, says you can't pay for off-label use. Now, we do all the time, right, and that's because we don't tell Medicare, and they don't look.

[laughter]

And so, we don't know, but there are some instances where off-label use was like so common that they've come back to part D plans and said no, you know, you can't just pay for this. We're not going to allow it, you know, which means we're not going to reimburse you, you know, for this unless you can show us that it's being used on-label, or something like that. So, there's been a few, there's very few instances like that. But it gets trickier when there's prior authorizations and other criteria where we actually do know how the drug is being used. So, in that case, the FDA giving the indication is really, really helpful. Otherwise, you have to go through this big process of showing that there's already good data. By the time you do all of that, the FDA could have given them a label, at least to some -- not every time, right. So, it's helpful to have it, it's not absolutely necessary, but there are times when you might as well do it.

Shari Ling:
And I would only add that I think one of the true opportunities that we have before us right now is that we are focused on delivering higher value, right, paying for higher value care. And in that context, what outcomes are achievable by a way of any treatment or service, whether it's a drug or other, I think, you know, the operational construct of value really is quite tied to outcomes. Value is also informed by cost, or price, or more likely cost. Although, even that is a tricky issue to measure. But with alternative payment models that are in the here and now, right, and we already have value-based purchasing for hospitals, for post-acute care with episode-based payments that are really how we pay for something that's different than just volume. These are all in the here and now, so all of that drives towards better outcomes, including those that are patient reported. So, I think there is convergence opportunity right there.

Female Speaker:
I think it's an excellent comment and very pertinent. And I would encourage the group to, you know, look at the expansive amount of discussions, including tomorrow. But from the biased FDA perspective, that I am, I do think that there is an important role for FDA to play in ensuring the safety and
effectiveness of products, including for indications other than the ones that were simply lucrative for a pharmaceutical company to study. So, I think we should -- rather than viewing it as an either/or, perhaps view it as a spectrum where one is pushing towards FDA approval, and ideally that is the goal, but recognizing that there inevitably is going to be data that is collected along the way. Now, as you say, at some points it may diverge, and the approach may differ depending upon one seeks FDA approval or not, but that may be a way to [inaudible].

Female Speaker:
One last question, and then we'll have [inaudible]

Male Speaker:
I've just got a really quick one because I know everybody's dying to go. And it's for Fran, who I don't think was involved in the last question. I think you've got a really interesting -- basically, a holistic opportunity with your -- with the structure you outlined to do really two things, one of which is to use a retrospective analysis to find out where the -- with some of your patients who have comorbidities of various kinds. You have a diminution of, whether cancer or the incidents of cancer, or diabetes, or Alzheimer's disease, or whatever, with drugs that are not actually being administered for that purpose. That's number one. And then secondarily, to actually try and investigate that in a prospective fashion because you said you're running clinical trials, too. It would be wonderful if you had an example of that. I don't know whether you do.

Fran Cunningham:
We -- I'm trying to think of an example where we've done it with a new -- no. No, I'm just thinking I don't have an example right off the bat where we've looked at something specifically. We have data where we do, looking effectiveness for specific products, but not necessarily off-label at this point in time. Not to say that we can't because that's one of the things that I know we want to do as a system. But not that I can think of outside of -- ketamine [spelled phonetically] is the only thing that we've done.

Male Speaker:
Okay.

Fran Cunningham:
Ketamine is the only one that I can think of that's recent that we've done.

Male Speaker:
What? Ketamine in depression?

Fran Cunningham:
Yeah, Ketamine --

Male Speaker:
Yeah, yeah.

Fran Cunningham:
-- using for treatment resistant depression.

Male Speaker:
Yeah.
Fran Cunningham:
And ketamine for pain.

Male Speaker:
Yeah.

Fran Cunningham:
That's the only one I can think of.

Male Speaker:
Maybe we could have a chat because I've got a lot of different examples of retrospective associations between drugs that have been found to have either an effect on the [unintelligible] of cancer, or diabetes, as I said, or Alzheimer's, or all kinds of things. So, if you want --

Fran Cunningham:
Right.

Male Speaker:
-- a list of things, ideas perhaps where you might want to look.

Fran Cunningham:
There may be things that are being studied that I'm not aware of.

Male Speaker:
Yeah.

Fran Cunningham:
So, I'm not the final say by any means. This is just ones that I know. That I'm aware of.

Female Speaker:
I think there's a comparative effectiveness study of two diuretics that are --

Fran Cunningham:
Oh, that's right, chlortalidone [spelled phonetically] and hydrochlorothiazide [spelled phonetically].

Female Speaker:
So I think there is one example.

Female Speaker:
Really fast.

Male Speaker:
I was just going to comment that perprantilo [spelled phonetically] has been used to decouple emotion trauma, so it's been repurposed, there's some literature towards that, so I assume a lot of your patients would probably need medication for high blood pressure. Therefore, you could monitor those that have been taking perprantilo --
Fran Cunningham:
Yeah.

Male Speaker:
-- and see if there PTSD is actually diminished the episodes of PTSD. And that could be a retrospective study that would probably be easy to do.

Fran Cunningham:
And you're absolutely right because just looking at the utilization of beta blockers in our PTSD patients, we definitely have perprantilo use there. So that would be, yeah. Thank you.

Female Speaker:
So, lots of possibilities for future collaboration and study. So, thank you so much to our panelists.

[applause]

And I'd like to invite Lynn Marks to give some closing remark, please.

Lynn Marks:
So, it’s great to be on the agenda with just the time of 5:00 p.m. written by your name.

[laughter]

I'm not sure if that means the hook is coming very soon. But I'm Lynn Marks. I spent most of my career in multi-decades in large pharma, so most of my comments and perspectives come from that point of view. And like several of you in the audience, I failed at retirement, so I came back as a consultant and an advisor to a different part of the federal government. But I'm part of Chris's advisory council, and a chair of the Cures Acceleration Network Review Board. And so, on behalf of myself, Ron Bartek, who's the vice chair, as well as the entire review board, this is an incredibly important meeting for us to make sure that we held the line and give feedback to NCATS and the team as to what we believe should take place. That's the difference between the CAM review board is that we don't just give them views on things. We push them for action and the call to this actionable agenda is really critically important.

I think in terms of just looking back over the day, I thought maybe for the first 45 minutes I would give you my comments.

[laughs]

Short break and then come back in. Just to go back and just reflect on what some of the things that hit me were across the day. And we all have our different perspectives in terms of what resonated and what might not have. And that's going to be the power of tomorrow is to bring our different backgrounds. The team have gone to a lot of work to make sure that we're paired up with people who are different than ourselves, to bring out that power. But Bobbie Ann started off by making sure we understood that the answers aren't simple. We don't just ask Siri for the answers. This is hard work. We have to work together. We have to learn from each other. We have to push the boundaries and come up with new solutions and answers.

Chris came after that and said, "This is very challenging, but the public health impact can be enormous."
He also talked about this power of diversity, to focus on the issue, and bring our experiences together. He said it was an imminently solvable problem and he's looking for solutions with an actionable, research agenda.

So, the CAN Review Board, the next meeting, is on December 13th, we will be debriefing the entire review board with the outputs of the next several days, so your information will be very fresh in our minds as we inform the group to see how we want to move forward.

And then I don't think there's any doubt in any of our minds what the true highlight of the this entire day has been, to have two patients and one parent experience about how their diseases impact them personally, then throughout their lives, gives us meaning in terms of why we are here, gives us passion to move forward. And some of their courage, perhaps, rubs off on us to break through new boundaries so that we bring solutions to people around the world.

When we came back, Bobbie Ann grounded us in terms of the focus of our structure. It is on drugs that have been approved, but do not have any remaining patent, or exclusivity protection. That's a tough group, but the lessons that we learn in that section may well apply to the other areas where we can ply those. So, it doesn't mean we can't utilize what we learned to apply it to the full spectrum, but it does give us a core bit to focus on.

No one owns the problem. Right, Bobbie Ann? Maybe this is the beginning of some group beginning to believe that they own the problem. Maybe that's you. We also talked about the regulatory pathways that come along. It looks like 505b2 gets the winner of the day in terms of that route, but with that comes responsibility. We don't just get approval and necessarily get to walk away. There may be regulatory updates. There may be fees to be paid. There may be annual reports. There may be phase 4 commitment, who knows what was in that. So, we need to think holistically rather than just ringing the bell, and walking off, and say, "Job well done."

Then we had a strong panel in terms of the regulatory environment, talking about the industry has an interest in this area, and all -- I am absolutely certain that all of you are much faster at figuring out that Eroom's Law is simply Morse Law spelled backwards. But it took me a lot longer than I would like to admit as I was trying to Google Eroom's Law. I'm not necessarily proud of that. But this return on investment dilemma comes up time and time again. It may call for new models, it may call for different approaches, but it is ever present as to one of the clear excuses for why not much progress has been made in this space is we can't make money. How do we change that?

The preclinical area focused on, you know, IND filing and all the data. Drug master file came up time and time again, and that may be one source of the data that is needed collectively, but there was a lot of talk about not being able to get information. Where is it? And the older the drug, probably the less complete the data. Where is it? How do I get to it? Who's going to give me permission to have it? Large pharmaceutical companies, if you've already dropped it, you may not even be able to talk to somebody that can find where it is, you know. They'd love to give it to you if they, you know, had the time, or energy, or whatever, but you just don't quite wind up with it. And the data can be in a variety of forms. And perhaps, I mean this bridging interventional development gaps, and the therapeutics for rare and neglected diseases with 35 INDs. I actually didn't know that, so that resonated with me, as a vehicle that is actually having some success pulling this information together. I know I should have known about that, Chris, but I didn't.
And then there was a thematic over the learnings, access to expertise. How do we get that information together? Where do we get the funding to look at this? Do we just ask experts to volunteer their time? Where are they? How do we get to them? What's that look like? Because navigating this space is going to be multidisciplinary.

And there several examples of successful repurposing already. Then we moved over the preclinical area. Again, the data necessary, the drug master file, kept up coming up as being part of what is necessary. There was a view that they're too many opportunities. How are we going to prioritize them? What a problem to have? Too many opportunities; probability of success, return on investment, developability, algorithms that might help us do this. Is it adequate for the purposes that we need in terms of being able to give the data to payers, to regulatory agencies, to health care associations that write guidelines, what is that body of information? Many, many questions even in that space.

And then we had the morning summary where there was a real-life example of a problem and a challenge. Thanks, Harry [spelled phonetically], for that one. In terms of one that's right in front of us. What are we going to do about it? We also learned that the role of FDA is evolving in terms of sources or expertise, reference, and guidance. And then perhaps on opportunity for an entirely different business model came up several times, but we also heard about one, you know, sort of the FFRDC type of principle.

And then we got into the clinical experience, repurposing data, evidence generation, real world evidence, and how do we study populations that we know very, very little about. I mean the Castleman disease piece I thought was very informative because there were subsets that weren't responding to the same disease, so I carried it around this idea that perhaps within a narrow spectrum, like Castleman's disease, that there would be a therapy that would be effective for that. Well, maybe Castleman's disease is actually three or four different diseases inside of a thing we call one disease. So the better we get at being able to understand the background path of physiology, the targets, maybe we'll be able to run better clinical trials because you could lose efficacy signal inside of a patient population where your drug only works for 20 percent of them, and you didn't have a way to stratify them. So really, really important to understand all that.

Limited patient numbers, non-profit funding models, label changes versus guidelines approach, need to learn from every patient. I love that comment. And patients at the center of their data. It's not how we do it. Patients can't even find their data, couldn't get their data if they wanted it, most of the time, right. It's all over the place. It's not aggregated. We don't wear it around with a little card that has everything on it.

And the value versus time. Whose time are we talking about? The patient's time? Or our time? And if we think of that with a patient in our front of our mind, then maybe that will help us with the compass of what we're trying to accomplish.

Heather [spelled phonetically], I wanted to thank you for the Cure ID piece, infectious disease physician by training. So, thanks for starting with ID. We need all the help we can get. And then we went into the economics piece. And we were introduced to a new character that I hadn't met before. Andrew Madoff Lowe [spelled phonetically].

[laughter]
He was -- I thought pretty helpful in terms of guiding us through that. But he did show another problem up front. You remember that regimen that he said was effective, had -- I don't know. I've lost county, life five or six agents in the regimen. And in terms of FDA regulatory standards of combination products. I've got to show the end of [unintelligible] contribution as well as the -- what's that? Six factorial is more than I can figure out right now.

And then we moved to understand is it a good deal from an economist point of view? The business -- investment point of view. Is it a good deal? For profit companies generally aren't in the business of losing money, at least not chronically. And the myth that there just isn't enough money. That is just an excuse. We need to maximize the value of what we have, and maybe we need to move to different industry models. I will admit the public utility didn't resonate with me, but the social investor concept did resonate with me in terms of our ability to do that because I think we want to drive innovation at the heart, and I'm sure that's what will be the intent.

And then at the end, we had the payment data for the [unintelligible] that we're slowly but surely, hopefully, shifting to patient outcomes, that comorbidities, are more and more common, and more and more complex, which is going to interfere with our ability to tease out are we making impacts on different parts of different diseases as they interconnect. Payers have a lot of data. We have a lot of information on who got what for what reason, but we don't have a lot of data on what happened after that.

And then, one of my favorite quotes was, "We just pay for generics but don't know why it's been used." Since, I don't know. 80 percent of our drugs are generic probably, in terms of utilization. So, I found that interesting.

And that the VA system is a source of the solution for testing hypotheses, especially real-world evidence, and pragmatic clinical trials. And I think all of understand that Fran loves data.

[laughs]

So tomorrow we're coming back. I think it'll be a great day. We'll get to work together to solve problems collectively, and we hope that we can reduce this to an actionable plan. So, thank you very much for your attendance.

[applause]

[end of transcript]