ACTTION - IMMPACT-XIX

Accelerating the Development of Precision Pain Medicine

June 3, 2016

A Matter of Record

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ACTTION

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

IMMPACT-XIX

Accelerating the Development of Precision Pain Medicine

Friday, June 3, 2016
8:09 a.m. to 4:45 p.m.

Westin City Center
Washington, D.C.

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P R O C E E D I N G S

(8:09 a.m.)

Introduction and Meeting Objectives

DR. TURK: Good morning. My name is Dennis Turk. I want to welcome you to the 19th IMMPACT meeting. When we had the third IMMPACT meeting, I had a slide that I made up, a humorous slide, of Dr. Dworkin and myself at the 20th IMMPACT meeting, and we were gray-haired and hobbled over. And I looked in the mirror this morning, and I was quite distressed to see that, in fact, we're approaching the 20th meeting, and I may have to revive that slide.

I do want to thank all of you for being here and welcome you to this particular meeting. As I said, this is the 19th meeting. I especially want to thank people who have come from great distances to be here, from U.K., from Germany, from all parts of the United States, from other countries that I'm not even remembering at the moment. So thank you all for coming.

Hopefully, this is going to be an enjoyable

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meeting, as well as a productive meeting. Let me tell you a little bit about what's going to happen, and, first of all, a little bit about what -- for those that haven't been here, there are a number of you that have not been to any former IMMPACT meetings. So I'll give you just a quicky overview of what's going to come.

I slightly apologize for the room. I know it's a little hard for people to see if you're sitting down there and asking a question or somebody over there, so we're going to count on the moderators to try and intervene and help out when they're up here, because I can see everybody, but when John Farrar wanted to speak to Bob Dworkin, he'd have a hard time seeing around the corner.

So that's why I'm going to apologize in advance, and I'm asking the moderators of all the different sessions to try to be aware of that when it comes to questions.

Housekeeping details are always the most important things. Make sure you sign in. That will be each morning that you're here. Silence

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your cell phones, and if you put them on airplane mode. If you're a speaker, by the way, if you're a speaker, put it on airplane mode, because if you get any messages on your phone while you're speaking, the mics will pick it up. So please do that.

Microphones are voice-activated, so speak directly into them. Are these the kind that you have a certain number of people who can light up or is it just -- there's six people. So if six people have started going to their mics, if you're the seventh person, your mic won't work until someone stops speaking. So it's not that your mic isn't working, it only means that you're being blocked out until there's room for that.

The meeting is going to be recorded, and, therefore, everything you say can and will be held against you.

All of these speakers' slides, we will ask their permission, but once we get permission, they will all be placed on the ACTTION website.

If you're a speaker and you have some

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proprietary information on any of those slides, we'll ask you to delete those. But we will ask your permission, and the reason for doing that is, obviously, there are many, many more people -- this could be huge, but there's not enough room and not enough conducive for discussion. As Dan Carr told me, it's the old Socratic method of getting people to talk to each other.

That's our goal, but the idea, for transparency, is to make sure that we do have a transcript so if someone wants to listen to a day and two-thirds or a day and three-quarters of us talking, they'll have an opportunity to do that.

The slides, we hope, will become available, as well. Usually, when we get permission for the slides, it takes about anywhere from a month to six weeks before they go up. But, for example, if you want to see somebody's slides, you will eventually be able to get access to them or you can send them an email, I'm sure, and they'll send them to you, as well.

Lunch is going to be in the Vista Terrace,

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which is on the mezzanine level, which is a couple levels up from here. Checkout time on Saturday is 12:00 noon. You can check your baggage at the bell stand or place it in the back of the meeting room, if you choose to want to do that. The meeting room is secured. So if you go to lunch and you're wondering about your laptop, can you leave it in here, yes, in fact, you can, and it's going to be safe.

Taxis can be ordered, and what we typically do is we have a signup sheet so that people can get to the airports and make sure they have plenty of time to do that. Valorie Thompson, who some of you have met, who we couldn't do these meetings without, and Andrea Speckin, who are at the registration desk, they can help you with any issues related to your room, transportation, taxis, what have you. So check with those young ladies, who are standing toward the back. I think Valorie I can see from here. If you need any assistance, check with them.

If you do have some call or something that

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you have to take, make sure that you don't do it in the room here. So that's just the housekeeping.

Restrooms, which they didn't put on the slide, if you go out the back door, turn to my right, you'll eventually bump right into them. You can't miss them. So they're very conveniently arranged.

Any other housekeeping queries?

Bob, anything?

(No response.)

DR. TURK: Okay. Meals are going to be taken care of, and we'll tell you where they are. The lunch is going to be at the Vista Terrace.

I want to thank those pharmaceutical companies who did support this particular meeting and ACTTION in general. ACTTION, as you'll learn, is a consortium and part of a public-private partnership between the FDA and the University of Rochester, and these pharmaceutical companies, in addition to the support that we get from the Food and Drug Administration, do provide some support to these meetings.

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You will notice, however, that there is some space available. So if you happen to know anybody, any company who would like to join in, we can definitely -- and it's prime location. So for anybody wants to do that, by all means, we would happily discuss it, and Valorie will be happy or Dr. Dworkin will be happy to talk to them about this.

So what IMMPACT is not -- and, Bob, close your eyes, because you've seen this slide too many times. It's not the International Micronutrient and Malnutrition Prevention and Control Program. So if you're here for that meeting, it's across the hallway.

It's also not the Interactive Massive Model Proximity Collision Tester. So for those physicists, this is the wrong room. It's not the Immigration Public Action Coalition of Trenton, New Jersey. So if you happen to be from New Jersey, you might be in the right place, but that's not the right meeting.

One of my favorites, the International Maine

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Maritime Potato Action Team, that is also not this meeting. The Infrastructure Management Mapping, Planning, and Coordinating Tool from Austin, Texas, so if you happen to be living in Austin, Texas, this is a entity that is helping develop the city and get it all prepared for you to enjoy your life there.

It's not the Double Impact Tae Kwon Do, although sometimes it feels like that in trying to get these meetings to move along. As you could see, we work very hard on trying to make sure that these meetings do accomplish what the objectives are.

I want to tell you that there's a new award that ACTTION has provided. It's the coveted Dworkin Award for the most tortured acronym that anyone can provide. For those that know Bob Dworkin, they know he does have acro-philia. The recipient for this year is the In-Hospital Mortality for Pulmonary Embolism Using Claims Data acronym.

Now, look at, obviously, in yellow, the

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letters to come up with IMMPACT. They had to go to great efforts to do that. So we want to encourage all of you to apply, because next year, you could be nominated to have your name up here to win the Dworkin award.

What is IMMPACT? So I told you what it's not. It's the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. It's an international consortium, with participants from academic universities or academic institutions, I should say, academic research people, governmental agencies. The majority of the ones are listed there who have participated and been involved in ACTTION, in IMMPACT in some way.

Then we have representatives from consumer organizations. Some of you like to call them patient advocacy groups, but several of these advocacy people don't like to view their clientele or their constituents as patients since they're not in treatment. So we'll just refer to them as consumer advocates.

IMMPACT existed prior to 2010 as an

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independent entity. It has now been absorbed in 2010 or 2011 within ACTTION. ACTTION is the Analgesic, Anesthetic and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks. Talk about acronyms. That's ACTTION.

The reason for having the double Ts like that, we went to great efforts to do that because if you go to Google and you put in action without the two Ts, you get a lot of other stuff, not us. So if you want to go to Google and find out anything about ACTTION, you can do that.

Bob Rappaport is somewhere in the room. I don't know where. He's in the back, and we want to always express our appreciation from Bob Dworkin and myself, because when Bob Rappaport was in the FDA, the head of the division that was sponsoring analgesic products at that particular time, it was his vision and his idea to take the kinds of things that IMMPACT was doing, expanding it and to do many other types of activities.

So we thank Bob Rappaport for all of his

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contributions and vision and wisdom. Hopefully, we have not let him down. We do let him come out, even though he's left the FDA, to still participate.

The mission of IMMPACT, very simple, to suggest methods for improving the design, execution, interpretation of clinical trials for treatments of pain, quite straightforward. When we first began this, talking about the first IMMPACT meeting 2001, Bob Dworkin and I were at the World Congress of Pain meeting. It was in San Diego, and we were bemoaning the fact that we couldn't compare across different studies because the designs, the methodologies, the kinds of outcome measures were so disparate that it was extremely difficult. And to try to do meta-analyses was very hard, and if we could only get people together to come to some consensus agreement about how we might do things. At that point, we were thinking of even measures, what are the outcome measures to use.

Since that time, that one meeting, the first meeting was supposed to be one, there was no

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IMMPACT really one, because it was just an IMMPACT meeting. Then we found out that people liked it, found it useful, valuable, and decided to continue, and, as you know, we're up to IMMPACT XIX.

Who is IMMPACT? Since the 2001 meeting or 2002 meeting, which was the first meeting, there have been over 225 participants at 19 different meetings. Many people have been to more than one, so we've had a lot. If you totaled the number of people, meetings run anywhere from 25 to 50. This is one of the larger ones. I think we have approximately 50 people who are going to be attending this particular meeting.

They come from academic and related participants from 12 different countries over the years, and the countries are listed there, and we are very pleased to have that international representation, because at least in our view, science and methodology and statistical procedures don't have boundaries to a particular country. Whether you're here from the United States or from Canada or from Sweden or United Kingdom or Germany,

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we're hoping that most of the issues are directly as relevant to you as they are within North America.

We represent over 85 different academic institutions who have participated here. So we are very pleased, because without the academic people, without the industry people, without the people from the different governmental agencies, we wouldn't be able to do this.

Fed support, I showed you the slides for this, for the current 2016 period --over the time since IMMPACT and ACTTION, we've had 45 different pharmaceutical companies who have supported us, and support is either for the meeting before there was an ACTTION, and the support into ACTTION is for all the projects ACTTION does. So industry cannot say we want to pay for this or support that particular project. They're supporting ACTTION, and they have to trust that we're going to come up with projects to do. IMMPACT is just one of those projects.

Consumer representatives from five different advocacy organizations, we have, I think, two of

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them here today, and we're delighted to have them with us, because they make us realize that the end user, if you want to use that term, is the consumer. So all the things that we're doing are really designed to find better ways to eventually, ultimately bring treatments to improve the lives of people who have either acute or persistent chronic pain.

What are the different governmental agencies? I'm not going to read them off here, but just to show you that there have been a range of different NIH institutions. We have a number of people from enforcement agencies who have been participant observers. We've always had people from the Veterans' Administration, from different divisions within the FDA, the Army, Department of Defense, European Medicine Agency, et cetera. So you can see those.

We have tried to, again, not only demonstrate that this isn't just a North America organization, but we try to be broad and we try to be across different organizations within the U.S.

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government and other governments, as well.

You're not going to be able to read these, but this is just the list of the different IMMPACT meetings. I will give you the IMMPACT website. So if you want to see what occurred at those meetings, who the speakers were, the background slides, when we were given permission, they're all available online. You could see that.

If you want to see who the sponsors were, if you want to see anything else about what happened at the meeting, those are available to you, and that went up through -- and this year's meeting is the 19th meeting.

It's on accelerating the development of precision pain medicine. If you're not here for that meeting, if you're here for one of the previous meetings, you're, again, in the wrong place.

We often get asked what does IMMPACT do besides having these meetings. Well, we definitely, in addition to having meetings of ACTTION and IMMPACT, commission and review papers

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and conduct and support research studies. So a number of the publications that we've published have come from studies that were supported by IMMPACT and/or ACTTION, depending upon where we were in time. Prior to 2010, it was IMMPACT. 2010 is when we incorporated within ACTTION.

Since 2010, there have been 54 ACTTION/IMMPACT articles published and in press. If you go back to the 2002, the first meeting, I think it's approximately 70 articles have been published. So the idea is to disseminate the information. It's not just for us to sit here and talk about this and to come up with great ideas and to give you opportunities and talk to each other, but to try and make sure the information gets out.

So our goal and the goal of this meeting, one of them, will be to make sure that we come up with some type of publication based on the discussions, suggestions that we have to advance the research in this area.

The IMMPACT manuscripts, articles, the first

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one came out in 2003. They've been cited over 5,000 times, and they've appeared in over 600 different scientific journals, ranging everywhere from addiction medicine to women's health, but my favorite is veterinary medicine. So veterinary medicine people are paying attention to the research design issues of some of the ones that we've taken. So that's sort of gratifying to see that what we're doing is, quote, "What's the impact of IMMPACT?"

If you want to go to the IMMPACT website, learn more about anything, this is the home page for IMMPACT. You can see that it tells who everybody is, what was going on. The SF-MPQ-2 is a measure that was developed to assess characteristics of pain that was sponsored by IMMPACT. It was actually ACTTION that supported that. We developed that with Ron Melzack, who was the original McGill Pain Questionnaire, some of you may know.

The reason for developing that measure was there was concern that the original McGill Pain

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Questionnaire didn't have sufficient neuropathic pain-type questions in there. So we tried to see could we come up with a single measure that could cover the different characteristics. And we also were concerned that the McGill Pain Questionnaire had a truncated range of scores. So there's some change. So if you're interested in that, you can go to that bullet, push that button.

The sponsors and the background about the Seven Summits, if you're interested, in the back of all the different pages, you'll see different mountain ranges and the reasons those were selected. That's IMMPACT.

ACTTION, what does it stand for? Another acronym, this is the Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks, A-C-T-T-I-O-N. We didn't add all the extras. It got to be a bit bizarre.

The mission of ACTTION is a public-private partnership with the U.S. Food and Drug Administration, which I've already mentioned, to

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identify, prioritize, sponsor, coordinate, and promote innovative activities that will expedite the discovery and development of improved analgesics, anesthetics, and addiction treatments for the benefit of public health. That's what this is all about.

While you're in your labs or in your clinics, this is what we're really trying to do. It's easy to lose sight or get very caught up with the rodents you're working with that day or the patients who are coming in and complaining about something, but the whole idea is that we want to take what you're doing in your day-to-day activities and bring them together and disseminate information about those.

The ACTTION website, if you're interested in ACTTION, is the www.acttion.org, very easy to remember. Make sure you use the two Ts. Sometimes if you hit Google and you put two Ts, they'll say are you really -- did you misspell that? Yes, you want that to be there so you can find it.

Who's here? I'm not going to read off the

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names. There are lists at your seats of who the people are. The people in the yellow that are highlighted are speakers or moderators. As you can see, we've got a divergence of people from multiple countries, as I said. We have a lot of different agencies that are represented.

The pharmaceutical companies that are supporting ACTTION and the IMMPACT meeting are invited and encouraged to send a representative, a single representative. No company should have more than one representative. We request, to the extent possible, that these be the scientifically-oriented people. This is not a marketing meeting. So for anybody who wonders about people from some pharmaceutical industry, some of the best science and scientists in these areas are in the pharmaceutical industry.

Therefore, we're delighted that you can attend, and they contribute just as much. They're not here to speak for their company. They're here to speak as a scientist on the issues that we care about, and thank them for being here.

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Objectives of this meeting, very simple: Discuss important considerations that provide suggestions regarding the execution and conduct of clinical trials to advance precision medicine. Very simple, very easy. We're going to accomplish that.

To disseminate these considerations, so it's not just we talk about them. We're going to then disseminate these considerations, observations, suggestions, and research agenda by publication in a peer-reviewed journal. All of you will be invited to be authors. What will happen, so you understand the process, is that Rob Edwards, who is sitting there next to the back -- Rob, raise your hand.

Rob Edwards has been asked to be the rapporteur, if you will, to actually take minutes, notes to draft up the initial manuscript. It will then be circulated to the organizers of the meeting for their input. Once we have a draft that we think is acceptable to send out, all of you will receive a draft. You can look at the draft and

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make comments on that.
I think there have been two instances, since I can remember in the 19 meetings, where people chose not to be there. People from the DEA, when they came as observers, could not be listed as authors or would not be listed as authors on any manuscripts, but everybody else has been pretty satisfied.
Those are the only ones I can think of. There may have been one other one who was unable to or chose not to have or have approval from their organization, which didn't give approval, but that really hasn't happened. So you will see a draft of the manuscript.
A, you're not going to remember this, but I'm going to say it. When you get the draft, and it's sent out to all 50 of us, don't use reply all when you want to send back comments. Rob and the coordinating committee, we'll take the comments and integrate them.
Trust us. You'll see them come up, but you don't need to send it to reply all, because there's

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usually two or three iterations of the manuscript. Fifty times 3 is 150 emails, and you probably don't want to see all those. So if you can remember, please try to don't use reply all.
We'll probably remind you of that when -- Rob will remind you of that when we circulate the manuscript, but we really don't need to see every "great job, guys." That's really helpful and we appreciate it, but I don't know if all the other 49 people need to see it.
In order to accomplish this, though, we have to do a little bit of herding. That is, we've got to get 50 people to come to a consensus in a day and a half or a day and three-quarters. I should say that's really not true. We have this room available until we come to a consensus. So it could be Sunday. It could be Monday.
As long as you guys want to talk and can't agree, we will stay here and meet. We can arrange the rooms. Don't worry about checking out. We'll be happy to keep you here. So in case you want to keep talking, we will do it.

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Now, herding cats, we've learned some things over the 19 years or meetings of doing these. So there's some notes we've gotten together on the gentle art of herding IMMPACT participants. Participants don't like to be herded. In fact, you can't really herd IMMPACT participants, but it doesn't stop us from trying.
We've learned that participants prefer to herd themselves, but aren't very good at it. So we do need to use our moderators and our other folk that are trying to move this along. Dr. Dworkin has a whip that he does bring out at the last part of the meeting.
Participants understand that sometimes they need to be herded. However, it doesn't make them any easier to herd, even though you know it. Harsh herding usually has negative consequences. So I try to restrain Bob Dworkin from using his whip, because we don't want to upset you, and sometimes it's like working very hard to push you guys together. But the goal is at the end of the meeting, whenever it should be, we will have enough

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information -- and we'll know this when Rob Edwards says we got enough, I could now write a draft manuscript. There's a consensus.
Now, the consensus is also a consensus about research directions. So it's not consensus, we have all the answers. It's not the truth, but rather it's that we have some agreement on where are we now, what's the state of the research, what are the unanswered questions, what kinds of directions might we encourage people to engage in research.
We can't require. We can't make anybody do anything. All we can do is try to inform them. The fact that the manuscript gets cited a fairly large number of times suggests that we do a reasonable job.
I'm going to shut up now, and I'm going to turn the meeting over to Roy Freeman. Dr. Freeman is going to be the moderator for the first morning session to invite the first speakers. And while he's coming up here, let me just say we intentionally have coffee breaks, and you can see

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when those are, and dinners, and we end the meetings early enough so people can talk, because what we found out is that people do like to continue talking throughout the meeting. We encourage that and we're delighted to see it.

So thank you all very much for coming. Any questions that you might have, Valorie and Andrea in the back regarding logistics. Any other questions you have, Dr. Freeman will answer all of those questions.

DR. FREEMAN: Well, thanks for the introduction, Dennis.

It's a pleasure to open up the scientific session of this meeting on accelerating precision pain medicine. In introducing speakers, I think all of us often say the subsequent speaker needs no introduction. It's usually not entirely true.

(Laughter.)

DR. FREEMAN: This time and for my entire session, the speaker really does need no introduction, and this will apply to all of the speakers. I will be very, very brief just because

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I was asked to introduce the speakers.

The first speaker is going to be Clifford Woolf, who will be talking about precision pain medicine accomplishments over the past 25 years and prospects for the next 10.

On the off chance that somebody wandered into this room from one of the other meetings by mistake and doesn't know who Clifford Woolf is, I will give three lines. It's not entirely out of the question. There was a meeting upstairs on ion metabolism, and I think I'd rather be at this meeting than that one.

Clifford is professor of neurobiology and neurology at Harvard Medical School. He directs, at Children's Hospital, the F.M. Kirby Center for Neurobiology. Since his seminal work when he was at University College of London on central sensitization, he's made substantial contributions to the field of neuroscience.

Viewed from the top, his interest has been in the structural, functional, and chemical plasticity of neurons, and this has had

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implications not just for pain, but for neurodegeneration and neuroregeneration.

With respect to the talk he's giving today, I think one must mention the seminal paper written by Clifford and Mitchell Max, whose shadow hangs heavily over not just this meeting, but over every pain meeting, the seminal paper written in 2001 on mechanism-based treatment. It's hard to believe that 15 years have passed, but I'm hoping that at the end of this meeting, we will have accomplished much to accelerate the development of precision medicine in pain.

So let me introduce Clifford Woolf.

Presentation – Clifford Woolf

DR. WOOLF: Thanks very much, Roy.

It's a real pleasure to be here. Actually, the privilege of starting this meeting gives me an opportunity to formally thank both Bob and Dennis for this amazing initiative. So please join me in congratulating them.

(Applause.)

DR. WOOLF: This is a logo that I downloaded

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from the White House site on the Precision Medicine Initiative, which was announced last year by President Obama, but precision medicine didn't arise out of nowhere, obviously.

It's interesting, as I was preparing this talk, to try and get a perspective, and certainly -- I am an MD/PhD, although for much of my professional life, I forgot about the MD part. It was towards the latter end, as I began to wrestle with translational implications of some of my work, I began to try and get a big picture of where is medicine and this interaction with science and how does that relate to the commercialization of novel therapeutics.

Certainly, my first exposure to that was very much in the setting of blockbuster drugs, one drug to treat as many patients as possible, the complete opposite of precision medicine, obviously. It's fascinating to me that we have now come around to the notion that we can try and target therapy to individual patients, and that is our challenge.

Hopefully, that will still provide

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commercial opportunity for the development of therapeutics, but without this notion that it doesn't matter if the majority of patients who are given a treatment don't gain any benefit as long as it's safe, which I have heard often stated.

My view is that that's not great. We can surely do better than that. We should be targeting our treatment in a manner that it can produce or there's a high chance of producing a benefit in individual patients. Hopefully, at the end of this meeting, we'll have some sense of what the challenges are, what the opportunities are, and how we can address it.

In being asked to try and give a perspective on how the notion of precision medicine impacts pain, I'd like to share with you through the lens of my own experiences. So this is President Obama announcing the Precision Pain Medicine. It happened to be on my birthday last year, and it's worth taking a little moment just to read what he says.

"Doctors have always recognized that every

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patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type. That was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

If you actually look on the website, next to President Obama is a big double helix model of DNA, and one of the issues that we can begin to discuss is that at least my take on this initiative is it's heavily based on the assumption that this is about matching our genetic variants with our response to treatment. Obviously, that is important, but it's not the whole story, and I think that's going to be particularly true in the context of pain.

Anyway, I'm delighted to formally announce today that the Precision Medicine Initiative has incorporated the Precision Pain Medicine Initiative, and, indeed, as you can see, my view is that this is as good a place as any to begin to

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start this initiative and hopefully see it through.

The whole notion -- and actually, how did we exist before Google? I just started on precision pain medicine. You just go in to Google, and there's your whole talk ahead of you. It's just a matter of -- like an a la carte, what image should I choose?

Here's a lovely image of a treatment as a bull's-eye. How can we design a treatment that is not scattered around, but is specifically targeted for the individual patient in a way that is safe? That has to be the theme that runs through our discussions here.

The notion of precision pain medicine, as I said, has been heavily tilted, I think, towards this idea that genetic variants will drive much of the choices, and this is most explicitly stated in this image from the NCI on precision pain medicine. It says, "Discovering unique therapies that treat an individual's cancer based on the specific genetic abnormalities of that person's tumor."

That, obviously, is a great idea. No one

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would have any issue with it, but it has led to this notion, as I've alluded to, that if we just study the genetic variants of our population, identify the particular variants that an individual patient has, then that is precision medicine. And I think we all appreciate that is not the case.

But be that as it may, we might as well start the discussion by thinking about, in quotes, "pain genomics." I don't want to anticipate a discussion that Alban Latremoliere is going to have later on this morning, and we're lucky to have several people in the audience who have made major contributions, primarily Luda sitting over there. So please chime in at any point. But one of the major problems in pain genomics is how little data we have, relatively.

When I look at my colleagues at the Stanley Institute, part of the Broad Institute, and the enormous impact they have made in identifying gene variants that drive schizophrenia and bipolar, and the way they've done that is by having access to worldwide, enormous cohorts of patients.

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That's what you require. We started off with several hundred, and then we thought a few thousand may be okay. But it's only now that we're reaching close to 100,000 cohorts that the data is beginning to be strong enough to confidently identify the individual genes and their variants that contribute to the risk of these major diseases. We have nothing equivalent to this in terms of pain genomics.

I remember discussing this at a meeting at NINDS when Story Landis was there, and at that time, she said, "I'm not going to put a penny into pain genomics because the outcome measures are so variable. There's so many confounding factors. Forget about it." And she was correct, not a penny went into it.

(Laughter.)

DR. WOOLF: But in spite of that and recently, I had the pleasure, as a reviewing editor for PLOS Medicine, to supervise a manuscript that will appear very shortly that has looked at three enormous cohorts of individuals: one from

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Scotland, one from England, and one from 23andMe.

Basically, what this study will confirm is that there is a very large heritable component to our pain experience; that if you just look at the general population and ask who has chronic pain, using these enormous cohorts -- I think one is 90,000, one 100,000 and 23andMe is several million -- you get a reasonable predictor of the heritable component, which is close to 40 percent, at least. These are, obviously, in cohorts that were not designed specifically to address pain-related issues.

What the study will also reveal -- which is something we had suspected, but it's just that the size of these cohorts give us much more confidence -- is that this heritable component is composed of a polygenic -- the pain risks, the pain variants, the odds ratio that is generated by particular polymorphism in genes is polygenic, and again, that is no big surprise, and Luda's work and others has certainly indicated that.

Hopefully, for these cohorts, the next step

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is -- which are the individual genes and which of them are strong enough that they replicate in multiple in independent cohorts. However, we're dealing with a complex disease state or syndrome, whatever one wishes to call pain, and the fact that it will all be polygenic and we don't know how many genes that means, if it's anything like schizophrenia and autism spectrum diseases, we may be dealing with hundreds of genes, each of which produce a tiny risk factor, but which collectively to an individual may drive an increased risk of the development or persistence of pain. It's going to be complicated.

In a very simpleminded way, in the way that the NCI says, "Oh, if you can just genotype cancer, identify the mutations, you can then design a treatment that will specifically target," and even that in cancer is turning out to be complicated because it changes over time, and I think it's going to be -- we're quite a long way off, but being able to genotype our patients and on the basis of that, say, "You have this risk of

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development of pain and this is the best treatment for you."

I think part of that challenge is to talk about that and to see what we can learn from pain genomics, but recognize that it's going to be incredibly complicated. There are many, many genes that are going to be contributing, each one of which has a small contribution, and, therefore, we need other tools.

I think that's a part of what we're discussing, because if we're relying entirely on genomics, as at least the Obama initiative was announced, I think we're going to fall short.

Where did this begin for me? Well, there was a meeting that I helped coordinate in 1998. It was soon after I arrived in the States from England. And as part of that transition from University College London to MGH, at that time, I used the opportunity of a change to rethink my approach to pain.

One of the issues that started bubbling out was that the way we classified pain needed to be

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reevaluated. So we got a group of people together in New York and, based on this, a short editorial was written. As you can see, it was one of those wonderful times where the manuscript was received on the 18th of May and it was accepted the 1st of June, but those days seem to have gone forever.

(Laughter.)

DR. WOOLF: But what we attempted to do was begin to define the notion of the problem, and frankly, it was a relatively simpleminded approach. Again, if you can bear with me, I'm going to give you a few extracts, but one of the themes that came out of this discussion was the notion that because pain is complex and because there are multiple mechanisms that are driving the pain that an individual patient has, we need to consider the possibility that a single monotherapy approach is not going to be very valuable.

This little paragraph essentially says we should think of pain as being analogous to some cardiovascular problem, where a cardiologist would be happy to prescribe an antihypertensive, as well

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as an inotrope, as well as a diuretic and think nothing of it, recognizing that cardiac failure may have multiple elements that need to be treated individually. And that the question we put to ourselves at this time was, is that true also of pain.

At least conceptually, in a metaphorical sense, we thought that this could be true, that as stated here, "We may need to treat neuropathic pain by poly- rather than monotherapy, blocking ectopic activity with sodium channel blockers, central sensitization with NMDA receptor antagonists, augmenting inhibitory modulation with alpha 2 agonists and sympathetic involvement with adrenergic antagonists, depending on which mechanism is operational in the syndrome or better still, if they can be identified in an individual patient."

As I looked through my own work, I think this was the first time that I articulated or was part of a group that articulated the notion of trying to identify in an individual patient what

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are the drivers of their pain and how to identify them; and, if we can identify them, how can we target them in a way that would make for a rational approach to the management of pain.

This led just chronologically to a review in Lancet that I wrote with a then MD/PhD student Richard Mannion, who is supposed to be at this meeting, but unfortunately could not make it. He is now the head of the clinical neurosurgery division at Addenbrooke's Hospital at Cambridge University, specializing in the neurosurgical treatment of pain and other disorders.

What we tried in this review was focusing on neuropathic pain, to try and grow from this first editorial. One of the statements we made there, in a paragraph on mechanisms as the target of management, was "Only when we have the tools to identify the mechanisms responsible for pain in a particular individual and then the capacity to reverse the mechanisms will the management of neuropathic pain really advance." So this was even more specific.

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As you can see, I find that repetition is one of the ways to potentially drive the field forward, and I think, hopefully, that when Rob Edwards put this manuscript together, some of these same messages will be in there, because clearly that has to be the case.

We then said, "The onus on the clinician will then be to use the history examination, investigation, and diagnostic tools as a way to identify the mechanisms that operate in the patients and use this information to select appropriate treatment."

Boy, was that easy to write. Then we waited for people like Mike Rowbotham to magically devise a set of ways of interrogating patients that would reveal the mechanisms so we could then treat them, not that we at that time necessarily had all the pharmacological tools to target each of the mechanisms that may be revealed.

So this, frankly, was wishful thinking, and it remains, to a large extent, true. But I think that's our challenge, and it remains the challenge.

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While we waited for the field to devise ways of identifying mechanisms in patients, it became apparent after some time that not an awful lot was happening. Although it was at that time that I had many detailed discussions with Roy Freeman and with Ralf Baron, and so there certainly was a kernel of interest in this which contributed to the German Neuropathic Pain Network and work that Roy did in the setting of pharmaceutical analgesic studies attempting to identify mechanisms and target treatment based on that.

In my own lab, at this time, we were getting heavily involved in expression profiling, looking at changes in gene expression in particular settings, be they nerve injury or inflammation. This introduced us to the concept of unbiased discovery science. Instead of the standard hypothesis-driven, which is, for example, ectopic activity in an injured sensory neuron is the driver of spontaneous neuropathic pain, that's a hypothesis, and you can then design experiments to test it.

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What expression profiling taught me was when you're looking at things at a genome-wide scale, your hypotheses are so simpleminded and incomplete that the chances are that if you just focus on a very small hypothesis based on what is known, you will miss what may be the major changes underlying whatever you're studying. The beauty of genome-wide screens was that it enabled us to begin to interrogate the entire universe of gene transcripts that may be involved in different disease states.

We tried, very naively, to see if we could take the same approach, an unbiased approach, to looking at the pain phenotype. This was one of my few little efforts essentially as a basic neuroscientist to jump the divide and participate in a clinical study.

We said, "Well, can we design an unbiased -- instead of using a microarray chip, can we get the equivalent of a pain phenotype chip, something that gathered a whole lot of information, and we could just see which of the elements, in an

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unbiased way, contributed to the pain phenotype in an individual."

We set out in a study that involved, at that time, a colleague at MGH, Jurgen Schulze, and Isabelle Decosterd in Lausanne, both of whom are physicians, to try and define what are the elements of the pain phenotype. Well, one major aspect, particularly in the setting of neuropathic pain, is the actual disease nature, the pathology, its location, its duration and extent. Then there are factors related to the patients, such as the age and gender and genotype.

For this study, we just chose not to look at genotype. Story Landis sort of said forget about it. Then the main thrust was, were there ways that we could capture the neurobiological mechanism, to go back to this theme that had been building up. Are there ways that we could potentially get a view of the mechanisms that are present in an individual patient?

The other bit that we decided to leave, not because it's not important, but it's just we wanted

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to focus on mechanisms, were the psychosocial factors that clearly play a major role in determining how an individual responds to a particular pathological situation.

The way we could potentially do this was by taking a history, conducting a physical examination, and then the other tools that one could use would be quantitative sensory testing and a variety of investigative approaches, such as clinical physiology and imaging. All of those will be on the scope of what we have available.

We just stuck to a classic approach using the standard tools that any physician would have available to themselves, particularly in a neurology type of setting, looking at the history and physical examination. So we came up with a way of interrogating the pain phenotype in individuals using an interview that looked at the current pain state, pain location, onset, time course, temporal characteristics, presence of pain-evoking stimuli, quality of the pain, effect of drug therapy, nonpainful sensations, sensory deficits.

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We constructed a questionnaire that comprised 46 items to try and capture this standardized interview, and then we, again, designed a standardized physical examination of 39 items that were targeted at looking at the specific aspects we thought related to the pathology, such as in the case of skin and appendages, skin lesions, swelling, change in skin color, altered sweating, et cetera; and, for the sensory nervous system, response to stimuli of various types and presence of phenomena such as temporal summation.

This together constituted 85 tags that we thought would represent potentially a pain fingerprint that may vary from one individual to the other.

This was the study that was published in April 2009 in PLOS Medicine with Joachim, who's now currently faculty at Columbia Medical School. We looked at four sets of patients, those with PHN, painful diabetic neuropathy, low back pain that was clinically diagnosed as being radicular with signs of nerve root damage, and axial low back pain,

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defined clinically. So 187 patients and all the patients had to have a pain score of six or higher.

Again, we used the same tools that we were doing for our microarray analysis. So we took these 85 items and see if they clustered together in what is called a hierarchical clustering technique. Basically, these are all the patients using the interview items, and essentially every patient was unique and individual.

There was no major big cluster of group 1, group 2, group 3, and this maybe reflects the notion of the questions we asked. But it also, I think, points to the fact that as we confront personalized medicine or precision medicine, every individual is unique and that we should not expect some very simpleminded clustering or grouping, although, frankly, that is the way that most outcome measures are designed based on history.

At least in our setting, we were unable to -- even though we had four different pathologies and we had presumably multiple independent mechanisms sometimes operating alone and sometimes

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together, we were unable from the history to get any sense of anything other than every patient was unique.

When we did the physical examination, we started to get some division, and the clusters that were revealed, one that was largely driven by the patients who had axial low back pain, so presumably non-neuropathic in origin, and the other cluster was essentially those with neuropathic pain. So at least it looked like the physical examination, the particular questions and tools that we used, was able to differentiate neuropathic and non-neuropathic pain in this way.

We then combined the two into a single mixture of history and examination, and this revealed not very clear clusters, it must be said, but eight different clusters that at least we could examine. What was interesting here was that when we combined the history and the examination, one clear division came, and these are the clusters 7 and 8, which were driven entirely by axial low back pain.

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So we now clearly were able to differentiate, even more so than just on the physical examination, between those patients that had been clinically diagnosed as having neuropathic pain versus non-neuropathic pain. Then the other clusters were more mixed, but generally, this is more or less how they appeared. The radicular low back pain was, clearly, not in these two clusters, but were across, whereas the other two conditions overlapped.

This is something we need to think about, because there have been many discussions in IMMPACT about whether clinical trials should be based on inclusion of individuals based on their pathology or based on their symptoms or even based on their mechanisms, if we have a means of identifying them. And at least in this metric, it was clear that neuropathic pain was a big mixture, at least as defined by history and examination.

This is what it looked like individually, and I'm certainly not going to go through it. But this is a way of looking at the proportion of

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subjects in the different clusters as responding -- this is to the history. And the reason why every patient was unique was that if you analyzed these different clusters, there was no real difference across the different clusters.

If you look at something like the presence of deep pain, it's present in practically every patient. These are pain quality questions that were taken from the McGill Questionnaire, and frankly, every single one of them were present in every single cluster. There was not anything that came out of pain quality that represented differences dependent on the pathology of the patients or, what we had hoped, clusters that would reflect different mechanisms.

This is why the history turned out to be much less valuable than what we had hoped, and hopefully, as we continue this discussion later, we can see whether things have improved and what are the issues here.

When we looked at the examination again, and these are examination of the skin, of the sensory

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nervous system, changes begin to appear. In these clusters that we now know represent the axial low back pain, you can see are very different from the others, different, it turns out, by the absence of things rather than the presence, and that was something we had not anticipated.

The other thing that was interesting is that the drivers of people going to the different clusters was more often negative symptoms rather than positive. So the positive are in black, and the negative are clear. It turned out that, for example, loss of sensation was an important determinant of which cluster someone would go into. When we designed this, we had not really anticipated that.

Again, using the same kind of tools one can do for expression profiling of messenger RNA, we did a classification tree analysis to try and see, from these total of 85 elements, which were the individual drivers to get into these different clusters, and this is what it turned out to be. The most important driver was a decreased response

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to pinprick, because not surprisingly, if someone has nerve damage, they have negative symptoms, loss of sensation, and something as simple as decreased response to pinprick was the biggest driver between those that had the axial low back pain and those who had neuropathic pain. It's obvious, but we didn't design the study to pick this up, but this is what came out.

We're not going to go through all of these, but the first two groups were largely driven by a loss of proprioception, indicating large fiber damage, but again showing the loss of sensation, and the others just had these other features.

But we could even simplify this further just based on using the same classification tree analysis to try and analyze what the groups according to their actual disease state, and this was the simple algorithm that we came up with. If you had normal response to a pinprick and you had pain, then chances are you were in the axial low back pain group.

If you had decreased pain and you had a

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positive straight-leg raising test, then you had radicular low back pain. This is something that everyone who is an MD and has done that would do that without even thinking, but it was very nice to get confirmation in an unbiased way that that is true.

Then, again, vibration, if you had reduced vibration, the chances were you had diabetic neuropathy as opposed to postherpetic neuralgia.

None of these were surprises or outliers. They made perfect sense. This is the way the art of medicine is practiced, but the beauty of this approach, at least it seemed to us, was that you could formalize it. It's evidence based, and you can come up with algorithms, actual diagnostic algorithms that are not just simple ticks in a box, but actually seeing how patients can be grouped in a sequential way by the presence or absence of particular features. I encourage us to try and think about that.

I must say that the goal of our study was to see whether we could identify clusters that may

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reflect the presence of particular mechanisms, and that, obviously, is the challenge, because how do you do that? This is completely hypothetical. We could imagine that patients with axial low back pain, the pain may have a large component of peripheral and central sensitization. There may be groups of patients who have central sensitization and those who don't, and those who have disinhibition, et cetera.

This is a total fantasy, and this is the black box that we struggle with. How can we identify what are the tools that we potentially can use to classify our patients, not only disease. I've indicated that it is possible to do that, and that's exactly what most of us who are physicians do all the time, even though we may not be aware of it in a formal sense. But how can we use the same approach? What series of tests can drive an algorithm that can enable us to identify these, because each of these mechanisms may represent a different way of treating our patients and that, I think, is our major challenge.

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Like many things, we struggled to do the study. As it turned out, the recruitment was always low. It was more expensive than we thought. It took much longer. Endless fights with the journal to get it in. Almost no citations of the journal once it was in.

It's just totally forgotten, which is also a lesson that these things take time, and at least our goal of trying to identify, in an unbiased way, what are the mechanistic underpinnings of pain turned out to be a rather naive approach and certainly one that we didn't succeed in.

However, as someone who -- I now have a leadership position, and I speak to my faculty or to our research fellows and sometimes ask what is the major predictor of success in a scientific career, and my answer always is persistence. It is intelligence is wonderful and it's useful to have, but I've seen lots of intelligent people burn out and be sidetracked. It's the people who just hang in there, who see things through the rollercoaster ride of science that succeed.

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I'm trying to live to my own advice, and it is at this point that the paper that Roy alluded to that I wrote with Mitchell, that was a wonderful opportunity for me to work with Mitchell, who, as we all know, a really sad loss. It reminds me of, when Mitchell died, a very moving obituary that Kathy Foley wrote just saying that the tragedy of depression is a fatal disease, and I think that is really true.

Be that as it may, it was a real privilege to work with Mitchell, who really was one of the major drivers of the application of modern clinical trial design to the study of analgesics. We had many, many wonderful discussions, trying to use his knowledge of how to design clinical studies and my attempt to study mechanisms and see whether they are contributors of the pain phenotype in individuals.

In this article that was published in 2001, we discussed the relationship between pathology, the disease injury and the mechanisms that pathology then initiates in the nervous system, the

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symptoms that those mechanisms will then create to produce a number of syndromes. Again, this is a theme that hasn't gone away. I think it remains relevant, as I'll reveal later.

We highlighted the difficulties of identifying precise pain mechanisms in humans, the same challenge, and we also rose the issue of whether distinctions among pain symptoms of pharmacological, tissue or disease diagnosis explain the differences in the response to analgesics.

This was trying to deal with the number needed to treat problem. Why do we have a situation where we need to treat at least four patients in order to get one patient with a clinically meaningful analgesia? What is the issue? Is it purely pharmacology? Is it a matter of bioavailability, PK or target engagement, or is it a matter, in the precision medicine mode, before it was defined as precision medicine, is it trying to identify the target, getting the treatment bulls-eye, as it were.

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We concluded in saying, "In conclusion, based on an analysis of the potential utility of a mechanism-based approach to pain diagnosis, we make recommendations for a new concerted effort by academics, the pharmaceutical industry, and drug regulatory bodies to jointly introduce new tools to assess pain, validate these tools, and use them to improve the sensitivity and value of clinical trials."

I'm going to take no credit for it, but frankly, this was a prediction of Bob's and Dennis' IMMPACT into ACTTION. I'm so impressed by the fact that you have with industry and with government agencies got together to try and address these questions, and I think you truly have made an enormous impact.

Persistence, what next? So having discussed this with a clinical trialist, my next approach to trying to move on was detailed interactions with Ralf, who is sitting there, and this led to this review that was published in 2012 in Neuron, where we took the same theme, trying to deconstruct for

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neuropathic pain its phenotype to reveal neuromechanisms.

At least Neuron had sufficient money to allow us to have prettier pictures, but the theme is pretty similar, which is if we look at neuropathic pain and trying to look at it from the proverbial 10,000-foot view, one could identify the etiological factors that are driving the syndrome. Obviously, this is something that people have spent a lot of effort on, whether it's metabolic disorders, injuries, or what have you.

We recognize that the individual genotype of the patient contributes to the way the patient responds to these pathologies, and there may also be environmental factors. But the bit that we were most interested was how could all of these combine, the pathology, the genotype and environmental factors, to initiate a series of changes in the nervous system that would then lead to the neuropathic pain syndrome and what were these changes and how could we measure them.

Again, this is the goal that we set

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ourselves, from pain phenotype to individualized analgesic treatment. So again, my theme, which may be beginning to be a little bit boring, but the notion of precision medicine didn't appear out of the blue. This has been a theme that we and others have been talking about for some time.

Clinicians encounter neuropathic pain patients with diverse genetic and environmental backgrounds in various degrees of nerve damage, all of which contribute to a complex combination of neuropathophysiologic mechanisms, which in turn manifests as the individual pain phenotype. So the same theme. The question is how we could move this forward.

This little cartoon was our attempt to say we've got an input, if you like, that drives the individual pathophysiology that is unique in an individual patient, which will then drive a pain phenotype, which Ralf hopefully will be telling about his approach to measure that in a quantitative way as opposed to ours, which was in a clinical way, and we need specific diagnostic tools

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to interrogate that pain phenotype, and this could be the basis then for individualized treatment pathophysiology.

The final one of my reviews is one that has been driven by Bob and Dennis, who invited me to contribute, with the American Pain Society, to a supplement in the Journal of Pain, which hopefully is going to appear -- do we know when, soon?

DR. TURK: Probably September.

DR. WOOLF: Okay. Our brief, yet again, was towards a mechanism-based approach to pain diagnosis, and this time, I think I'm mature enough to know that if I'm delving into something like pain diagnosis, I need my hand held by clinicians who see the patients as opposed to my theoretical approach. So I was fortunate to have Richard Mannion, who joined yet again, now with his perspective as a neurosurgeon, and Dan Vardeh, who's a neurologist at Brigham and Women's, who's in the audience here, who is to set up a neurology -- he's splitting half. He's half anesthesia, half neurology, and he's setting up a

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clinic at Brigham and Women's to deal with pain patients and has hopefully a fresh approach to this.

We decided in this review to tackle one of the most difficult pains, which is chronic low back pain, and to illustrate in that setting where there are both pharmacological and surgical treatments, how this individualized treatment potentially may work.

To cut to the chase, this is our attempt to define -- and something has happened to the image somehow. But we defined a slightly different algorithm, one where we could define a state, a particular state, whether the presence in the patient of nociceptive pain, inflammatory, neuropathic, or dysfunctional, and then, again, this endless desire, can we identify the mechanisms that are activated in that state that are present that led to the involvement or engagement of particular targets that can be treated.

As you can see, nothing has really changed other than the way we illustrate it. I'm not going

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to go through this in great detail, other than to say that I think we've become a little more sophisticated in the way at least we can define pain states, such as nociceptive. We know quite a lot more about the way in which nociceptors function, the transduction mechanisms that enable them to be engaged by noxious stimuli, the kinds of noxious stimuli that will act on different kinds of nociceptors, the fact that there is heterogeneity and specificity of these different nociceptors, and they express different targets, enabling us to -- so the underlying neurobiology has certainly moved.

But the notion here was very simple, that in the setting of low back pain, there may be some conditions where there is a noxious stimulus sufficient to activate nociceptors that will then engage the nociceptor system to lead to pain, whereas in the setting of an inflammatory pain state, there may be conditions where the immune system is engaged in ongoing inflammation, and the consequent crosstalk between the immune and other

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system will produce an alteration in both of them that maybe contribute to the underlying mechanisms responsible for the pain, whereas with neuropathic pain, clearly, there needs to be fine damage to the nervous system in some form.

The recognition of whatever one wants to call it, centralized pain states or central amplification, but that situation, we recognize that it's there, but it's quite difficult to define where there is no noxious stimulus, no ongoing inflammation, no detectable nerve damage, and yet there clearly is pain hypersensitivity. And the question, what is driving that increased excitation, decreased inhibition, is there a peripheral input that is required for that, or does it become totally autonomous as some altered function of the nervous system, something which we can perhaps discuss further.

As we looked at low back pain, we attempted to define some common features of low back pain in the setting, identifying which of these were nociceptive, inflammatory or neuropathic. We

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couldn't really define which were the dysfunctional, because it is a definition by absence of the other features. But we then said, "Well, what are the clinical diagnostic criteria to identify these general pain states or pain mechanisms?"

This is where we started, as usual, falling into the problems that for something like nociceptor transduction, the activator on the nociceptor, one clinical diagnostic criterion could be that there is a proportionate pain in response to an identifiable noxious stimulus and that removing the stimulus would remove the activation of the system and relieve the pain.

The trouble is, how do you identify a noxious stimulus? How do you actually identify whether nociceptors are being activated? So again, there is a remove from being, at least theoretically, defining this state and the way in which it may be engaged and the clinical reality of in an individual patient, how do you know whether they have nociceptive pain. But at least once

again we could look at the existing pharmacological therapeutic armamentarium and ask ourselves which of the current therapies may be potentially useful for a patient in this situation. One may argue that high-dose opioids, at least acutely, would be able to reduce nociceptive pain.

I won't go through all of these. I think the main issue that we're trying to come up to is that the same theme that started way back in 1998, that if we can identify mechanisms that, based on our understanding of the way in which the mechanisms operate in the nervous system and the molecular components of those mechanisms, we can potentially come up with molecular targets.

What is new since 1998 is that there may, in some cases, be genetic validation, and this is going to be discussed in our section on Nav 1.7. So that is a useful additional tool that we now have. And again, can we then have treatments that can target them? Part of the problem there is many of the treatments we use now are not specific for individual mechanisms, but are pretty broadly

based, and, again, we can discuss that in more detail.

However, the biggest challenge when we try to see this again in the clinical setting, and maybe Dan can say something more about this, but when he sees a patient who comes in with low back pain, what are the tools that he or any of us who see these patients, what are the tools that we can use to phenotype the patient, identify the mechanisms, come to a reasonable conclusion on which is the target they're involved in, then make a treatment choice based on that.

The reality is that the tools that we use, as indicated here, have poor specificity or no specificity or are inconsistent. We do not have the tools yet to define pain phenotype in a way that reveals mechanisms that is robust, and that is our biggest challenge.

I'm not going to give the answer to that, because I think that's what we're going to be all discussing over the next two days, but I would like to end on an upbeat note. Where can personalized

pain medicine lead to? Where will we be in 10 years' time, when Bob is still inventing acronyms and Dennis is admonishing us to hit repeat all?

(Laughter.)

DR. WOOLF: I'd just like to share with you some recent work that we're doing in the lab that I think adds another tool, and that is that we and others now have the capacity to generate many different kinds of neurons from a patient's induced pluripotent stem cells. So we can take fibroblasts or white blood cells from the patients, we can transform these into pluripotent stem cells and use that as a starting material to make, using direct differentiation, any set of neurons we'd care to, as long we know the recipe.

We've been working on making nociceptors for about the last five, six years, and Simon Tate, who is sitting here, was the person who, when he was then in GSK, invested in that. There was an alliance between GSK and the Harvard Stem Cell Institute. I think there were five programs, of which one that Lee Rubin and I were involved in,

trying to make these sensory neurons.

After three years, we had gotten nowhere, absolutely nowhere, and based on that, GSK, the programs that were successful were terminated, whereas we were a complete failure, so we got renewed. It was wonderful.

(Laughter.)

DR. WOOLF: In fact, I think it was just shortly after the time we were renewed that GSK took the wise decision of closing down their entire neuroscience division. They then replaced it by a much smaller stem cell division, which they then closed down, but somehow our project continued.

We finally did find a way of making human nociceptors, and this is what they look like. They look remarkably like DRG neurons, and they express the appropriate genes.

We can do RNA-Seq now, single-cell RNA-Seq, and identify them, and, in many respects, they offer then a possibility of exploring individual variations, based on the hereditary component that I started off discussing, that may be reflected

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when we -- an individual's genotype may determine the properties and functions of the nociceptors, which we can now study, because we can make the nociceptors and we can test them.

I'll just give a couple of examples of that. One of them is we can study ion channels, such as Nav 1.7, and these are just showing that the sensory neurons express very large Nav 1.7 currents. We are currently working with Steve Waxman looking at patients who have inherited arithromyalgia and we find changes in the excitability of these neurons. We can also use CRISPR CAS9, that's a genome editing technique, to introduce and correct mutations, and this is a fantastic way.

We can now begin to delve into the individual genomic variations of individuals and see whether it affects the functional properties of their neurons. And at least for channelopathies, the chances are that this is going to be very successful, and I think Simon will have more to say about that.

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The low-lying fruit that we've identified and the project I'll share with you that we're about to try and start off with -- again, it's so early that we don't have any NIH funding yet. And, Dennis, this is going to be the slides that I will request to be taken off the server. But I'll share with you something that we're trying to do, because I think it offers the way in which the future may lie, and that is chemotherapy-induced peripheral neuropathy.

We have this amazing well-known phenomenon that you have patients with, for argument's sake, breast or ovarian cancer, who are exposed, for example, to paclitaxel. They are, as far as we can judge, identical in every sense of the disease, age, and other identifiable characteristics.

You give the patients the paclitaxel, identical exposure, dose, time, and some of them develop terrible neuropathy, so bad that they actually terminate their treatment. And that's quite a significant minority who actually cannot continue their chemotherapy and others who do

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continue, but then have terrible ongoing peripheral neuropathy, both the neuropathy and pain.

What we can now do with this IPSE-derived approach is we can identify patients who have had the identical exposure who developed the neuropathy and pain or not pain and those who got the same treatment and who didn't.

It so happens that a collaborator of ours, Eileen Dolan at University of Chicago, has collected exactly those cohorts, and we are currently making a set of -- a pilot study of patients with and without neuropathy in response to paclitaxel.

This just shows you that if -- this is from a control subject -- if you expose these human sensory nociceptors to paclitaxel, you get a very nice dose-dependent neurotoxicity. It's really very tight, as you can see. Our hypothesis -- and I've talked about discovery science and unbiased, this is a hypothesis. Our hypothesis will be that there are some individuals who are more sensitive to the chemotherapy, and we'll be able to pick it

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up in their stem cells.

If we can, you can envisage this is an individualized treatment where before the patient has their chemotherapy, you can test them through a full range of all the different chemotherapeutic opportunities. You can see which ones cause neuropathy and which ones may produce hyperexcitability, which may be a surrogate of the pain.

I think individualized treatment is possible. It's going to be challenging. We've been struggling for 15 years on how we can identify pain mechanisms in patients. That remains a struggle, but something we can discuss. But there are technologies that are emerging that will enable us to hopefully define how to target our treatment in a very precise way or how to avoid targeting our treatment in a way that produces adverse effects.

Thank you.

(Applause.)

DR. FREEMAN: Clifford, thank you for that broad and very personal perspective on precision

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pain medicine.
We have time for a couple of questions. Make these directed questions at Clifford. There is a moderated session, that will be at 11:30, in which we'll deal with more extensive views of this.
John?
DR. FARRAR: Your last example demonstrates a feature that I didn't hear you talk about and I'm interested in hearing, which is with the chemo-induced neuropathy, a fascinating topic. You're trying to prevent the development of the pain syndrome by being knowledgeable about who's likely to get it, who is not, and that's key in our world in post-thoracotomy, mastectomy syndromes, a whole bunch of things.
What has always struck me is that that's very different than understanding, once they get it, what is ultimately going to treat them. The analogy that I use is that once the car is wrapped around the tree, fixing the brakes doesn't help very much.
I just wondered if you have a sense as to

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the differences between those two approaches.
DR. WOOLF: This is the low-lying fruit, the identification of risk, because hopefully, if there's going to be a phenotype here, we'll be able to capture it. But we can use the same approach, once we've got patients. And if it turns out to be true and I have no idea, that there is an increased risk that you can pick up by greater sensitivity to these agents, we can then run screens to look for neuroprotective agents. That's still trying to identify a treatment.
Then we could then take the same cells and run a screen to see things that are pro-regenerative in the setting, maybe. Even that is possible.
I think all those are different questions, but I'm optimistic that we are developing -- one of the biggest changes in my lab is that in the last four years, I've moved from a post-doc doing a single experiment with one head at a time to everything is 380, 4-wheel format. That has been a case of embracing the industrialization of science

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by industry, but putting it in an academic setting.
So all of these, which we could never do before, the kind of thing that the NIH study section would say too ambitious, is now possible, and I'm optimistic that we will be able to address each of those. But we'll start one at a time, going for, hopefully, the one that is going to be easiest to address.
DR. TURK: Just a comment. Since these are being transcribed and taped, when people ask questions, please say your name so that it will be on the record.
Luda?
DR. DIATCHENKO: Luda Diatchenko, McGill.
Cliff, may I ask a technical question? Maybe it's naive or stupid. But did I understand this right, this is DRGs?
DR. WOOLF: Yes.
DR. DIATCHENKO: How did you get DRGs from these people?
DR. WOOLF: We made them. This starts off with fibroblasts from the patients or white blood

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cells. We make stem cells from them, and then we make our DRGs. As you well know, it's not so easy to get.
DR. DIATCHENKO: I wondered, yes.
DR. WOOLF: So this is what the technology is enabling us to do. So I'm not going to pretend this was simple. Maybe the DRG neurons that we're making here are not identical to what a patient has, because we're also wiping out the epigenetic influences. But at least it's a strategy that may have utility or at least we can test.
DR. FREEMAN: Last question from Serge.
DR. MARCHAND: Serge Marchand. Do you think it's possible -- I think it's great. I really like this idea. Do you think it's possible to go to these neurons and do some electrophysiology and just sensitize them, for example, and look at different drugs on them?
DR. WOOLF: Yes, absolutely.
DR. MARCHAND: That's great. Do you think that if you take -- just hypothetically, do you think that the patient that has chronic pain for

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ten years, for example, and if you sensitize the same neurons, they will already be sensitized or they will just be easier to sensitize?

DR. WOOLF: That's a great question. We just don't know.

DR. MARCHAND: But that's possible.

DR. WOOLF: One of the problems that we struggled with in trying to make these neurons is that in the end, not surprisingly, they are like embryonic sensory neurons, and we're now trying to get them to replicate.

If we want to study something like idiopathic small fiber neuropathy that only manifests when you're 70 or something, how will these cells -- will these cells be able to reflect that?

In other work using motor neurons from patients with ALS, we have seen phenotypes that we think reflect the disease and that it turns out to be hyperexcitability. Patients with familial ALS, their motor neurons made from stem cells are hyperexcitable relative to controls. That enabled

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us to identify a cause, which is a reduced potassium current. We identified a drug that opens potassium channels, retigabine, which is an antiepileptic agent, and within 18 months of that discovery in my lab, there is now a 10-site trial looking at the effect of retigabine in patients with ALS.

This is not a single mouse study, which I've been devoting my whole life to doing mouse studies, but this approach enables us, so that at least if we could see a phenotype, I don't know if we can, but if patients who develop neuropathic pain -- and we know post-surgically some do and some don't -- if we could identify some phenotypic marker that reflected that disease risk and then we could screen for a treatment that could intervene in that, we can then test it. Ideally, if it's repurposing, it's much easier, but I think that's the exciting element of it.

When I did that first Pain editorial, if anyone had said to me that we would be able to make human sensory neurons in a dish and, also, genotype

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them and identify variants that may affect, it would have seemed total science fiction.

I think we have made enormous progress, even though some of the themes are a matter of going round and round in a circle.

DR. FREEMAN: Thank you very much.

We'll save some questions for the moderated session at 11:30.

Continuing on the theme of speakers who need no introduction, let me introduce Andrew Rice, who is professor of pain research at Imperial College London. Andrew has brought his unique creativity and vision to basic translational and clinical pain research. He has done phenotyping work, deep phenotyping work, in particular, on inflammatory/infectious neuropathies, but also HIV and carpal tunnel syndrome.

His work that is relevant to the presentation he's going to give is on determining the internal and external validity of animal models of pain. Andrew's talk is entitled "Preclinical Research Obstacles and Opportunities in Developing

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Precision Pain Medicine: An Overview."

Andrew?

Presentation – Andrew Rice

DR. RICE: Roy, thank you very much for that kind and generous introduction, and many thanks to Dennis and Bob to invite me here to give a presentation on one of the topics I feel most strongly about, and, also, for aligning it with a meeting where most of the preclinical scientists are on another continent, so I can actually be even bolder in what I say than what I normally am.

As Roy kindly mentioned in the introduction, I work both in the clinic, clinical research and clinical practice, and in animal models, and I'm not very quick on the uptake, but I've come to realize, after some 30-odd years of doing that, there is a lot of disconnect between the animal model literature and the clinical literature for what purportedly are the same diseases, and those are some of the aspects I would like to explore.

Can I have my first slide, please? I'm going to talk about neuropathic pain or use it as

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an illustration, and I'm going to talk about behavioral studies in animal models. That's because that's what I know about, but also because I think the concepts around that regarding preclinical research are largely generic. I think unless we get a really substantial change, animal models are still going to be the final common pathway of all the other fancy things we can do preclinically to try and identify new drug targets in terms of validating that before going forward to clinical development. I think it would be a very bold step if we go beyond that, and I can't quite see how it would work at the moment.

I'm going to talk about three areas of external validity. The disease models themselves; there is, of course, no such thing as a model of neuropathic pain. There is a model of a pain for neuropathy. The two are not the same. How we can use some of the things we now know as outcomes measures -- should actually be profiling measures, and, therefore, we've got to find new outcome measures. And then I'm going to talk about the

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susceptibility to bias in the design, conduct, analysis, and reporting of preclinical data, probably the easiest thing to fix but actually in some aspects, the most challenging, as well.

Let's start from a really cold position. This is the meta-analysis we did and treatment guidelines. And on the left here, you can see the first, second, and third-line drugs that we recommended for the treatment of neuropathic pain.

I think you would be very challenged to find any of these drugs that have been developed through the conventional route of identifying the target in animal models validating that before going to clinical trials.

Conversely, all these drugs do actually have efficacy in animal models as far as we know, and I think the two possible exceptions are Capsaicin 8 percent and possibly duloxetine, although the mechanism came from other fields.

We have some drugs that are modestly effective for neuropathic pain, but by in large, they were not developed using a conventional animal

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modeling technique, and that's an uncomfortable fact.

This group doesn't need to be reminded of these things, but I think it's important just to remember a few things about the definition of neuropathic pain and what we're trying to do when we're modeling the animal models. Most animal models, at least in the way they're reported, are shown to give 100 percent of the outcome measure. And that may be an ethically right thing to do, but we know it's very rare for patients with peripheral nerve injuries to develop neuropathic pain, maybe 20 percent.

Only about 10 percent of people with acute zoster end up with postherpetic neuralgia, whereas the animal models are generated to provide 100 percent outcome, at least in the way they're reported.

Really, we only measured the evoked pain, whereas in clinical trials, we tend to measure spontaneous, ongoing, or sometimes in conditions like trigeminal neuralgia paresthesia pain.

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There will be a lot of talk about sensory profiling in this meeting, but, of course, there are two broad concepts: sensory loss, which we might call anesthesia dolorosa, and then some phenomena of sensory gain. And pretty much exclusively, the animal models are active in the area of sensory gain, where certainly most of the patients we see and profile are predominantly profiles of sensory loss. So we're looking at two different aspects of the same problem.

Dealing first of all with the model, reproducing the disease, again, it's not a model of neuropathic pain. They're a model of neuropathies that may be painful. And as usual, Pat Wall, in 1979, was spot-on, and then we forgot what he said. So he came up with probably what was the first modern day rodent model of a traumatic nerve injury, a complete transection of the sciatic nerve, but he recognized this was a model of anesthesia dolorosa, in other words, pain and sensory loss, and not the sensory gain phenomena that every single other model ever since has

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focused upon.
Then in his second report, he recognized that you had to measure a complex behavior. This was autotomy, a self-mutilating behavior, that nearly all of us now don't think have anything to do with pain. It has probably to do with a desensed set limb, although Marshall Devor has some evidence that it may be pain related.
He was looking in a model of sensory loss for a complex outcome measure. But pretty much all the animal literature, until very recently, around neuropathic pain focused on one clinical condition, and that's partial sciatic nerve injury. Quite a small part of my practice and there's no ingenuity of my colleagues and myself in how many ways we can partially injure the sciatic nerve of a rodent. There are many of these models around.
If you contrast that with the vast range of conditions that may be associated with neuropathic pain, you can see that at best, we're probably only modeling one clinical syndrome that I think, in sensory response terms, is actually quite different

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than many of the other conditions we study in clinical trials.
I've been very lucky to be working with a group in Edinburgh headed by Malcolm Macleod, where we've taken on the challenge of producing major meta-analyses of animal model literature. Just for the neuropathic pain literature, we had to start with 65,000 publications, huge numbers compared to clinical trials. We've now whittled them down to only 35,000. But these are the ones we've screened so far. It's a fairly complete picture of these conditions.
In black, you'll see the reports of animal models of traumatic nerve injury in some degree, and you can see that they rule the roost. And certainly, in industry, chronic constriction injury has and probably still is the major model used. But luckily, as Clifford pointed out, we're beginning to see other perhaps more clinically relevant models being described.
There are questions around the diabetic models, but certainly some of the models of spinal

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cord injury, chemotherapy-induced neuropathy, we spend a lot of time looking at anti-retroviral neuropathies and HIV neuropathy. We are beginning to establish a portfolio of the conditions that we also do our clinical trials on.
That actually allows us to look at the heterogeneity of those models, because people tend to focus more on the homogeneity of those models rather than the heterogeneity. I'm just going to give you three examples from things we've done using different animal models.
This is a while ago now, but a gene microarray of rat dorsal root ganglion cells, and we took animals that had had an L5 spinal nerve transection. You can see that roughly 2 and a half thousand genes are upregulated and 2 and a half thousand genes are downregulated, and we externally validated those against other reports and similar models.
If you take a model of HIV neuropathy, you get a much lower number of genes going up or down in terms of their expression, which is probably

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what you'd expect from the severity of the injury.
What surprised us or didn't surprise me, but it surprised some of my colleagues, was that there's very little overlap. And actually, if you add in a model of varicella-zoster infection, there are only 14 genes upregulated between the 3 and 2 in expressed sequence tags. So either that is the magic bullet drug, but I don't think it is. I think the point we need to take from this is there's considerable heterogeneity between the animal models of these different conditions, and we need to spend quite a lot of time actually cataloging and documenting that and seeing what the differences are.
That also applies to the cell level, to the protein level. Here are three markers, ATF3 and GAP-43. ATF3 is, to put it very crudely, a marker of cell stress. GAP-43 is a marker of the ability of axons to regenerate. Neuropeptide Y and galanin are two peptides that have been associated with traumatic nerve injury, and certainly in the case of galanin, it is a, so far, failed drug target.

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Those go up in neuropathic pain at various different time courses, but when we look at a well-established model of drug-induced neuropathy, we can find no changes when the experiments were done exactly in parallel. So in other words, we see something in nerve injury that we don't see in another model that is purportedly associated with neuropathic pain.

The drug-induced neuropathy model is model of antiretroviral toxicity that's been well characterized from both the anatomical and the behavioral point of view.

Then thirdly, we were slightly worried about what was going on in the microglia arena. All studies that were done purporting to or which were showing increased microgliosis in the spinal cord following peripheral nerve injury tended to be done with histology-based techniques, immunohistochemistry-based, which require analysis of an image. Even with the best will in the world, you're beginning to introduce all sorts of biases there.

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So we did these studies. I haven't shown them with the histology, but the histology comes out about the same. But we also did the -- and the histology, of course, gives you lots of information about important anatomical facets by developing flow cytometry-based techniques, which provide better quantification of the cell numbers in response to a particular nerve injury.

For a model of spinal nerve transection, as you'd expect, there's an extensive microgliosis in the spinal cord, less for a model that does require some nerve trauma, but is essentially a model of neuropathy, and hardly any at all for drug-induced neuropathy or actually, most surprisingly to me, one of varicella-zoster infection. So again, the gene at the molecule and at the cell level, there seems to be differences between models associated with neuropathic pain that we need to catalog and take into account.

Why is this important? Well, of the just over 4,000 animal reports we've looked at for neuropathic pain, over 70 percent of those reports

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are in models of traumatic nerve injury, and the number will actually be much bigger than that if you take into account publication bias, because most of the work that has been done in industry will have tended to use those traumatic nerve injury models, at least historically, whereas if we compare that with the number of conditions studied in clinical trials, you can see that over 50 percent are done in diabetic neuropathy and postherpetic neuralgia.

Even if we add in amputation, we get only 8 percent of them have been done in the corresponding condition to which the animal models were justified. So what I'm trying to say is I suspect there's something of a disconnect.

I think the first challenge we have if we want to align, should we call it, late-stage preclinical work in animal models with what we need to know in order to conduct a clinical trial, I think we have to systematically develop and profile a portfolio of animal models that reflect the range of clinical presentations and the pathological

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heterogeneity of diseases associated with neuropathic pain, and that can only really be done in a sort of consortium or collaborative approach, I think.

How can we profile that? A lot of this meeting is going to be talking about profiling measures in humans. So conventionally, in a model of pain for neuropathy, we would measure the limb withdrawal thresholds to mechanical heat and cold. We all do it. It's very reliable. It's repeatable. But I just wonder to what extent we should be regarding this as an outcome measure rather than as a profiling measure, especially when you compare the wide range of domains which we collect information about in clinical trials of corresponding conditions.

If we look at this table that rather arbitrarily we've drawn up, really the only outcome you currently see in animal models these days is -- the situation is improving, as I'll come on to -- is evoked hypersensitivity. That's very, very rarely reported in outcome measure in clinical

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trials, certainly in the meta-analysis of what we've done. If anything, it's used as a phenotyping of baseline measure.

The usual outcome measure is continuous spontaneous pain, and a lot of very smart people are now trying to think how you can measure that in rodents, and it's by no means a trivial challenge. Then there are a whole lot of other things that, of course, impact on the outcome of a clinical trial that we never take into account when we're, if you like, doing our clinical trial in the animal model.

So should we be changing what are currently outcome measures into sensory profiling measures? Ralf and others are going to talk a lot more about this later on, but I just want to draw your attention to one point. In the diseases we've studied -- and we've done quite a lot of deep profiling studies now using the German Neuropathic Pain Network protocol, it's been a great collaboration with them -- you get these sort of profiles.

The one in black is traumatic nerve injury

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that Christoph Maier gave me. Red is leprosy. Green is HIV neuropathy, and blue is diabetic neuropathy. You will see that they share a common but in most cases -- and these are representative profiles of the whole group, but what has surprised us, including the diabetic neuropathy model profiling that we've just reported in Pain, is the lack of heterogeneity in terms of the sensory profiles within a single disease.

All these diseases tend to show loss of cold and warm detection. It's quite difficult to show loss of heat and cold pain detection threshold for either technical reasons about the normative data and the temperatures to which you can take the probes. But they show rather different outcomes in the mechanical measures.

The traumatic nerve injury is one of the few where you see a sensory gain phenomena, as well. But in terms of these neuropathies here, HIV and diabetic neuropathy tend to have a very similar picture, which is what you'd expect from a distal sensory polyneuropathy of loss of both mechanical

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and vibration threshold, whereas leprosy, which is one we have a special interest in, has a unique profile that we've never seen in another disease, where we picked up a profound loss of mechanical sensation relative or preservation of vibration detection.

We thought we'd been extremely careful, taking all this expensive kit to Mumbai, done lots of work there, and the wise leprosy doctors who have been studying this forever who told us, "Oh, yes, we knew that about 70 years ago."

(Laughter.)

DR. RICE: I think the other importance is to get the profiles of some of these very rare conditions. Dave Bennett and I are looking at -- Dave is doing most of the work -- the military condition called non-freezing cold injury, where people seem to get a hypersensitivity to cold and everything else is rather preserved.

I don't know if, Ralf, you'd agree that probably the one condition where you see a mixture of profiles within the disease is postherpetic

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neuralgia, and that's the one you used for your original paper. And I think that's an important point about discussing the homogeneity between these disease conditions.

Of course, we know, we'll talk about in these meetings, that it is now evident from clinical trials that measuring these kinds of things, conditions, pain modulation or sensory profiles, can, in certain circumstances or appears to, predict clinical outcome.

This is the oxcarbazepine trial from the Danish group. All I'd like to point out is the information we have from animal models at the moment only tells us about this sensory gain group, because that's all we measure in the animal models. We know nothing about these other groups.

We need to develop profiling tools for use in animal models, which are basically aligned with the profiling measures that you guys would like to use in clinical trials and clinical practice. The obvious ones to us at the moment seem to be sensory profiles, although we don't have a comprehensive

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sensory profile for animal models yet, because clearly we can't do all of them in animals, and some aspects of DNC stroke condition, pain modulation, but there may well be others.

If I've kicked out the outcome measures and made them profiling measures, where do we need to go for the outcome measures? This side is just meant to put a message very starkly, because you often hear people talking about measuring the symptom of pain in a rodent. And all of us remember the first day at medical school, there's a difference between symptoms and clinical signs. You can't measure symptoms in rodents. You can only measure the signs associated with their changes in their behavior.

It took me quite a long way to realize -- and if you look back, in some of our papers, we do talk about depression and anxiety in rodents, which are rather ridiculous concepts, actually, if you think about what the animals mean.

We need to think about what pain would mean in an animal's world, and that's where this concept

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of ethologically-relevant behaviors has come through. Certainly, I encourage anybody who's working with the animal models to go back to the classic textbook, this wonderful one by Barnett, still available on Amazon and everywhere else, a deep study of how rats behave in the wild. If you want to look at these rats in your laboratory, you should know what their natural behavior is.

Clifford, do I remember that Pat actually had a rat alive running around in his office for a while? I think one of the ideas was that he wanted to see how it behaved. But I'm sure there were lots of other reasons why he did it.

(Laughter.)

DR. RICE: Then, also, beware of anthropomorphizing human behaviors, particularly mental human behaviors. Alex Kacelnik, a field biologist from Oxford, has written very well on this. We need to see things in the rat's world. So you need to remember how rats live.

For those of you who don't work in this area, rats are very different to mice. Mice tend

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to be solitary creatures. They don't necessarily live in a big social group. Male mice fight a lot. Rats live in complex social systems where they eat, they watch out for predators, they clean, boys meet girls. The consequences of boys meet girls are dealt with in the burrow system, where they store food and seek shelter from predators.

These are complicated systems. Once these systems start breaking down, the rat colonies start breaking down. But I think what we have to remember is that rats and, for that matter, mice are prey species. So their behavior is related to prey species.

There just happened to be examples from our work, because there are a lot of people working on this kind of thing. This is one example. It's a behavior called thigmotaxis, where if you put a rat into a box, dark box, it will explore mainly the edges of the box. That's thigmotactic or wall-hugging behavior, but occasionally it will go into the central zone.

If it's exhibiting increased predator

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avoidance behavior, which is what you'd expect a rat in pain to do, then it will stick almost entirely to the edge of that, and that is indeed true, certainly in our lab, across quite a wide range of models in neuropathic and inflammatory pain, and it responds appropriately to pharmacology.

One of the problems with these kind of things, though, for any of you who have worked with them, is they are quite difficult to transfer from lab to lab. They're really susceptible to very minor changes in environmental conditions and things.

Another technique we came up with, with Nick Andrews, was to take Robert Deacon's work relating to burrowing, where we basically rely on the natural fossorial behavior of a rodent to maintain its burrow. Of course, we do most of our work on teenaged rats, teenaged male rats. So for all of the parents of teenaged boys, this is a completely flawed paradigm, because it supposes teenaged boys are interested in doing housework.

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(Laughter.)
DR. RICE: But apart from that, the paradigm is okay.
Basically, when a rat colony breaks down or rats become ill, they stop burrowing. So we have a very simple paradigm where we put the rat into a tube, and Nick showed with one nerve injury model, we showed it with another, that rats burrow less and that it's reversible pharmacologically. And a lot of other people have done that.
That allowed us to do something, because of the simplicity of this assay, that I've been wanting to do for a very long time through the mechanisms of the IMI Consortium, Europe Pain Consortium, and that's do a prospective multicenter study, including Japan and the United States, to try and validate burrowing as an outcome measure. Believe it or not, this has never been done in neuroscience before. It's never been done in pain certainly before, just to see if the same outcome measure works the same in all these different places when you do it to the same protocol. This

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will appear shortly in Pain. It was accepted last week.
Normal ways of validating a new model or outcome measure are haphazard. They're inefficient. They're uneconomic, and they're inherently susceptible to publication bias. So we could do this within a few months within this consortium, and it's why I'm particularly keen on consortium approaches.
I can't tell you the whole story here, but basically, we treated rats with Complete Freund's Adjuvant. The rats that had CFA, and we chose CFA because of a high possibility of spontaneous pain, stopped burrowing or reduced burrowing for quite some time and then that came back after a few days, whereas the sham and naïve treated rats maintained their normal burrowing behavior.
Now, that wasn't true across all centers. Most centers were able to reproduce it, but as we all know, in clinical trials, there are one or two centers that didn't have such success at reproducing it. But it gives us a chance to go in

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and see what the different factors were in that center. But the majority of centers reproduced it and on a group level, we've been able to prospectively validate a novel outcome measure, and that's never been done in the pain field before.
These complex behaviors, like burrowing, all they do is tell you that the rat is not well or he's not happy. Nobody will ever claim that these are pain-specific outcomes. So you have to validate the particular scenario you're interested in by showing that the burrowing behavior is reversed appropriately by analgesics that have known and known lack of effects on the appropriate clinical condition, and that, for example, Kris Rutten has recently done with burrowing.
The third challenge is to develop and validate a proper range of ethologically-relevant, being the important word, and pharmacologically-validated pain outcome measures to replace the things that I would rather put as profiling measures. And there are already a huge number of labs working on developing these outcomes measures,

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but unless they prospectively validate them in a multicenter way, it will take some time to sort out ones that do and don't work.
What I want to end up with in my last few minutes just talking about what should be the easiest problem to fix, but maybe the most difficult, and that is we can have all the animal data reported in the world, but if we can't believe it or understand the rigor to which the experiments were conducted, then one has to question, to be blunt, how much value it is. This is perhaps the elephant in the room.
We've just published a precise recommendation that is from the IMMPACT family. I think Bob and Dennis will agree this is probably the one where we had the most difficulty of any of the ones you've done in getting consensus, but we're slightly disappointed to hear that it didn't hold the record for getting to publication. There are a huge range of opinions in this area from preclinical scientists and emotions.
This was really started by a great friend of

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mine, Malcolm Macleod, in the stroke area, and he's revolutionized many aspects of preclinical stroke research by looking at these factors. He came up with what he called good laboratory practice and suggested a number of domains that are potentially associated with increased susceptibility to bias. And anybody who does a clinical trial is pretty familiar with all these.

We want to know really to what extent they're reported in the literature and how we can judge the veracity of a study in that regard. And what Malcolm showed is that the more these measures are actually reported, the less of effect size of a certain intervention there was. This was a drug that failed in stroke, NX-025, I think it was.

We have begun to look at this quite extensively, and it is difficult to get the information out. The worst journals to get information out of are actually the highest impact factor ones because of the way they report their information with the methods at the back. Doing meta-analyses on them is really tough. But this is

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CCI.

Of nearly 1,000 CCI publications, 29 percent of them say they had a blinded assessment of outcome, but they didn't. You can see the allocation of the animals to the operators; 25 percent randomized to drug, but less than 10 percent to model; 17 reported animal exclusions, but not necessarily the a priori criteria by which those exclusions were made, but that's still less than 20 percent; 0.4 percent report a sample size calculation.

We put these other two things at the end in because there are things that journals insist on now, and you can use them as a sort of metric with the journals.

If you were looking at that for clinical trials -- and, effectively, these animal studies are clinical trials in rodents -- I think you would be a little bit uncomfortable. But, of course, the CCI model was published years ago, so the quality score of the reporting must have improved over time. It's remained rock solid over time, and that

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is predominantly down to these last two metrics of outcomes.

We've also down a couple of other exercises that I've not got time to talk about, but the traditional metrics we use when deciding whether to read a paper or not, who published it, what university they were at and what journal it was in, impact factors are not a predictor of the study quality. Some of the highest quality journals, highest impact factor journals have slightly lower scores in that domain.

We also took the top five universities in the U.K., including my own, who generally performed worse than the other studies, the other ones in the U.K. Maybe that's why they're successful.

(Laughter.)

DR. RICE: We extended this across a number of other models, alcohol-induced neuropathy, chemotherapy-induced neuropathy, and, basically, these figures continue.

The other thing we've become aware of is that people often report that a study is blinded

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and there was randomization to groups and sometimes animal studies are even reported double-blinded, which tells you what you need to know about that study. So we took the metrics that are used for assessing clinical systematic reviews in Pain, originally developed by Henry McQuay, and applied them to a randomly selected bunch of things from Pain.

Whilst 30 percent, roughly, were reported as random or blinded, there was absolutely no detail of the randomization or the blinding method used in animal studies, and, therefore, they would have failed to get into a clinical systematic review. And we compared that to a larger dataset.

Two other forms of bias before I come on to the solution. The file drawer problem publication bias, we all understand it. There are ways of estimating publication bias. The statisticians are divided on the value of these. I'm not a statistician, but if you have effect size and you plot out each one of these as a single study, there's a reasonable assumption that it should have

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a normal distribution.
What you can do is called a trim-and-fill analysis, and in yellow here are the number of theoretically missing studies and you can see they're all on the negative end. This is for 700-odd animal reports of chemotherapy-induced neuropathy, and there's a secondary method called an Egger plot.
We only took the studies where some kind of intervention was being looked at, a new drug, a new drug target. The estimate from this publication bias issue is that there's a 53 percent overestimation of efficacy if you take into account the impact of publication bias.
Now, there are problems there, because pharma are unlikely to publish a lot of their early stage research, but that is still really quite a high distortion by publication bias. It's much larger than the effect size you would see in those studies.
There is no such limitation on clinical trials in neuropathic pain. In the one we've

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recently published in Lancet Neurology, you can see there's only a 10 percent overestimation of efficacy, and in a rather neat metric developed by Andrew Moore, really the only drug in the first, second and third-line ones that could be susceptible to that is capsaicin 8 percent.
To me, one of the most worrying things in this area is the exclusion of animals. When you're already dealing with sample sizes of 8, 9, 10, typical sample sizes found on model studies, to start excluding animals becomes rather difficult. Some people use a statistical measure where they say any animal lying outside two, or is it three, standard deviations, you can exclude. Others will openly tell us that they exclude animals and don't report them, because they know they're outliers.
Uli Dirnagl has done a lovely paper in PLOS Biology that I would recommend to you. He's done statistical modeling of this, particularly interested in stroke, and basically random attrition, where you just take any animal model, doesn't affect things that much. It reduces your

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statistical power, as you'd expect it to.
Targeted attrition of outlier animals has a huge effect, as you'd expect, on effect size, particularly when you're dealing with this very small number. So a nearly doubling in effect size just by going from 8 and 8 animals to a group to 5 and 8.
We need to know if people declare their studies, and part of that can, I think, be done by the rather poor way we show our data from animal studies. These group sizes tend to be quite small, and we tend to report them in bars with some kind of measure of -- error bar of variance there.
Many people are moving to box-and-whisker plots, which tell you a bit more. But with these small numbers, what we've come on to know is to give you the points for the individual animals, which is, I think, quite reasonable. You'd want to know actually, for precision medicine purposes, what's going on with that animal there, and I can also tell you that from a lot of studies, that animal would have been excluded.

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All I've been talking about is reporting. We don't actually know what goes on in the experiments, but until they're reported, we can't judge their rigor and their validity. The NC3Rs in Great Britain, it's quite a while ago, came up with a bunch of reporting guidelines. If you like, they're CONSORT for animal studies, and they've been widely accepted. Certainly, in the U.K., our major funding agencies require them.
They are quite clunky. Story Landis led a similar analysis in the U.S. a couple of years ago, and Shai Silberberg, who was just here, has been championing this approach at NINDS.
I think to take a less complicated and perhaps even more rigorous role, if I'm right, Shai, not only did you require data that's funded reported in this way, but anything people submit supporting a grant application has to be recorded in this way, which is a major step forward and I think probably slightly more easy to use than the ARRIVE ones.
DR. SILBERBERG: I think so.

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DR. RICE: This is my final slide. For these complex behaviors, we're using video recording. And rather like clinical trials, we think the time has now come that if you're publishing a paper with this, you should download the original video files for others to analyze.

We've just been the first people to do that in the pain area. We had to go to F-1000 Research to do that so other people can scrutinize it. They can reanalyze it. They can find different things, and they can test new paradigms.

The fourth challenge is to develop appropriate ways of conducting, analyzing, and reporting these studies, which allow you, after deciding to do a clinical trial, deciding which patients to do the clinical trial in for precision medicine, how rigorous those experiments are done. You can then perform meta-analyses of those experiments if they're reported using a similar format.

Hopefully, we can have a dream, which would be open access to all animal data so we can go and

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look for it. And this is just a summary of what I've said.

Thank you.

(Applause.)

DR. FREEMAN: Andrew, thanks a lot for that really illuminating talk. We're going to be thinking about double-blind animal studies for a while.

I think in the interest of time, we'll save the questions for the moderated session. Why don't you burrow your way to the coffee break and burrow back by 10:40, when we'll begin the second session? Thanks.

(Whereupon, at 10:19 a.m., a recess was taken.)

DR. FREEMAN: The second part of the morning session, it's a pleasure to introduce Dr. Michael Rowbotham. Again, we all know much of what he's done, although not all.

He's a senior scientist and scientific director at the California Pacific Medical Center Research Institute, and I think there are few

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people more qualified to talk about precision medicine from the clinical standpoint than Michael. I think his work with Howard Fields on the irritable nociceptor, which then was translated into topical anesthesia to treat postherpetic neuralgia, I think embodies much of what we are trying to move forward.

There are a couple of little known facts about Michael, which are worth mentioning as we move into the clinical sphere. The first is that he won the Mitchell Max Award at this year's American Academy of Neurology, which is a remarkable achievement and a wonderful award. The second is that he holds the record for surfing at the highest latitude. He surfed very close to the Arctic Circle waters, freezing temperature, and I think he is a suitable candidate for Dave Bennett's study on freezing injury.

(Laughter.)

DR. FREEMAN: So we're moving along. Let me introduce Michael.

(Applause.)

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Presentation – Michael Rowbotham

DR. ROWBOTHAM: Thank you. Before we get started, Bob tells me that I have an opportunity to propose an acronym, and Serge Marchand and Ian Gilron I saw last week at the Canadian Pain Society meeting and I promised them I would not talk about walls or Donald Trump. So that's it, no more on that, but here's an acronym.

It's a potential biomarker that might differentiate between clinical researchers and basic scientists. So how many people here are involved in clinical research? The majority. So there's a few basic scientists. They'll be a blood testing afterwards.

(Laughter.)

DR. ROWBOTHAM: It's called IMPACTIN, okay? Imminent pain clinical trial initiation. It's that little surge of hormones you get just when you're about to enroll your first subject.

(Laughter.)

DR. ROWBOTHAM: So we'll wait to hear about the biological basis.

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Can I have my first slide?
I'm going to talk about clinical research obstacles and opportunities for precision pain medicine. So this picture here, these are Fijian firewalkers, and lest you think they have some kind of a peripheral neuropathy that allows them to do this, here's what they look like. This guy's looking really concerned. He's only about halfway across the burning rocks. He's still got a ways to go.
You can see, this is not the Babinski sign for you neurologists in the room. This is, "My God, this hurts," and these are Fijians who really don't wear shoes very often and they do a lot of walking around on coral reefs and fishing and things like that, and you really rarely see them wear shoes.
I don't know if they iced their feet down before they walk across. I wouldn't be surprised if they do. But you can really tell they've got a little extra jump in their step by the time they get to the end.

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Things I want to talk about a little are just some definitions. Because there are many different ways of defining biomarkers in precision medicine, I think it's useful to take a second to look at that.
I want to talk about pain biomarkers versus cancer biomarkers, and I want to talk a little bit about things that have bedeviled us in the clinical trials area with the use of the 0-to-10 numerical rating scale as our primary outcome measure. That's really placebos and also about refractory patients, and then I want to end talking about pragmatic trials.
Some of the things that I'm going to say today may be not well received by some in the audience, but I just want to preface that by saying that it had to do with my experiences in the past seven years, having been recruited away from UCSF and running very much a patient-oriented clinical research center to leading a large and diverse research institute that has basic science almost exclusively in cancer biology, and then clinical

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trials in areas as diverse as transplant medicine, ALS and things like that.
It's part of a big healthcare system, Sutter Health, which is 27 hospitals across northern California, from very small rural hospitals to big academic medical centers like CPMC in San Francisco where I am.
It's the single largest installation of EPIC in the world. There's about 3 million patients, and when you're in a system like that, the way you approach clinical research is really very different than what we might be doing in more the purely academic setting.
So biomarkers defined. If you look at the NCI's website, the National Cancer Institute, it's clearly oriented towards cancer precision medicine. So it's biological molecule, also called molecular marker and signature molecule. That's on their website. That's how they define it.
Wikipedia, which is always my favorite go-to place for learning about just anything, is that they defined it in most of the same ways that the

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very nice FDA draft guidance that was sent as our pre-reads defines them. So it's an indicator of disease or some other physiological state. It can be a substance introduced into an organism to examine organ function or other aspects. It can be a parameter to assess disease progress or treatment effects.
Then what's really important for us here is looking at things like predicted biomarkers, which would indicate the probable effect of treatment on the patient, or if a disease already exists, but it has to be diagnosed, a diagnostic biomarker, or something about the patient that tells what their likely natural history is to be, such as a prognostic biomarker. Then I think very important for those of us in this room are drug-related biomarkers that indicate whether or not a specific drug will be effective in a specific patient and then also things like PK and distribution metabolism, how the patient's body will process it.
We need a PrM approach, precision medicine approach, and for that we really need pain

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biomarkers. I think therapy for chronic pain is really never going to move very far forward for as long as we have a 0-to-10 numerical rating scale as our primary outcome measure.

When I talk to my colleagues who are oncologists and doing cancer trials, they have really good endpoints: disease progression that's easy to measure on scans, death, stuff like that that nobody really argues about whether or not the patient had the outcome or not.

We're instead looking at things where you have these false equivalences. For example, these are two studies we had going on at the same time. We had a clinical trial for patients with chronic severe postherpetic neuralgia, most of the patients in their 70s, as you know, pain on entry averaging about 6 out of 10.

At the same time, we had this minor sports injury trial where mostly young people got hit by a baseball playing in the park, fell off their skateboard, bike messengers crashing into stuff, which happens a lot in San Francisco. Their pain

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on entry is 6 out of 10. Their pain is going to go away in the next week or two, and it's a very short-term trial, but yet, they're rating their pain 6 out of 10. So if you look just at the numbers, they're equivalent, when we know that there's really nothing at all equivalent about that. That really tells us something about that as an outcome measure.

We need this precision medicine strategy for subject selection to maximize the value of enriched enrollment studies and to enable pragmatic trials, which I'll talk about at the end, where expert examiners are not available to evaluate and screen all the patients. When you really want to do large, large studies, 500 patients, 1,000 patients, 2,000 patients, there's limits on what you can do in screening each patient.

We also need surrogate measures of response that are objective and responsive to what happens to the patient.

So how do you assign a relative value to different biomarkers as we look to incorporate this

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into precision pain medicine? Well, the best are ones that are low cost, easy to obtain prior to study entry and then serially during a study, and that are really minimally invasive. So what that means is basically blood tests.

The worst or the ones that are the most difficult to really implement are ones that are very expensive, very equipment-intensive, that are invasive or that entail other risks, that require highly trained experts to implement and that also rely on patient reports, which we know are subjective.

The highest values ones are ones that are going to predict individual response to a treatment with a low false positive and false negative rate, and it reflects the current state of the patient with a reasonably short lag time.

For example, if you were doing a study of just diabetes management, you wouldn't ask the patient so much how they're feeling, you'd measure the hemoglobin A1C as a composite measure of how well their diabetes has been controlled in the last

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three to four weeks.

We need things like this for pain to act as a surrogate outcome measure so that we're not so dependent on the patient-reported outcome.

Now, measuring propensity to develop chronic pain, so that acute-to-chronic pain transition, is important, but it's, I think, for the purposes of this meeting, of less value compared to predicting response to treating ongoing chronic pain.

Then, also, one thing that's visible in a lot of the literature are correlation plots between a biomarker or phenotyping or something else and drug response within a group of patients, but that's a much lower bar to get over than something that predicts individual patient response. This is really something where the cancer biomarker field is so far ahead of us.

So what are pain biomarker candidates? What types of things? So skin biopsy would certainly qualify as an objective measure, but thus far, it's only weakly predictive and it's difficult to -- it's not difficult to get the skin biopsy,

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but the actual analysis and processing is expensive and slow and involves uncertainties, especially when you get into double labeling.

FMRI and other brain imaging techniques qualify, but they're costly and they're logistically complex. It's certainly not something you can drive out to a patient's neighborhood and do the testing near their home. They really have to come to a very specialized study center to do that.

Phenotyping using QST, sensory exam, provocative tests like capsaicin response or delivering some local anesthetic to an area, those all depend on patient response. They're fatiguing. There's a lot of training that's involved with both the investigators and the patients how to do it. It's not something that can be done in a community setting.

Doing a composite phenotyping approach is still likely to include patient-reported measures. So things like genomics and other omics, including what Clifford was talking about earlier, developing

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IPSCs, they're objective, but it's still really in its infancy. There's a lot of promise in this area, but we don't have an IMMPACT equivalent for them yet.

Another way of enriching populations is doing things like intravenous infusions of different compounds or other kinds of very short run-in treatments. Those help enrich the populations, but they add a whole other layer of inclusion and exclusion criteria, expose the subjects to the risk of not just the experimental drug, but the drug that's being given to help select subjects. It certainly adds some risk, and it definitely adds a lot of expense to conducting a clinical trial.

I think you could even say that given how we're characterizing patients beyond just diagnostic differences -- it's pretty easy to tell who's got PHN and who doesn't, it's pretty easy to tell who's got diabetic neuropathy and who doesn't, but are the populations that we're actually studying now homogenous enough to use for omics

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type of research and other biomarker discovery and validation research. I think we need to ask ourselves that question.

In contrast, what about cancer biomarkers? So now almost all new treatments are targeted treatments toward tumor-specific abnormalities, usually a mutation or some way in which the tumor is able to evade the immune system. Generally, the drugs are developed as a biomarker and therapy pair. So the biomarker tells you something about the treatment target, and then the treatment itself is very specific to that target.

There's been some very nice meta-analyses published in the past year or two showing the overall impact of this kind of approach on outcomes across a wide variety of cancers and involving upwards of 600 studies. The impact is really very, very clear. Survival is much longer. The time of disease-free state is much better.

The other thing is that the trials often are quite specific in the title about who they select, and so response to prior therapy is usually part

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not just of the inclusion/exclusion criteria, but actually even in the study title.

But there's limits to cancer biomarkers. One is even though many of these things are available now, the uptake in clinical oncology practice is not quite what you would think. Most of the treatments are still based on older style pathological examination and staging, and the molecular markers, the mutational analyses are only done in patients who are refractory or patients who happen to be coming to an academic center.

So many of the patients who would qualify for a targeted therapy aren't actually investigated to see if they have the right mutation. They go through really a very standard guideline-driven chemotherapy protocol.

We don't really know that well yet what the total universe is of patients who might be eligible for targeted cancer chemotherapy.

There's a very interesting study that's about to restart after its first iteration. This is the NCI MATCH Study or Molecular Analysis for

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Therapy Choice. The first iteration of this required patients to have a fresh tumor specimen sent to NIH for evaluation and doing a mutational analysis and seeing if the patient had any of the mutations that would allow them to match with one of the chemotherapies that they were going to provide for free, because as I think many of you know, these new targeted chemotherapies are extremely expensive, 60 to $100,000 just for a few months of therapy. If a patient's going to be on it through several courses over a year, the cost can be -- or on combinations of targeted therapies, the cost can easily exceed 200 to $250,000 in just one year.

The problem was in the first iteration, they had about 10 drugs that they were going to offer, and they evaluated a large number of patients. In fact, Sutter Health across our cancer research consortium, we enrolled or we submitted fresh tissue from 55 patients to try and get people into this study. Only one qualified, and by the time all the analysis came back, the patient was far too

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ill to be in any kind of a clinical trial. Really, at that point, they were on death's doorstep. So that's a problem, the time lag.

The other is that overall across the country, they only had 5 or 10 percent of patients who had submitted tissue actually had an actionable mutation with their list of drugs. So they expanded the list of drugs to 24 drugs. They now allow you to use the archived specimen that's kept in the pathology departments, but even with that, they only expect about 23 percent of the people for whom archived tissue is submitted to actually have a mutation that matches them up with one of the therapies. So the promises that you have a specific abnormality that's driving your cancer, you get a treatment targeted to that abnormality, but that still leaves a very large number of patients kind of with nowhere to go and really more non-selective, older style chemotherapy.

I'll talk a little more about this at the end in terms of pragmatic trials, but it's a different approach. We're trying to figure out how

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to treat all patients with chronic pain. This NCI MATCH, that molecularly-targeted cancer therapy, is trying to cherry-pick the best candidates and get them on treatment and the rest they worry about, but that's really more in the province of the clinicians and not so much in the research realm.

Here are a couple of issues that continue to be problems given our current outcome measures, and that's placebo controls. So can we really trust placebo controls? I know there's been a lot of talk at IMMPACT meetings about how to manage the increased assay sensitivity and reduce the placebo response.

I'm going to show you two examples, one where placebo increases efficacy and the other where it loses efficacy.

This is from a paper that was put together from data that Steve Quessy was able to get from a number of different companies, and there are two things that are apparent in this work. One is that the placebo response differs by condition. The percentage reduction during placebo treatment is

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much greater in patients with diabetic neuropathy, about 26 percent, compared to patients with postherpetic neuralgia at 15, 16 percent. That's not just across a single study. That's across a whole group of studies for each disorder.

The other is that the response to placebo isn't something that accrues right away and then is static. It seems to increase over time. So that as trials become longer and longer, if the FDA starts requiring every pivotal phase 3 trial to be six months long, if you see this trend here, what happens is that at some point, active treatment and placebo treatment will become very difficult to distinguish, because the active treatment benefit tends to accrue fairly early in this study, the first couple of weeks, and then levels off, whereas placebo starts out without much benefit and then it seems to get better and better over time. Then at some point, when the curves converge, given the way that clinical trials are analyzed, you end up with no significant difference between the two treatments, because it's not an area under the

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curve analysis.
The other is what happens if you follow a completely different design with multiple exposures, and this is a paper from 1989 by Fedele, where they did a five-period enriched enrollment design. What they did is they selected patients who responded to placebo for dysmenorrhea, and this was in the early days of NSAIDS. So what they did is they took all the placebo responders and then enrolled them into a -- either to be getting an NSAID during each menstrual cycle or to get a placebo during each menstrual cycle, and it was going to go through five cycles.
They ended up stopping the study at the end of four cycles because while NSAIDS stayed pretty good through all of them, by cycle 4, only 11 percent responding to placebo and they were facing very steady subject attrition in the placebo group. Basically, none of the women wanted to come back and participate in it any longer, because it was clear to them that this was ineffective therapy.
This tells us something about periodically

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exposing people to placebo as opposed to giving people placebo at the beginning and then just keeping them on that throughout the course of a long clinical trial.
Efforts to try and reduce the placebo response have relied on these patient-reported outcome measures like the 0-to-10, and it really can't substitute for a more precision medicine approach.
Some things are obvious, like increasing training of both subjects and investigators, and Nat Katz has talked a lot about that over the years and done some very good work.
Excluding subjects with very high baseline pain is something that Bob has expressed an interest in and I think is a good idea, because patients with 10-out-of-10 pain are really different than patients with 8-out-of-10 pain.
Then things like dropping placebo responders, which means that you have to have a really good definition of what's a placebo responder. There is no numerical definition, and

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especially with a 0-to-10 scale, in a single-blind run-in period, it's really hard to tell whether or not excluding placebo responders actually benefits your trial or actually hurts it.
That's really something that is almost exclusively a problem of the way we do trials now because we are relying on this 0-to-10 outcome measure.
The next thing I want to turn to is what happens, who should be getting into these phase 2a trials, and there's some important lessons -- I'll show you the data in the next slide -- from the epilepsy field. So one is that patients who come from academic sites, they tend to be really refractory or what people would consider hopeless cases, and it's becoming more difficult to find completely untreated patients.
We did a study of untreated postherpetic neuralgia patients. It took about eight years to fill the cohort because most of the patients, by the time they get to an academic pain research center, they've generally undergone quite a bit of

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treatment.
The ideal subject, though, is someone who's healthy, without obvious drug contraindications, and relatively treatment naive, but I think from a number of perspectives, putting them on an experimental treatment, especially in a phase 2a study before trying the FDA-approved alternative really falls below the standard of care. You would not want to be on the witness stand in a legal case defending why you put the patient in a phase 2a clinical trial without having tried any of the FDA-approved alternatives first.
Would a validated objective biomarker be able to resolve this conundrum? I think that's an unknown, but let me just show the data on what happens in epilepsy.
This is a study that's been going on for many years. Patients with newly diagnosed epilepsy treated with the first anti-epileptic drug, about half become seizure free.
So then the ones who are uncontrolled still get a second trial of monotherapy with a different

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drug, and you pick up a few more becoming seizure free. Then you go through the third iteration of this. You pick up just another 1 percent, and then you start going to double therapy, combination therapy and you pick up a few more.

So that at the end of this really four sets of distinct trials of single and monotherapy, you end up with 36 percent who still have uncontrolled seizures.

These are the kinds of patients, I think, that we tend to see in the pain clinics. The average number of prior drugs that patients have tried before they see me in clinic is far more than three or four. It's usually everything you can think of alone and in combination. So these are probably not the patients that we really want to be recruiting.

What's interesting in this work is that it made no difference which drug you started with, whether or not it was an old drug or a new drug. When they updated this dataset in 2011 where they were up to over 1,000 subjects and where many new

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drugs had come along since the project started, the failure rate, meaning uncontrolled seizures at the end of this, had only gone from 36 percent to 32 percent. So despite having that many new drugs, they still couldn't figure out how to manage these patients.

The question is do we want to focus in on these newly diagnosed pain patients who are treatment naive, or do we want to have all of our trials really be in this group?

Are there trial designs that are not compatible with the precision medicine approach? I don't think so. I think they really pretty much all are, including ones that have become quite en vogue these days, like the EERW, enriched enrollment and randomized withdrawal design.

If you have a biomarker that's used for screening and then also as an outcome measure that's, let's say, a blood-based biomarker, it's no problem at all, especially if it responds in a fairly short time lag to the effects of treatment. You can easily measure it serially as you go

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through the initial treatment period where everybody's exposed to the active therapy and then again when they go through the randomized withdrawal phase.

What about rescue analgesics? So those are a real problem in clinical trials, because if you have a highly effective rescue drug, you're reducing the treatment effect size on your 0-to-10 scale. It's a big confounder. So if you give people liberal rescue, they may say this is great. This placebo is working fantastic, right? I may be taking five or six or eight codeine a day as rescue, but that seems to be controlling my pain and I'm much better than when I started in the study.

But would this actually extend to a surrogate outcome measure? So if the outcome measure was really more mechanism specific and was not going to be affected spuriously by the use of the rescue analgesic, it might get us out of this particular problem.

Would it extend to some of the techniques

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that we have available to us now like brain imaging or our skin biopsy or electrophysiologic techniques, or would it have to be something like a blood-based marker? That's still to be determined.

This is my last slide. I want to talk a bit about pragmatic trials. So these are effectiveness trials, and they're different from explanatory or efficacy trials. They take place within medical practices, not in specialized study centers. The research patient actually never leaves their ongoing care situation.

These are the kinds of studies that you can do in big integrated healthcare systems. So you can do them in Kaiser. You can do them in Sutter Health. You can do them in Intermountain West. Any of these big conglomerates that have dozens of hospitals in one or more states are really set up, built around electronic health records, and with a large proportion of their patients in a primary care practice. And the primary data platform is really the electronic health record.

You can do randomized controlled trials with

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this with a cluster randomization technique. So for example, if you have 20 hospitals or 20 practices and you pick 10 for the experimental intervention and another 10 that are equivalent in every other way in terms of what kinds of patients they see, you can assign the one group of 10 practices to treat pain a specific way or with a specific drug and the other 10 continue to do what they're doing or they're giving their patients a placebo.

The consent may be at the subject level, but it may be, depending on what you're trying to do, it actually may be at the level of the practice. You don't have to actually consent patients on an individual basis.

An obvious one would be you're introducing a new MRI machine and you want to see if the accuracy of diagnosing something is better. Well, you don't have to really ask the subjects, but you look at the 10 centers that have the old MRI machine compared to the 10 centers that have the new MRI machine and you look at some kind of standardized

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metrics, that's a pragmatic trial.

In these kinds of studies, the cost per participant is much lower, and you can recruit large number of patients. You can recruit patients using an entirely Internet-based approach. So EPIC and most of these other electronic health record systems now, with patient consent, they can enroll in sort of a My Chart or My Health Online or some other kind of thing like that that allows them to email their provider, allows them to see their medical record, and it allows them to be contacted to see if they want to participate in a study.

If they want to participate, they can then go to a site that contains questionnaire data or other kinds of screening tools. They can set up an appointment through telemedicine to be evaluated for participation in this study.

The consent form can be delivered electronically. They're already in the system behind the firewall of the electronic health records, so there's no issues really with what their identity is. You really already know who

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they are and they've already consented to be contacted that way.

You can do this entirely that way, and thank you spell check, once again, every time I put in EHR, it changes it to HER. It's hard to get that turned off.

You can do a lot of your research visits using telemedicine. So you kind of release the restrictions that come along with having to always do everything within study sites.

Here's where the precision medicine approach is. We need to have ways of doing this, because if you're working in a very large health system, you really can't realistically do the kinds of very complicated QST and other sorts of phenotyping techniques, skin biopsy, all those kinds of things when you're trying to screen 1,000 patients with chronic pain to enroll them into a trial. But if you have something that you can use as your screening tool that allows you to confidently pick out who the subjects could be, you can enroll 5 to 10 times as many patients per dollar as you would

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using the more traditional approach.

There's probably better generalizability, because you're not screening for people who are able to travel and are willing to travel. You're really getting much closer to the community level where most pain treatment takes place anyway.

I'll stop there, and thank you for your attention.

(Applause.)

DR. FREEMAN: We'll have a handful of quick questions and save the tough ones for the moderation.

John first, then Lee.

DR. FARRAR: Nice talk. I appreciate a number of the things that you -- I'm sorry. This is John Farrar. I apologize.

Very nice talk and covered a lot of territory. The one area that I would ask a little bit more clarity is in talking about placebo and placebo response; that we just keep very specific the fact that what you're discussing in the data you presented is the response in the

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placebo-treated group. It is not the mind or brain-body placebo response that is in really some ways an active form of treatment.

The issue about dealing with run-ins and others is that we are excluding patients who basically get better over time for a variety of reasons. So I think we just need to be very careful about the definition there, and I wondered what your thoughts were in terms of the data you presented as to what the groups were.

DR. ROWBOTHAM: Yes. So let's say you set a criteria that if a patient, during a single-blind run-in, has their pain go down by 30 percent with placebo, single-blind run-in. So there's lots of opportunities for the study center personnel to unblind the patient, which they often do because they're not really interested in the patient the same way during the placebo run-in period than they are once they randomized to active or placebo.

The bigger one is how do you know that that patient that you're going to drop because of the 30 percent response wouldn't actually have gotten an

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80 percent reduction with active treatment. You've dropped him. You'll never know.

How do you know that you're not excluding all those patients whose pain is responsive, can fluctuate, and just selecting for those people who 9 out of 10, 9 out of 10, 9 out of 10 every day. Nothing evokes the pain. Nothing makes it better, et cetera, et cetera, as you do those studies. So that's really what I'm trying to get at with that.

Then the other is if you look at curves, in trials even going back to trials of tricyclic antidepressants, generally, the pain reduction with active treatment accrues pretty quickly, whereas the reduction in pain with placebo tends to accrue quite slowly. So if you do an area under the curve analysis, you'll see a difference. But if you're doing sort of beginning to end as just that endpoint analysis, if the placebo starts to gradually catch up and it could be the milieu, the TLC they get from the study staff, et cetera.

I agree with you that placebo is an active intervention. You end up with this close enough to

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the same point by the end of the trial that any treatment difference has been removed.

DR. FREEMAN: Lee, then Troels, then we'll stop. Lee.

DR. SIMON: Lee Simon. Very nice talk. I just wondered if you could expand about that a little bit more and how you interpreted this rising placebo response rate over time in the context of the rescue therapy, which a lot of people forget to impute in the context of outcome. Are you at all taking into consideration the fact that they are on rescue and then asking the question are there more patients on rescue with placebo than on active therapy, or are they imputed out and they're not actually in that dataset so that you're actually seeing real placebo rising response as opposed to getting better because everybody's getting rescue?

DR. ROWBOTHAN: Good question. There's limitations in the dataset. Basically, Steve Quessy got a variety of companies to submit their data, and it was really more top level data and not data that included the rescue.

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We do know that some studies are hopelessly confounded. When the placebo group is using significantly more rescue than the active treatment group, then it becomes just impossible to parse out how much of the difference is due to the rescue analgesic.

DR. FREEMAN: Troels?

DR. JENSEN: Thank you very much. So I have a question. I had a little difficulty in understanding the comparison between cancer and pain. I can understand it in a way if we are talking about an acute pain condition, but in a chronic pain condition, we know that the pain system is so dynamic. So even one specific condition, even one such as postherpetic neuralgia, when it becomes chronic, there are so many other comorbidities that it's going to complicate the clinical picture.

We can understand it for erythromelalgia that we can define a specific mutation and so on, but when it comes to other chronic pain conditions, I think it may be difficult to find these, because

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I think we're going to be confused by the chronicity of the condition and the dynamic nature of the pain system itself.

DR. ROWBOTHAM: Yes. You're exactly right. There's some natural advantages that the cancer field has. One, you find the tumor on imaging, you take it out. You can analyze it. The tumor is following its own pathway. You can look at tumor-specific mutations. It's not something you can readily do in a pain disorder.

You have serial biomarkers. The latest ones to just be approved are what's called liquid biopsy. You're looking at circulating tumor DNA as an initial measure, and you can pull out the tumor-specific DNA from the large amounts of circulating non-tumor DNA. You can follow that as an outcome measure.

There's certain natural advantages the cancer field has that the pain field will never have, because what we're really talking about is two patients have shingles. One ends up with severe postherpetic neuralgia. The other resolves

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completely.

From our own natural history work, it's really hard to tell early on which path they're going to go down. Some of the ones in our natural history study, at two or three months, they looked terrible. I was absolutely certain that they were going to be in terrible pain at a year. We saw them in a year or in six months, no pain, completely gone. Still had some sensory abnormalities, things kind of slowly resolving.

I don't know how to -- and that's really much of the purpose of this meeting is how are we going to figure out predictive markers or prognostic markers, who's going to go which direction, and then figure out with that prognostic marker what the intervention needs to be in order to put them back, move them to the path of just resolution over time.

DR. FREEMAN: Thanks very much, Michael.

(Applause.)

DR. FREEMAN: It's a pleasure to introduce the last speaker, Dr. William Riley of the NIH.

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Dr. Riley is the director of the NIH Office of Behavioral and Social Sciences Research.

Now, Dr. Riley will feel right at home here at ACTTION with two Ts or is it two Cs and IMMPACT with two Ms, because -- and I'm not making this up -- the office that he directs has the acronym OBSSR. So you should feel very welcome over here. I think even Bob and Dennis will be willing to accept that that's not a bad acronym.

He's been at the NIH since 2005. He's had a variety of missions while he's there. He's been the health scientist administrator and deputy director in the Division of AIDS and Health Behavioral Research at the NIMH; program director at the NHLBI; chief of science and research technology branch in the Division of Cancer Control and Population Science at NCI.

His special interest is in mobile and wireless technologies, as to how that relates to clinical research. So it is with great pleasure that I introduce Dr. Riley.

(Applause)

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Presentation – William Riley

DR. RILEY: You guys are good. You got clapping at the beginning, as well as the end. Thank you all. And I've enjoyed, to the degree that I've been able to stay focused and not have to bounce back and forth between conference calls this morning, getting up to speed on some of the pain research and that sort of thing. So that's been really useful, and I hope to be able to do that as much of today as I can.

I'm going to focus this on the Precision Medicine Initiative and walk you through where we are right now and the things that we're doing, tie it a little bit to the pain work that I think is possible to be done within the Precision Medicine Initiative, and move us forward from there.

As we already talked about, the President announced this about a year and a half ago now. I was working on this project before that. There are not many ways that you can be fired in the government, but one of them is to upstage the President. So we had to be fairly stealth and

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quiet about our work until he announced it in the State of the Union about a year and a half ago and then soon after that in a White House event.

At the same time that that announcement was made, this was the initial publication in the New England Journal of Medicine from Frances and Harold Varmus, who was then the NCI director, about the vision of a new Precision Medicine Initiative.

It's a really nice overview, and I think, for the most part, we've carried this forward throughout.

Subsequent to this, there were a number of workshops and an advisory committee to the director on precision medicine and a report from them, and we've tried to follow that fairly closely along the way, and I'll try to give you a sense of where we are as we move forward.

Let me, as a start, point out -- and Michael talked a bit about the NCI MATCH program. There's a little over $200 million in FY '16 going to the Precision Medicine Initiative at NIH; $70 million of that goes to NCI. It is actually to accelerate their NCI MATCH program and some of the precision

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medicine pharmacogenetic studies that they're doing there. About 130 of it is going to the research cohort or the cohort program, and that's what I'll focus on, because that's what I've been spending most of my time on.

Not a lofty goal at all, a million-plus volunteers in the Precision Medicine, and actually "plus" is the important part of that. A million is our minimal. If we don't get there, we will have not succeeded, coming from two places, from health provider organizations and then from direct volunteers. So one of the things that the President has made clear is that he wants anybody, including all of you and your brothers and sisters and mothers and children and everyone else, to raise their hand and say "I want to be a part of the Precision Medicine Initiative and be able to participate in the project." So that's been one component of this.

The one thing that I think has been really interesting and exciting about this is the degree to which participants are going to be involved in

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this. We've been able to sort of think about how we use technology to give them back information much more readily than we typically do in most studies. So as opposed to when I was doing clinical research, we sent a newsletter out every six months to the participants in the study about what we were doing, here we're able to actually get people almost real-time feedback about the data they provided us in some summary form that we might not otherwise be able to do, tell them when researchers are coming in and using their data for a particular project or purpose, re-contact them over and over again as necessary for additional studies moving forward to do that, and incorporate their feedback in how the study's being run and how we can keep them engaged in a long-term project that's going to last 10, 20 and hopefully even longer than that.

This new model has engaged participants in responsible data-sharing with the appropriate privacy protections along with it as, well.

This is, obviously, not a new concept.

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We've been doing this for a lot of years, as many of you have talked about already this morning. It's something that the pain management field has been doing for a period of time, as well. So whether it's been prescription glasses or blood transfusions, we don't do sort of the mass all things are good for everyone, but specify our treatment to the specifics of the individual moving forward.

So none of that's new, and I was actually perseverating when I was doing slides. So I realized I did that twice.

I want to take you back a little over a decade, though. This was my boss' perspective back in 2004. He was criticized for proposing this back then because we weren't quite ready to do this work, to put genes and environment together in such a way that we would understand better how people respond to treatments and how those things work moving forward.

At the time that he proposed this, it would cost us about 10 mil to do GWAS as opposed to about

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a thou. Only about 13 percent of EHRs in non-federal acute hospitals had an electronic health record at the time. The Office of National Coordinator had just been created back in 2004, so we had a long way to go in being able to use EHR as a platform for the work that was being done.

We had summary self-measurement, self-report measures, but new things such as the PROMIS Initiative, the Phoenix consensus database of measures, those types of things were just beginning to start functioning, and we now have, I think, much more precise and much more accurate self-report measures that we've had in the past, as well as the ability to co-calibrate them so that we're at least sort of tying some of these things together on the same metric as opposed to having different metrics for different tools.

The actograph, the first research grade accelerometer, came along in about 2004. So our ability in terms of sensor technology, especially in the last three, four years has really exploded. And our ability to be able to use those passive

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sensors to assess behavior, assess it in context, assess a variety of sort of phenomena, physiological and otherwise, has really changed over the years.

I have to tell you, this Caltrac was one of the first studies I ever did, and it just blew up because -- this was back in the late '80s. I was trying to actually track psychomotor retardation in depressed patients using a calorie accelerometer. It didn't work. It was terrible because the technology was so bad. So every time I see that picture, it reminds me of one more study that went bad over the years.

Then if you were really cool in 2004, you had a Motorola RAZR, right? This was your smartphone. It wasn't a smartphone, but it was about as cool as you could get in 2004. The number of apps you could buy in the app store for your iPhone was zero, because there was no iPhone until 2007 and then no Android until 2009.

So a lot has changed in our capability in communication technologies and other types of

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technologies to be able to do the kind of work that we're thinking about doing here moving forward.

The components of this are that we have this patient partnership that we're trying to develop as part of the Precision Medicine Initiative, using electronic health records as our base of the data that we can get, and I'll talk a little bit more about that, because there's, obviously, some challenges in that process; all the technologies that we can actually bring to bear and utilize them, to the degree that we possibly can.

Again, if I'm telling you that 10 years ago that it was this bad, then we also know that 10 years from now, we'll look back and go, "Boy, this technology was really bad, as well." It's dated and obsolete. So we also have to be able to keep up and keep moving forward and co-calibrate newer technologies with older ones as we move forward over time.

This can't be a static cohort project. It can't be one where we lock it in place in 2016 and say this is the way it's going to be and it will

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never change again. There's got to be versioning of it and improvements on it as we move forward.

The genomic piece, as well, obviously, and then a really significant piece of data science when you've got all this data coming in and flowing in with over a million people, so a lot of work that needs to be done there as well. Fortunately, for us, our associate director of data science, all the people who do this kind of work at the NIH have been really focusing again on big data and computational approaches that allow us to do some of that work.

Since I'm the behavioral and social scientist at the NIH or at least the person who's the face of it, I have to at least say a word or two about behavioral and social sciences and their importance here, and it's related to some of the earlier points that were made today.

I think it's really critical that we recognize that this project is much more than genes and drugs and disease, that it is looking at the full scope of the environmental and social

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influences and all the other factors that are influential in health moving forward. And we're not only looking at genetic markers.

Now, I understand why it's easy to think that. It's what everybody has used to say this is why we need to do this work. At the White House event in February, most of the stories that people told in that White House event were people who had some rare genetic sort of disease and all of a sudden, someone miraculously found the cure for it and they got better. Part of that is because it's really hard to find somebody who can tell the story of "I was having all this potential heart disease and that sort of thing, and then they did indoor smoking bans and miraculously, I didn't have heart disease anymore."

You can't tell those kinds of stories very easily. So it's difficult to do the behavioral, social, environmental end of the spectrum even though -- and that's a really nice story, by the way. Indoor smoking bans across the board produced about a 15 percent reduction in MIs in the year

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following that smoking ban, and one really nice county allowed us to do a reversal of that, because they put the smoking ban in place. Then all the restaurants and bars screamed about it. So they removed it for about a year or two, and then they put it back in later. So we had a nice reversal design in which their MI rates went down and then they went back up and they went back down again.

There's a lot more things like that that we can do along the way. But the critical piece here is there's a fair amount of behavioral and social science work that's going on in this space, as well.

Regarding behavioral interventions, again, it's not new to us, as well, that we've been doing tailored and personalized precision treatments. Precision is now the new adjective, right? I will in advance apologize on behalf of the NIH that we've now made it the adjective that people put in front of every medicine noun that we have. So who knows what it will be later on, but right now, precision is the one that we're currently using all

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the time.

The tricky part for the behavioral interventions, the nonpharmacologic interventions for pain included, is that it's more than just trying to figure out for whom this particular treatment works versus not, but also what context that treatment tends to work, because that's also one of the other problems that we have, is that the same intervention that didn't work for this person at time A will actually work for them at time B. So how do we understand context and prior experience and how those influences are part of that?

The letters on the right are just in time adaptive interventions or ecological momentary interventions. It's the concept that we're able to deliver these things now in context and in real time, which we weren't able to do in the.

Then in what combination and which sequence? One of Michael's graphs, the epilepsy projects is a really nice example actually of almost a smart design, a sequential, multiple, random assignment

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process. At each point where someone makes a cut, you then re-randomize and you make another determination. So there's these various cut points along the way.

So there's some nice designs that allow us to understand combination and sequence, and, once again, behavioral interventions are one of those where we have multiple components, not just one active ingredient, so it makes it complicated.

Then a lot of things that we have to do, but one of the critical things is we need to have more and better longitudinal data. So my last behavioral slide, but I do want you to recognize that I think we're at a dawn of a really new behavioral science, and this includes measurement science, as well.

We've been using ecological momentary assessment for over a decade, but we now can just employ it on people's smartphones without even having to bat an eye to be able to both randomly monitor and prompt and get data back from them over the course of time, but also do that event based.

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For instance, the Healthy Heart study no longer asks people how many times have you been hospitalized in the last year. Instead, when they're in the location that's around many of the hospitals in the greater San Francisco area, they ping them at that point and say, "I notice that you're at hospital X, are you there for a procedure or were you admitted or are you just there visiting someone," and they can actually get better prospective data of hospitalizations and events moving forward.

We also have all the data coming from the digital -- Sandy Pentland calls them digital breadcrumbs, all the data that we just scatter about the day as we go through various things, and most people have thought about that in terms of social media. But when I drove my car here this morning, it has a lot of data about what my experience was in driving the car and how much traffic I went through and all the things I had to go through to get there.

So a lot of data like that that we can pull

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from; then all the passive sensor technologies that we currently have available.

Physical activity is the one that we probably have the most experience with and done the most with, but there are now sensors for smoking behavior and sun exposure and environmental exposures of various types, chemical, physical, et cetera, assorted dietary sensors, at least in the sense that we can do camera pictures of food, and then do them pre and post and get a better sense of what people are eating, and a range of other sorts of things like that; and, again, physiologic sensors being a prime example of that work; then all of the backend computational modeling, new statistical techniques that we can use to work with that data.

Back to PMI. It's always interesting to me to talk about PMI, because people think they know what it is, and I've been in it for over a year and a half and I still don't know what it is. So keep that in mind as you think about that, because the bottom line that I'm going to show you, all the

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various pieces and what's been funded and what hasn't, the major project itself is just beginning to be funded this month.

So no one has written a protocol yet. No one has done anything yet. So actually, this is a very opportune time for you to give me feedback about how we might be able to move that forward.

The things in pink are the things that we've awarded in the early phase, in a pilot phase. One of them was a project -- because we're going to do this mostly -- if you think about a million-plus people scattered out throughout the entire United States, we have to reach them via technology.

So we've got to understand how we can use web and mobile interfaces to be able to interview people, respond to them, use the telemedicine approaches we've talked about before already, all of those sorts of things and be able to get back and forth and keep people engaged. What's going to keep them engaged moving forward?

We've got a communications effort that we're looking at now in terms of how we get the word out

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and how we brand this and move it forward and do those kinds of things. And then the federally-qualified health centers, we've been very concerned about how we can make sure that this sample is as diverse as possible, which is lower SES groups and minority groups. So we've got some work in federally-qualified health centers to be able to help us better understand how do we reach into community health centers and use them as another health provider organization to be able to get those folks coming in.

We just recently funded the Biobank. Mayo-Rochester will handle the Biobank for the project. We are about to fund the PMI coordinating center relatively soon, which will have an administrative core, a data core and then the part that everyone else, all the other researchers, will come to, which is the research support core, where you come into a data enclave and are able to extract the data, be able to propose additional studies that you want to include in it, and that database will continue to build moving forward.

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Then probably in the next month, by sometime in July, we'll have funded the health provider organizations, probably closer to seven different centers, maybe even more, along with the VA, who we'll also include as one of those health provider organizations moving forward.

Then a participant technology center that is specifically focused on addressing how do we employ technologies to be able to gather data better than we've been able to do in the past. So all of those are the pieces that we still have to fund, are yet to be funded to get us moving forward.

I do want to, just to finish up on some things, give you a sense of what we've been doing at the NIH has been thinking about how do we jump start this, because the one thing that's important here is that -- and this is just a very political part of this. It would be nice to leisurely build this sort of a cohort, but we don't have the capability to be able to leisurely build this cohort.

We know that there's an election coming up

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and that if we're not up and running and there aren't participants already in by the time the next president shows up at the door, it will be a lot easier to kill this project than if it's already got people in it and people who are engaged and people who are running and that sort of thing.

So we're on a fast timeline. We talk about it as PMI time, where we move faster than I think I've ever seen the government move before. But our goal is to have 80,000 people already in this project by the time the new president comes in place. So we've got a lot of work to do given that, as I just said, we haven't awarded a single major award yet, other than the Biobank.

Part of what we did to speed that up is some of the groups at the NIH have started to build these implementation papers to get people a sense of what we need to do.

So this is just as a start to tell you that although we'll start in adults, we think that's the easiest way for us to start, we'll engage families moving forward so that we can actually incorporate

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both family data, as well as engage children, as well, and be able to expand our reach in terms of life course from early to late as we do that and some of the things that we need to consider for that.

Like I said, electronic health records will be our core to this. We, obviously, have experience, all of us do, with pulling in electronic health record data from HPOs of various types and being able to do that. The part that's going to be particularly tricky is how do we do that with direct volunteers. They're not coming from health provider organizations. We've got to figure out who's their provider, who's their vendor, can we actually extract their data, and can we turn this into a blue button project on steroids that would allow someone to just say "I want to donate my electronic health record data."

It goes and authenticates that at the place where their data resides. That data gets shipped or transmitted to the coordinating center, and so all of their data then gets pinged periodically.

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So we keep that updated moving forward, but that's going to take a lot of work.

Right now, we have Zak Kohane's group at Harvard doing a Sync for Science pilot that's specifically focused on that direct volunteer process and whether we're able to be able to quickly shift that data and move it from direct volunteers back to the coordinating center.

We have to do a really lean physical evaluation. People go, "$130 million, that's a lot of money." All you've got to do is do the math. That's $130 per person for a million people. And when someone says, "Oh, I have something that will only cost 20 bucks to add to the project," well, that's 20 million bucks. It doesn't take long for this to add up quickly.

It's a very lean physical eval that we're proposing initially, right now. Again, these are not set protocols. These are just recommendations to the steering committee that will then make these final determinations, but blood pressure, heart rate, et cetera.

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It has been an interesting discussion about heart rhythm, and we, obviously, don't have the capability to do 12-lead all over the country. And then we don't know for sure if we have the capability to do 5-lead or 4-lead across the country. So we've been playing around with the concept of even just doing a 1-lead.

Those of you who know a live core, basically, it's just an attachment to a smartphone and you put your hands on it for a few seconds, and you get a pretty "decent," decent in quotes, tracing from that.

Our biobank efforts, we're actually collecting a fair amount of blood. We're drawing fairly strongly from the U.K. biobank effort on this. So what you'll see is almost exactly what the U.K. biobank draws, and actually with a little bit more. So I think we'll have a decent amount of biobank available to people, both EDTA and clot activator and urine, as well. So we'll have a number of different ways to look at that.

Physical and social environment, to get some

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of these environmental data, we clearly have to get location. We have to get location data at work. We have to get it at home. We have to get it in the past, as well as the present. And ultimately, thanks to GPS, we can actually just track it on people's smartphones, for the people who allow us to do that. So we can get even better exposures, both physical and social and otherwise over the course of time, and then, again, use sensor devices for doing some of the other things that we need to do.

To a certain degree, we'll rely on the bring-your-own-device. This says something about bring your own beer, BYOB, but BYOD in this situation, the people who already have devices. So the diabetics who already have wire glucometers, those type of things, people have wireless weight scales, to the degree that we can use what they already have and be able to draw that data in, we will. In certain situations, we'll probably have to provide it to certain subgroups.

Then, of course, one of the key pieces of

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this is all the survey participant-provided data, both the self-report stuff and the performance-related measures. So you can see a list of some of the things that we're thinking about, but again, these are all -- I will tell you that I think what we've done is make it so that no one is happy with the full range of what we're asking, and that's probably a good thing, because you know how this goes.

If everybody is totally happy with it, it means that we've hung so many ornaments on the Christmas tree that it falls over and dies on its own weight.

So we've tried to be very lean with this, and I'll show you specifically on the pain measures at the bottom some of the things that we're looking at. So right now, the core pain items -- and I could certainly use the feedback of this group as we think about this moving forward -- the National Pain Strategy, just the pain in the last six months question to kind of get a sense of whether they have been or haven't been in pain recently; the

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Simple Pain Intensity Score and a pain interference measure; and, then, like I said, these are sort of the core, base level, foundational level.

What the assumption is is that people then come in and propose additional studies in people who, for instance, have certain types of pain and then subsequently add on to that in subgroups of people moving forward.

I didn't get a chance to read all the papers, though I actually did read some. It's actually kind of nice to read a little science every once in a while. I don't get to do that very much anymore, Dennis. But the one on pain phenotypes, I was looking at it in relationship to what we're asking about. So the psychosocial form of that, we do have depression measures and anxiety measures included in the process.

We'll have data on pain variability, especially in the folks that we can ask, in a subgroup of people that we can ask to do the more ecological, momentary assessment of their pain over the course of time.

We don't have a quality measure. So I certainly would appreciate feedback on which type of quality measure might be useful to think about there.

We have sleep and fatigue measures, and then, of course, we, obviously, won't have quantitative sensory measures as part of this effort, but that's the sort of thing that someone could come in with as an additional study moving forward.

I will stop there for questions and comments or go to the panel. Thank you, Roy.

(Applause.)

Q & A and Panel Discussion

DR. FREEMAN: In keeping with the theme, let's have two or three very quick, succinct questions, and then we will have everybody who participated come up and sit at the panel. In fact, why don't you start moving up already, in the interest of time?

Questions? Cliff?

DR. WOOLF: What is the peer review process

for deciding who gets funded and the composition of the phenotyping?

DR. RILEY: You mean for subsequent studies?

DR. WOOLF: No. For this, the ones you've done already. Is this top-down or is this consensus-building or expert advice?

DR. RILEY: So far, we've done both internal, as an initial step, and then we've had an advisory committee that's given us feedback on that. But again, these are nothing more at this point -- what you've seen are nothing more than suggestions/recommendations of the NIH to the steering committee, and my assumption is that steering committee, though it has to move quickly, will very quickly begin to get feedback from various groups about how do we improve this, modify it, that sort of thing.

The other thing I will mention, though, Cliff, that I think is important is this is not your mom and dad's cohort study.

Everybody rushes into a cohort study to get their stuff in at the beginning, because if you

don't, it's gone. We think about this in various versions of this moving forward. So version 1 might look like this, and then we have feedback from various communities that say I think we should add this, or I think we should add that, or in a certain subgroup, we think we should do these additional things, so that those keep building over time as we move forward.

DR. WOOLF: Will the patients be genotyped?

DR. RILEY: Yes, though that will take a little time for us to get there. In the first stage of this, we're just collecting the samples, and we'll eventually, of course, genotype, yes.

DR. FREEMAN: Luda?

DR. DIATCHENKO: Luda Diatchenko. McGill. Did you think about -- because right now, you're talking about new enrollment, right? Did you think about actually to collect the samples which already exist?

DR. RILEY: Yes.

DR. DIATCHENKO: Because there's a lot that exists which are already characterized for the drug

response or disease case versus control.

DR. RILEY: Yes. I have to tell you, on some of my earlier slides before the advisory committee to the director, one of our sources was existing cohorts, existing datasets. The advisory committee to the director, after a significant amount of discussion about this said let's just start anew. We can certainly tie to existing datasets.

You'll see in some of the participant-provided information pieces, we've tried to make sure our stuff is consistent with NHANES and others so that we can link, same thing with U.K. biobank and other existing projects, so that we can do more linking. But, yes, the bottom line is they decided to start anew as opposed to existing.

DR. FREEMAN: Last question, Roland, and then we'll move to the panel.

DR. STAUD: Roland Staud. My question is the timeliness of the data that you're going to collect, because the data will change over time.

DR. RILEY: They will.

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DR. STAUD: How are you going to approach this?
DR. RILEY: One nice thing about doing this via technology is that we don't have to be wedded to the fact that our follow-up is because the earth revolves around the sun once a year. We can do it in other ways than that.
So we can be a little bit more focused on how frequently do we think this phenomena is going to change. And so, as a result, how much more frequently should we ping somebody?
So depression measures, pain measures should have much more greater frequency of follow-up, every week, every month, that sort of thing, whereas some of the other measures could actually only be asked every two or three years, because they're fairly stable phenomena.
We'll be able to tailor that based on how often the phenomenon itself is actually changing, how dynamic it is.
DR. FREEMAN: Quick, let's get the speakers to take their chairs for the [inaudible - off

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microphone].
I said if we're going to move precision pain medicine forward over the next 25 years, we're going to need to do the right experiments. I'm going to ask two questions of each of you, short answers, although they're complex questions.
Just imagine -- this is question 1 -- you had unlimited money and you had an unlimited supply of old and new chemical entities. What's the experiment to do or what experiments would you do? That's question 1.
Question 2 is if Story Landis was here and you had just about no money at all, what's the experiment you would do? And maybe start with Clifford.
DR. WOOLF: These are very personalized.
(Laughter.)
DR. FREEMAN: Everybody knows, by the way, and I'm giving him time to think, these are not easy questions, and this is not --
DR. WOOLF: To me, I think the challenge of your first question is do we have the tools, the

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pharmacological tools, to address this topic to do it. I think not at the moment.
So I think, as a kind of evasion, can we develop pharmacological instruments that would be very specific in their action and then partly use them, once we have identified aspects of the phenotype that reflect mechanisms, as a therapy. But, also, at the end, I think one of the ways we're going to make progress is the very specific chemical entities will help us elucidate mechanisms.
If we knew that X was very specific for acting in a particularly defined mechanism and had no other action and we had patients who responded to it, we'd now have a very powerful tool to help us advance.
I think it's changing the question a little bit, but it's recognizing that the existing armamentarium is, I think, very limited.
DR. FREEMAN: Andrew, why don't you go next?
DR. RICE: It's not a coward's way out. It's a way that -- it's what I honestly feel, is

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that I agree with Clifford. We don't have drugs of sufficient specificity to drill out these kinds of things at the moment, with one or two exceptions, and that's probably why there's so much interest in some of the more specific channel blockers that are coming along, not only for their potential utility as drugs, but their potential utility as experimental tools. And metrics in humans for measuring whatever mechanism we're interested in.
I think we're quite a long way from that, and I think we probably need to resist the temptation to rush too far ahead before we have the methods right.
DR. FREEMAN: I think what we're hearing is, I think, whenever there is a problem, blame the pharmaceutical industry.
Michael, why don't you go?
DR. ROWBOTHAM: I think in both circumstances, I would initiate what you were calling a smart trial or pragmatic trial in health systems, where you take patients who are newly diagnosed with something and run them through a

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very defined protocol, but you randomize as to what drugs they get exposed to.

You could do an interesting comparison with highly effective, but wildly -- I wouldn't say non-selective, but they just kind of hit everything, like tricyclics, as opposed to more mechanism-selective drugs. But that would give you a lot of information as to what the real response rate is.

Then if I had tons of money to add to that, then I would start doing more of the kinds of measures that we're talking about here, so blood biobanking, maybe collection of fibroblasts for IPSCs, doing the QST phenotyping, other kinds of things that require expensive and specialized techniques and tools.

DR. FREEMAN: William, it's a good segue to you.

DR. RILEY: I'm outside of my area of expertise, but I'll at least sort of highlight one of the things that Michael said, which I think the more pragmatic trials that we're thinking about,

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smart trials, rapid learning system approaches in which we're doing more work within the context of where these patients are seen on a regular basis and how we treat them I think would be a useful approach for a variety of areas where we've done probably far too much efficacy work and not enough work in the actual setting in which these treatments are occurring.

DR. FREEMAN: Clifford?

DR. WOOLF: I have a second opportunity. Something we really haven't brought up yet is the big data side of this, the promise of whether it can be realized that if we collect more data, which you're doing to do, will that reveal things that we haven't been able to collect by the biased kind of trials that Andrew discussed for preclinical studies, and let's face it, for the clinical studies, as well.

Are we going to have enough information from the million-subject cohorts to start getting algorithms that we would not necessarily have predicted in our current targeted approach?

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DR. RILEY: I'll just respond to that by saying I think you're absolutely right. We always have the garbage-in-garbage-out problem. So if we don't go a good job of what it is that we collect and don't get feedback -- this was your point about feedback from expertise about exactly what we should be collecting to better look at those mechanisms. Then at the end of the day, it won't matter whether we have a million or 200 million people, it won't be that great of a project.

DR. FREEMAN: Andrew?

DR. RICE: Can I start another -- I've got tons of questions.

DR. FREEMAN: Of course.

DR. RICE: But it relates to Clifford's point, and that's what I wanted to ask William. The Icelandic have been doing this for at least 10 years, slightly longer. They managed to get a very high uptake for what is a very small country, but they did it for most of the country, 300,000 population, roughly.

They also had another bunch of information

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that, by their law, they're allowed to do. They collect the genealogical information probably going back a thousand years for many families.

When setting up the systems here, what did you learn from the mistakes the Icelanders may or may not have made? Because they haven't delivered huge amounts, but they've delivered interesting things.

DR. RILEY: Well, they have, and I think you're right. There are things about those systems that you realize are clear advantages. And we talk about a national healthcare system, but if we put that aside and if we just had a national electronic health record system instead of this disjointed, disconnected, having to pull data from 45 different places to be able to have a better sense of -- if you think about this, we have no national surveillance system in the United States.

We have it for meteorology. We have it for plate tectonics, but we don't have it for health. We have no way to monitor that over time. So that's clearly one of the advantages that the

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Scandinavian countries -- and we've studied what Iceland's doing, Norway, Sweden, those groups, as well. Part of this is just the fragmentation of the system that we have in place that we have to figure out how to best patch together.

The other thing I would just note, one of the things that -- like I said, we've been talking a bit with the U.K. biobank and using their model, to a certain degree, but there are clearly differences with that, as well. The U.K. has a much more homogenous population, much more urban-focused, and not so much spread out across a wide swath of country like we have, which makes it more complicated.

They also, surprisingly, even though they have a pretty decent, large dataset, haven't had researchers going to it and making use of it. And that's one of my big concerns is that we build something that people then don't subsequently use as much as we'd like for them to use.

DR. FREEMAN: John first and then we've got a number of other people.

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Oh, sorry, I missed that. Michael?

DR. ROWBOTHAM: I'd say in response to the comments I just heard that we are approaching something that could be considered a national electronic health record, and I'm not paid to say this because I have no ties to EPIC, but they've sort of taken over the universe in the U.S. and actually starting to move into other countries.

For example, Denmark is now installing EPIC as their electronic health record system, replacing all their little local homegrown systems.

One installation of EPIC can't necessarily talk to another one, but you're at least getting closer to the same platform so you could do these kinds of data queries now all across the U.S., in big health systems, and then also to other countries.

The other is that there are some specialized precision medicine platforms that have been developed. One is a northern California one that has rolled out to Intermountain West, and UCSF has taken them up on it and some other big providers,

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is something called SIAPS, which is cancer precision medicine.

It's a platform designed to facilitate clinical trials, but also can integrate the kind of genomic data that you get from doing mutational analyses of tumor specimens, circulating tumor DNA, all those other kinds of things, and able to integrate that within the electronic health records so that you can follow a precision medicine approach.

DR. FREEMAN: John Markman and then John Farrar.

DR. MARKMAN: John Markman, University of Rochester. I have a question for Dr. Riley and Dr. Rowbotham, but I think it pertains to all four of the talks.

In trying to conduct a cluster randomized trial in our own electronic health record, one of the challenges that I've confronted is the notion that clinical care is a grand experiment and we really don't know what the right thing to do is. It's unsettling to patients and it's unsettling to

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healthcare administrators and to IRBs.

This idea of the experimental culture being wholesale migrated into clinical care is something, which in our own experience, meets a lot of resistance, not even when we're talking about choosing treatments, just when we're talking about doing different types of assessments on patients, from 100 primary care practices versus another 100 primary care practices.

So I guess I'd like to understand from your perspective how do you think we're going to overcome this obstacle of telling patients in routine clinical care that we really don't know what the right answer is, it's all just a giant experiment, and you've been randomized to half the country.

DR. FREEMAN: Andrew and Michael seem to be the right persons to answer that.

DR. RICE: I can't answer it, but I can make some more comments. We've been very keen on trying to use electronic healthcare records in primary care in the U.K., even though Kays of Scotland is

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much, much better at the state they're at.
At the primary care level, we face two problems that I wasn't entirely expecting. I thought they might be there. They have really become quite docile. The first is coding of disease.
GPs certainly in the U.K., from the work we've done, are brilliant at coding diabetes, because they get paid for it. They're not good at coding diabetic neuropathy. They're good at coding zoster, but they're not good at coding postherpetic neuralgia.
The way we've got around that -- and you can do it in both Scotland and England now -- is to look at healthcare records and align them to prescription data. So you can find all the diabetics that are taking gabapentin, for example, a more reasonable chance that those will have diabetic neuropathy.
The other issue -- and I think one of you, maybe it was Michael, touched on this -- is the issue of consent, and we have to have consent at

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the level of looking at the healthcare records. That really is a big stop as opposed to if we could take consent later on or some kind of generic consent. So coding and consent are the two biggest practical issues we've come up against.
We're using those electronic healthcare records at the moment to recruit to phenotyping studies rather than actually to clinical trials for that reason.
DR. FREEMAN: Anybody else want to comment on that?
DR. ROWBOTHAM: I would say that that would be an interesting pragmatic trial, John. You randomize the patients to whether or not you tell them that we don't know what we're doing, and it's all just one big --
(Laughter.)
DR. ROWBOTHAM: -- and the other half continue the more paternalistic doctor-patient relationship, where you just don't want people to lose faith in you.
The coding issue is a big one, because if

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you actually look at all the codes and what they describe in the pain area -- and this has been a big effort by Rolf-Detlef Treede at IASP is to try and get the diagnostic codes changed by the time ICD-11 comes along. Except for a few diagnoses, they're kind of nonsensical, and that is a big area to improve.
Also, on the consenting issue, there is in some countries -- and, Troels, correct me if I'm wrong, but in Denmark, it's really more implied consent. So patients opt out of being in the national biobank rather than having to explicitly sign a very long consent form.
We're trying to launch our own biobank, and the shortest we've been able to get the consent form is eight pages. That really is an obstacle, trying to do that.
There are e-consenting tools that allow you to explain it better to patients before you expose them to the dreaded eight pages of fine print, but that's another area where it's really important.
Then I agree in terms of getting around the

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coding by looking at prescription records and then tying that back to more straightforward diagnoses to say this patient has diabetes but yet they're on gabapentin. Maybe they've got diabetic neuropathy pain.
DR. FREEMAN: Okay. John Farrar, you had a question.
DR. FARRAR: A quick comment about coding. There's an obvious solution to coding, which is the Google autofill, which allows people to actually type in what they think the patient has and allows the computing system to decide what the appropriate coding is.
I think it's been absolutely crazy this concept that we actually have to decide, and with ICD-9/10, you simply get a much longer list and you just pick the first one that comes close, which I think is going to be problematic.
But it gets at this issue I wanted to ask the panel, which is what advice would we give to the NIH for actually being able to use this, any of this data for pain?

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The problem with all the datasets is they don't record pain, and even in my patients that I see with chronic pain, all of the other practitioners hardly ever record whether they have it or not, never mind the phenotyping.

I'm wondering whether there is a way to sort of think about this to actually garner in the dataset or in the things that we want to do, information that would make it useful for some of the undertakings Clifford was talking about or, Andrew, you were talking about.

DR. WOOLF: One of the concerns when you put your list of pain and the presence of pain and its quality and its duration and its interference, all of that's very well, but if you don't know that the pain is in the context of a nerve injury or inflammation or some other, frankly, its use from a mechanistic point of view is very, very limited.

I agree, John, this is a real issue, because it's not just inclusion of pain. That will only be the beginning, but hopefully in its capacity for this to be dynamic, we can try and capture more

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relevant pathophysiological information that will make it more relevant, because we'll know -- Troels and I wrote a review for Lancet on postsurgical pain, and it turns out that patients who are having inguinal herniorrhaphy, there are hundreds of thousands every year, about 10 percent of them turn out to have pain, and there are no predictors of that. If you just ask if someone's got pain, that's fine, but if you don't have a context in which to put it in, it's going to be very difficult to maximally or most efficiently use it.

DR. FREEMAN: Andrew, do you want to comment?

DR. RICE: I agree with what you said, John, but I think it's actually an issue that goes much further. We've just written a commentary on one of the major studies that comes out every so often, Global Burden of Disease. It comes out every three years, roughly.

The last two paragraphs, which were written by Fiona Blyth, who's one of the 860 authors of the GBD paper, it's exactly this with regard to the

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pain data. Of course, we use it to justify what we do, and at the moment, it looks good for justifying what we want to do.

But the collection of pain data is very, very crude. It comes from lots and lots of different sources, and a lot of it doesn't get to exactly this kind of issues that Clifford was talking about, information we actually need, without hopefully overloading Bill's Christmas tree so it falls through the floor.

But I would say that that issue goes way beyond this business of big data. It goes to the collection of epidemiology data and the way it's done in the GBD project.

DR. FREEMAN: Dan Carr, Shai, then Serge.

DR. CARR: Just two small questions for consideration. The first is that there are many modalities on which a lot of money is spent for pain treatment that are not pharmacologic, and it might be worth keeping in mind for the future if there could be a better allocation of people to receive one procedure or another.

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For example, a sympathetic nerve block, that still is paid for, or epidural steroids that are paid for or spinal cord stimulators, if those indications could be sharpened up through some better phenotyping and genotyping, that I think would be an opportunity also for precision medicine. And by the way, that applies also to things like physical therapy or psychotherapy.

There are a lot of modalities that are used by a lot of people that cost a lot of money other than simple pharmacology, although, clearly, pharmacology is very attractive.

The other is whether some evidence might be garnered as to what is the minimum necessary duration of a trial, if one could guide the prediction of subsequent trajectories based on a relatively short period of observation.

One would think that issue had been fully addressed and it is in the ICH guidelines, but in the past year, we've seen that the entire literature on opioids for chronic non-cancer pain was actually discarded from the Center for Disease

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Control recommendations that stated there was no evidence for that modality based upon setting a very high threshold for study duration. So study duration was not seen to be a very controversial matter, but, in fact, it turned out to have a great deal of practical importance.

DR. FREEMAN: Any comments?

(No response.)

DR. FREEMAN: Serge. I'm sorry. Shai, then Serge.

DR. SILBERBERG: Shai Silberberg, NINDS. I've got a very ignorant question or I'm trying to wrap my brain around this whole morning session.

In my simplistic way of looking at things, if, 20 years ago in the cancer field, someone would have said we want to do precision medicine, it would have sounded, I assume, like science fiction, because we knew so little about the different genes involved and so on and so forth and the differences between the different patients.

So my thoughts are where are we in this domain when it comes to pain? My impression from

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what little I know and what I've heard is we're nowhere even close to that. So where is this going to when we're talking now about precision medicine? Is this just about let's collect a lot of data and then maybe we'll learn something about it, or does the effort have to be on, hey, we've got to go back to the basics and try to get the data so at some point maybe in 20 years' time, we will be able to do precision medicine?

DR. FREEMAN: Who wants to take a shot at that one?

(Laughter.)

DR. RICE: I can make one comment, Shai, that I agree with you, and my biggest concern here is that we might end up collecting lots and lots of data that would turn out to be not relevant. So until we have sorted out what we should be measuring, which I don't think we are yet, we may want to run before we can walk.

DR. FREEMAN: I'm going to stay focused on this question. Clifford, then Bob Dworkin, addressing specifically this somewhat provocative

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question.

DR. WOOLF: I think it's the emperor with no clothes question and I think it's appropriate, but as I look at it, what strikes me about the nervous system, how complex it is and how many parts it has, that you would think there'd be an almost infinite number of diseases, but, in fact, there are relatively few.

I'm globally looking at the whole of neurology, and it seems to me that there's some stable states of disease phenotypes that can be caused by multiple genes or multiple pathological -- and that's true, I think, in pain, as well. It's not an infinite -- there are varieties that are individualized, but there are clusters of features that are common, postherpetic neuralgia, diabetic.

I think the big data will capture that in ways that we have not been able to do by doing -- we haven't had enough information. If we will be able to see what are the drivers of these different clusters, as long as we can, we have

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enough information. That was my concern, that if we just ask does the patient have pain or not, we may not have the ability to cluster in a way that is meaningful related to different kinds of diseases.

DR. FREEMAN: Bob Dworkin addressing this specific question.

DR. DWORKIN: I think we're much further along than apparently the distinguished panel thinks, going back to your first question, Roy.

I think we have drugs where we know the mechanism of action and we have phenotypes and we have hypotheses about the connections between existing phenotypes that we can assess, and drug mechanisms of action.

Is there anyone in this room who wouldn't be interested in a trial of patients with chronic OA joint pain using duloxetine, where we phenotype the patients to determine whether they have abnormal condition pain modulation? I think the hypothesis would be that we'd want to use a two-tailed test, as Nat will show us this afternoon.

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My hypothesis is that patients with abnormal descending inhibition are going to respond -- who have OA joint pain are going to respond better to duloxetine than patients with intact descending inhibition.

I can go on, but I won't, with three or four or five other very specific hypotheses like that involving sodium channels, involving NMDA receptor blockers like memantine. So we have the hypotheses, we have the drugs. These are all generic drugs.

What we don't have -- and this goes back to Story Landis -- is the money to do those clinical trials. If we had the money to do the clinical trials, I think by this afternoon -- we don't even have to have a meeting tomorrow -- but late this afternoon, we would all agree on six clinical trials that would be critical proof of concept of precision pain medicine.

Maybe that's a kind of idiosyncratic view, but I know how to spend the money if someone wants to give us the money to test whether precision pain

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medicine is plausible, given existing drugs and existing knowledge of mechanisms. What we don't have is the money.

DR. FREEMAN: That is the response I anticipated. Does the panel want to --

DR. ROWBOTHAM: I'll comment a little bit on this. I think that I can't say for certain exactly where the cancer field was 20 years ago. There was certainly recognition that there were certain families with inherited predisposition to cancer and then sometime more recent than 20 years ago, BRCA mutations and its prognostic implications were understood. Then we started having the first of the targeted chemotherapies.

It was starting with really a very specific condition and then applying it to more and more cancers as the information came along. So, for example, more modern targeted therapies, the BRAF mutation in melanoma was picked as a target, several drugs came along, and then it started spreading into other tumors as they realized that that mutation existed outside of melanoma.

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So to follow that sort of approach, we would take something like we were talking about this morning, pachyonychia congenital or patients with inherited erythromelalgia where you can very precisely characterize what is the molecular abnormality, try and figure out, using available drugs or experimental drugs, what really works in that target, and then start going into other pain disorders to see whether or not there's a fit there, whether or not that specific mechanism, those specific abnormalities that are in these rare inherited or sometimes spontaneous disorders are present in the other ones and work from there.

I think that's a productive approach, but it means that you're starting with very, very narrow slices of the pie and working outward.

DR. FREEMAN: Any comments directly addressing Shai's question?

Ajay?

DR. WASAN: Maybe this isn't too oblique. This is Ajay Wasan from the University of Pittsburgh.

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So one thing I haven't heard related to what you're saying and where this is going is also that I haven't heard much about precision medicine for pain medicine as a process, because we're talking about mechanisms, we're talking about specific new treatments. But it seems to me that right now -- and we actually can study this using some of the big data that Mike mentioned -- is that some of the best examples of precision medicine are the good pain clinician who appreciates the individual variability in treatments and in presentation and then designs a specific multimodal treatment plan.

So that sounds basic, right? That's our basic stuff for 50 years, but that's actually, I think, the highest quality precision medicine we have happening right now. We all know that there's probably a dearth of that happening. It's not happening as much as we would all like.

I wonder if there are some comments about -- just reactions of what you all think, because I think you can actually use some of the big data from big medical records and from

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integrated systems. The VA, for instance, is a big system, of course, that you could do such a thing to study the process and that the process itself is an outcome that would be laudable, we should pursue.

DR. FREEMAN: Michael.

DR. RILEY: I think we probably should distinguish, though, between a personalized medicine approach that's really tailored to the individual patient and a precision medicine approach, because precision medicine, at least from NCI's definition, you're looking for signature molecules. It's really very much either some circulating substance or something that you can pick up with genomics or expression profiling to distinguish among groups of patients.

DR. FREEMAN: Addressing the specific question? No.

Shai, any closure? You asked a provocative question. You've got to, there's a duty.

DR. SILBERBERG: I have no closure. I know Story Landis very well, but I can't offer you any

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funds.

But I'll add another provocative question to Bob here, and that is, do we know that these hypotheses are well founded, that it's right to invest tens of millions of dollars in clinical trials?

DR. DWORKIN: I wouldn't invest tens of millions, but I would invest enough for phase 2 trials, proof of concept trials to test existing hypotheses about irritable versus non-irritable nociceptor mechanisms, conditioned pain modulation, DNIC, central sensitization in the context of deafferentation with an NMDA receptor blocker.

I really do believe, Shai, that if -- and we're not going to hijack this meeting and change it, but if we had three or four hours with this group, we could end up with somewhere between four and eight hypotheses that could be tested in a phase 2 clinical trial like the ones that were done by the Danish group and published in Pain last year.

So I personally think we're much further

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along if we consider the criterion of far along being able to launch a phase 2 proof of concept trial to test a hypothesis that either all of us or almost all of us would think is a reasonable hypothesis to test.

DR. SILBERBERG: I'll close on a positive note. NINDS has NeuroNEXT. I highly encourage you to apply for a phase 2 clinical trial through NeuroNEXT.

DR. DWORKIN: My understanding is you want, for a NeuroNEXT trial, to have a biomarker, and I don't have a biomarker. So I would be wasting my time. That's what Walter told me. He says, "Don't bother applying unless you have a biomarker." We don't have a biomarker.

DR. DIATCHENKO: We can take an end biomarker, no problem.

(Laughter.)

DR. FREEMAN: Andrew, last comment on this topic, and then we'll move along to Serge.

DR. RICE: It relates to Ajay and Bob's question. Early on, people invested a huge amount

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of money in this concept of collecting an awful lot of information. So the genomics people and, for example, the Wellcome Trust invested huge amounts in the Sanger Center. It is difficult to know, except for some very rare diseases and those are important observations, what it's exactly come out with.

Those people are now turning around quite reasonably and saying, "Well, exactly the issue was the depth of the phenotyping and did we have really reliable ways of phenotyping what we wanted to know." The answer, of course, was no. So now they're moving much more to getting interested in the phenotyping issues.

Taking Bob's case of CPM, condition pain modulation, there's something we spent the last three months looking at for a European project, because, yes, lots of people have described those different paradigms and they've all got their own favorite paradigms, but when you actually want to do an analysis and see which of those paradigms is the best one, which conditioning stimulus do you

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leave it on for, how long do you leave it on for, which test universe do you have, that hasn't been worked out.

We've done a meta-analysis of this reliability that hopefully will be published soon, but until we know that information, you're just pulling half a metric off the tree rather than knowing actually which one is most reliable and, most importantly, most reliable across lots of centers.

DR. FREEMAN: So using moderator's prerogative and because we want actionable items, Luda, what biomarker would you suggest? And using biomarker, I think I want to make the point in the narrowest and most restricted sense of the word, because some of the things that we think of as phenotypes are, in fact, potential biomarkers.

DR. DIATCHENKO: Luda Diatchenko.

I think we saw today actually a list of very credible biomarkers. And I'm trying to remember, I think this was from Michael's presentation. I think maybe each of the people showed at least one

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slide with the molecules we know for sure are involved in the process.

Now, how many of them -- what kind of biomarker? Are we talking about SNP? Yes, half of them have more or less credible SNP, which we can assess. If you would like me to go look one molecule by one, I can do this.

(Laughter.)

DR. FREEMAN: No. Thank you for offering.

Serge?

DR. MARCHAND: The question goes exactly in the same direction. How much was it? How many million is it for the 1 million patients from the NIH? It's 20 million or something like that?

DR. RILEY: It's 130 million a year.

DR. MARCHAND: Let's say I'm the one who decides on this 30 million. I'm the NIH and I'm asking every one of you rapidly and I will tell you what I will do. I have 30 million for you. You have two choices. You can go and have millions of patients tested for different things and you cannot do everything you want or you can have a few

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thousand. I mean, you can decide on how many thousand, but you can measure whatever you want. You can take everyone here. I can tell you what I will do with it anyway.

What would you do? Let's say that you don't have a choice. You have one or the other. What will you choose today?

DR. FREEMAN: Michael?

DR. WOOLF: I think the choice is both. They're different.

(Laughter.)

DR. MARCHAND: You cannot take both.

DR. WOOLF: I think we need to collect the epidemiological data and it's an enormous investment, but if it means it's at the expense of the very deep phenotyping that Andrew's doing, then it's going to be a wasted effort. So it has to be a partnership.

DR. RILEY: Well, there has to be. And in keep in mind, I don't -- I'm going to do the same thing, which it's not either/or, both, right? The concept around the Precision Medicine Initiative on

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the cohort program is not that we're going to answer all questions across a million people. We're going to lay a base under which all this other more deep phenotyping, biomarker work, that sort of thing is done in drilled-down, focused effort in some subgroup of people that meet whatever criteria it is that as researchers you have to have met to be able to pull that.

So, Bob, some of the clinical trials you're talking about, hopefully, we actually are saving some money, it's not costing us much, because you can reach in and say, "Okay, here's 50,000 people that meet these criteria that I'm looking for." I'll ping them and ask them if they'll participate in a much more drilled-down, focused, deep phenotyping project related to these particular things and get enough people to be able to do that quickly.

DR. FREEMAN: Michael, you had a comment.

Then we're going to go somewhere at the back there, there was a question, then Ian Gilron and then Simon Tate.

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DR. ROWBOTHAM: I'll cut to the bottom line, and that is who really controls American healthcare. I'm not going to talk about Trump, but a lot of that is the insurance industry. Doctors' practice is really dictated by what are the standards within their healthcare organization and what insurance companies allow.

Some of you may remember when some of the drugs came around for specific GI disorders or Imitrex for migraine, there had to be a neurologist or a GI specialist sign off. So it doesn't cost any money to require a certain amount of pain phenotyping and evaluation in order to get some of the expensive and specialized procedures that patients are asking for. So there is an incentive to collect the information.

Let's say, for example, if you're going to get chronic treatment with an opioid in the Kaiser system or Sutter or someplace, could be anyone, the requirement is that the patient undergoes certain evaluations. They have to have a psychological evaluation, some kind of sensory testing,

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confirmation of their diagnosis, et cetera, et cetera.

That gives you a basic dataset that you've collected on everybody. Same thing if they're going to get an epidural block or if they're going to get a spinal stimulator. So these are more administrative, legislative things that can be done to collect the data without necessarily requiring that there be a big grant to go out and collect the data.

The grant is then really to collate the data, pull it together, get it out of the electronic health records that are around the country and follow a big data approach to actually analyzing it and see what falls out of it.

DR. FREEMAN: There was a question at the back?

DR. KERNS: This was actually a comment earlier and a question really about big data, and I have the benefit of working with clinical epidemiologists and biomedical informatics specialists in the VA in this space. One thing

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we've learned, I think, through lots of cohort projects using electronic health record data, is the value of investing in the very tedious, sometimes expensive effort of validating CPT codes, ICD codes, you name it. So that's one part of this enterprise I think that's critical, I guess, foundational, but costly to do.

The other part is I'm working with an NIH-funded project to explore the value of machine learning and natural language processing to extract pain relevant information from unstructured text notes, and I wonder if the panel could specifically speak to the potential value of that as a complement, I guess, to relying entirely on structured data.

DR. WOOLF: One related comment I see as an observer at Boston Children's Hospital is that we've got a cultural conflict between two ways of doing medicine. One is you have physicians who've collected cohorts of patients with particular mutations with great difficulty and it's taken them many years and their scientific and clinical

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careers depend on it.

Then you get Zak Kohane, who you've mentioned, who is able to come in and just suck in all the data without any consent, because it's anonymized patients and comes out with the -- so one of the things we have to confront is if, Mike, if we do collect all this data, what you as an individual physician is trying to generate your New England Journal of Medicine paper on your favorite set of patients, how are you going to deal with the fact that Will here can somehow get it all without your consent, involvement and collaboration?

DR. ROWBOTHAM: That's a good question.

(Laughter.)

DR. ROWBOTHAM: I think you're seeing that already because a lot of the data is going into these national collaborations. Certainly, it's happening with all the cancer genomics. It's being driven by the companies that are going into that space. It's driven by other consortia.

Interestingly, as the size of these datasets gets larger, there are now multiple -- at least in

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the personalized medicine area, there are now multiple very, very large genomic datasets that don't necessarily talk to each other.

So I don't have a solution for what the individual investigator does, because the data gets de-identified or even anonymized and it really is out of our hands. But to me, that's okay because it's still going to be very high level analysis of the data rather than the kind of very individual case report style work that a lot of us have done during our careers.

DR. FREEMAN: Okay. Ian Gilron -- sorry. Why don't you --

DR. RICE: Can I just get issue around Robert's point? And it comes from a slightly related area, but it relates to these existing big datasets that can be massive in some cases.

I'll give you two examples that we're working with at the moment. Shai is very aware of one of these. The advances in machine learning and text mining machine learning are just incredible at the moment, what these people can do. How much of

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it will be relevant to us, I don't know.

But as I mentioned in my lecture, we're dealing with a very large dataset of preclinical research reports, and we've just had a grant to explore machine learning or text mining machine learning to extract those data. So in a year or two, I'll be able to tell you exactly how that went.

There are other quite large datasets that already exist. So for example, at the end of the First World War, there were 41,000 British amputees who were all followed up for the next 100 years. Their data are freely available because they're over 100 years old now. We currently have a grant in to use text mining to look at their medical care and what happened to an amputee and their pain over the next 70-odd years.

So all I'm saying is that we should keep our eyes open and look what is happening in the text mining and machine learning area, because quite a lot of those reports might actually already be out there. The problem is they weren't recorded using

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the information or even perhaps the language we use today, but they perform impressively in other areas.

DR. FREEMAN: Ian Gilron, then Simon Tate.

DR. GILRON: Ian Gilron, Queens University. So far we've heard a lot about maybe neurophysiological mechanisms of pain. We've talked about quests for biomarkers of pain. I'm thinking back to Melzack, Wall, Casey where we've got sensory discriminative and motivational, affective, and I'm just -- I feel like we haven't been talking much about psychological or psychiatric influences on pain, and I'm wondering whether inherently does precision medicine neglect that aspect of patient subjectivity and whether patients are being marginalized. And if not, how do we incorporate those aspects of pain into precision medicine?

DR. WOOLF: The fact that NIMH, at least in its previous director, was moving away from the standard classification, which as we do the genomics, turns out to be a real mix that we call

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bipolar or schizophrenia turns out, at least according to the genetic evidence, not to be as rigid so that it's -- I think we're going to have to relook at the whole enormous tranches of medicine as we get more information on it.

The clinical presentation may only be part of the picture, and the subjectivity needs to be captured. But we need to have an open mind about what it means, and that if someone says they're depressed, what does that mean and what does it reflect.

DR. RILEY: I'll just add I think that that is an excellent example of trying to rethink how we look at these phenotypes at that level. But even beyond the psychological factors, once again thinking about some of the environmental and contextual factors that are related to pain, as well, is going to be an important component to this.

Some of that is also predictive. So we have to think about these predictors not just residing in genetic code but even beyond that in a lot of

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other areas where we need to pay more attention.
DR. FREEMAN: Second last question from Simon Tate, and then we'll close for lunch.
DR. TATE: Simon Tate, Convergence Pharmaceuticals, U.K. I want to bring it back actually to one of Mike's comments, which was about this kind of drug refractory group that we often study in clinical trials. So you do your sequential. You showed the epilepsy example, and we know that's true in pain.
You do your sequential drug treatments, and you end up with 30, 40 percent of patients who are refractory to the commonly used neuropathic pain treatments.
Of course, the pharmaceutical industry, that's the population of patients that the pharmaceutical industry now tends to target because the commercial organizations will drive you to that, because if you've got a patient who's treated by gabapentin or duloxetine, then you're not going to get reimbursement for that patient. So you go after the patient who is refractory.

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So my question to the panel is really if we concentrated our phenotyping efforts or translational efforts, the precision medicine efforts on those patients who were refractory to the known analgesics as well as -- I mean, I fully agree with Bob Dworkin by the way, that doing those studies would be fantastic on the known analgesics, but if we focused on that group, would we get the pharma industry more interested then in studies, because that's the very group that payers are going to reimburse.
DR. FREEMAN: Comment? Michael?
DR. ROWBOTHAM: So I agree with what you're saying, and that points up the value of trying to get patients at the time of initial diagnosis really in more of the community setting because you know a certain number of them are going to end up being -- at least from the epilepsy example, about a third being refractory to everything.
So if you capture everybody in the system at the very beginning, then you will be able to see who's resolved, who didn't resolve and what's

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different about the ones who turn out to be truly refractory and just really how different are they and on what parameters from the ones who went on to resolve spontaneously or in response to a particular drug. That would be a big advance.
DR. FREEMAN: Bob Kerns, last question.
DR. KERNS: Thank you. Actually, kind of pulling some of this together, I've recently become aware of work by John Krystal in our psychiatry department at Yale, chair, looking at kind of symptom clusters and the benefit of specific medications really setting aside diagnosis and looking at clusters of symptoms.
So thinking about pain, I know we're interested in pain, pain, pain, but thinking about how the question was raised, I think by Ian, about pain in the context of psychosocial distress, more broadly psychiatric mental health problems. I think at least one possibility even looking at our present medications, finding value in improved value of the medications we have for identifying clusters of problems, I guess, symptoms in people

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with pain that takes into account the psychosocial context and other symptoms could be important.
Back maybe the last thing I'll say is to Bill's challenge in building the database, not on the table yet is -- and you raised the question. We need help figuring out how to measure quality of pain. I think in that context of what I was just saying, I think that really is critically important to move -- maybe not deemphasize pain severity or intensity but to up the ante on better characterization of the quality.
The value potentially of machine learning and text mining, looking into the notes of providers who are maybe documenting something about the person's experience of pain-like experiences.
DR. FREEMAN: Final comments from the panel. Andrew?
DR. RICE: There are two questions. I think what you're describing is exactly the kind of thing we should be doing with a large -- particularly the existing therapies with a large pragmatic trial based in primary care. The only assumption as far

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as I can see if do we have actually the drugs of sufficient specificity, possibly, probably, I don't know, and are the symptom questionnaires adequate for detecting effect in neuropathic pain. They probably are now. A lot of people have been working on them.

But I think you've just written the ideal trial, pragmatic trial in primary care.

DR. FREEMAN: Any other final comments? Clifford, Michael?

DR. WOOLF: I'd just like to say I echo Mike's comment that by identifying who will respond to the available drugs is as valuable as identifying the refractory. I think we can't just do one or the other.

Just moving away from the -- I think that's what precision medicine is, moving away from an empirical treatment, treatment by trial and error to one that is targeted. So if we can target a generic drug that's just as successful as getting a very expensive new one.

On the pain quality issue, I'm very

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unimpressed by pain quality as a variable. I'd like to know if anyone has done a good meta-analysis of the McGill Pain Questionnaire and found anything of value that's come out of it even though there must be thousands of papers that have been studied.

DR. FREEMAN: Michael, you had a comment?

DR. ROWBOTHAM: I'll duck Clifford's question because there's other people in this group I think that can answer that better than I can, but I just want to just make one comment about the -- we want to look at both the patients who fail treatment as well as the ones who succeed.

So kind of buried in the fine print of our New England Journal paper on levorphanol for neuropathic pain, which is now 13 years ago, we did an analysis of who went on to fail. By looking at their dose escalation -- because this was a patient-determined dose escalation protocol, they determined how many pills they took within limits, but we didn't push them to do anything.

What we found was that the eventual failures

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had more side effects and fell behind the successes very early on in terms of their dose escalation. So in other words, they didn't really tolerate the drug very well, and I think if you -- or were unwilling to keep pushing up as the study went on.

So I think if you were working in a community setting even with the first drug trial, it would probably be largely independent of which drug you started with, the patients who go on to this nothing's worked for me are ones who have generally had trouble tolerating or finding very acceptable any of the treatments that are offered to them.

That's something that's going to be very difficult to get at with a precision medicine approach because it just has to do with so many kind of cultural, environmental and psychological factors.

DR. FREEMAN: Okay. I think on that note, thanks to the speakers.

(Applause.)

DR. FREEMAN: Back at 1:45 or 1:30 or

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what's --

DR. DWORKIN: 1:40.

DR. FREEMAN: 1:40, back on at 1:40.

(Whereupon, at 12:48 p.m., a luncheon recess was taken.)

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A F T E R N O O N S E S S I O N
(1:51 p.m.)
DR. KATZ: Good afternoon, everybody. I'd like to invite everybody to take their seats to begin the afternoon session on sodium channels as targets for precision neuropathic and musculoskeletal pain medicine.
For those of you who I don't know, my name is Nat Katz, and I'll be moderating this session. The only thing I'll say in my very brief introduction is that it feels great to be in a room filled with speakers who need no introduction and be the guy who does need an introduction, because that suggests that you're really in the room with the leaders in the field.
(Laughter.)
DR. KATZ: It's a great opportunity to learn from those who are really helping us carve the path forward.
Without further ado, I would like to introduce Alban Latremoliere, who is a research fellow working with Clifford at Children's

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Hospital, who will be speaking about rare versus common gene variants as guides to pain mechanisms in drug development. We had started a little bit late, but I will try to keep everybody to their half-hour. So I'll wave you down when it's time to wrap up.
Presentation – Alban Latremoliere
DR. LATREMOLIERE: Thank you very much for the nice introduction, and I would like to thank Dennis and Bob for inviting me and giving the opportunity to present in this exciting meeting.
In this session, I will be actually not talking so much about sodium channels, but I will be talking about how we can use rare and common gene variants to identify new drug targets for the treatment of neuropathic pain.
As Andrew said this morning, the vast majority of the recent attempts to develop new drugs from preclinical models have failed, and it was mostly due to a lack of efficacy. As a result, all the treatments we have available for patients at the moment are based on fairly old molecular

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targets. They're shown here. Those are mostly either the first line of medication for neuropathic pain or they are most commonly used treatments.
These treatments, however, have moderate efficacy, and they have a lot of serious side effects. There is, therefore, the need, a critical need for novel targets to treat neuropathic pain.
So how to increase the translational success to find new drugs. One strategy we followed in the group was to start not from the animal model, but start from the patients and to select from patients a clinically relevant pathway. Then from this pathway that will have some proof of efficacy at the clinical level, we would move it to animal models to confirm its validity and study it more in detail.
From there, if the pathway is valid in preclinical models, we would use our knowledge we can gather from animal models to determine new drug targets, with the hope that once we have this new drug target, we could go back to patients to apply this strategy.

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How to select a drug target or at least a potential target from patients. So one strategy that has been developed and become very, very successful in the last few decades is to use genetic studies, and this approach allows for the notification of molecular targets.
One strategy is to look for phenotypes, patients with very strong phenotype with their pain sensitivity. That can be either total congenital insensitivity to pain or a gain of function in pain. These states and pathologies have very strong effect size, but they are very rare in the population.
Two examples from such identification of potential targets from these conditions would be the TrkA loss of function or the Nav 1.8 loss or gain of function in patients, and we will hear more about those two potential targets in various talks during this meeting.
The ideal outcome we could expect from such targets would be that they could be potent analgesics based on the nature of the phenotype of

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patients with gain or loss of function. One caveat, though, is that these molecules will mostly target nociceptive pain or at least nociceptors.

Another strategy then is also to try to identify targets from the very patients we're trying to treat and the patients that suffer from the pathology were interested in. So in our case, that would be chronic pain patients.

Then the idea would be to try to isolate, to identify patients that either develop less pain than the majority of patients suffering from the same disease or more pain, then try to associate which gene or pathway is associated with that.

So using this approach, one could hope to find several polymorphisms that will have a more moderate effect size. One of the reasons is that, as Clifford mentioned, chronic pain disease states are multifactorial, polygenetic.

So it's extremely improbable to find one target that will be able to solve the whole disease. Rather, we would find different haplotypes that can modulate the development of

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pain hypersensitivity in these patients.

The ideal outcome we could hope from such targets isolated from these studies would be that these targets would be disease-specific and mechanism-based rather than just an umbrella, just pain target. They would be specific for the type of pain you screen your patients for.

One could hope that these treatments based on those targets would target maladaptive pain only while leaving nociceptive normal pain intact in these patients.

In this talk, I will describe a little bit of the work we've been doing in Clifford's lab for the past several years about one such polymorphism, which is GCH1. So the first thing is to define what is GCH1, and GCH1 stands for GTP cyclohydrolase 1, the first enzyme in the rather complex metabolic pathway responsible for the synthesis of tetrahydrobiopterin, also known as BH4.

Then usually the second question that comes is what is BH4, and BH4 is a critical cofactor

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required by several enzymes, such as the three isoforms of the NOS, the tyrosine and tryptophan hydroxylases, as well as the phenylalanine and hydroxylases. Recently, it's been shown that the alkylglycerol monooxygenase also requires BH4, which means that BH4 levels are essential for the proper prediction of NO, serotonin and dopamine or epinephrine or proper metabolism of phenylalanine and various lipids.

This pathway is very interesting, because 10 years ago, there was a so-called protective haplotype that was isolated from neuropathic pain patients within the GCH1 locus. The patients carrying this haplotype in the homozygote form that can be found in roughly 2 percent of the population were strongly protected against the development of abnormal pain hypersensitivity after nerve injury, but also, together with that, there was evidence showing that those patients were producing less BH4, meaning that the GCH1 enzyme was leading to less production of BH4 in these patients, suggesting that less production of BH4 was

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associated with less development of abnormal pain hypersensitivity.

From this original study in 2006, there's been several different additional cohorts that have been testing the GCH1 pain protective haplotype, and at least, so far, 10 independent cohorts have been used and confirm this haplotype.

I'm not going to go through all the cohorts and studies, but one thing that is very interesting is to note that the GCH1 pain protected haplotype is mostly efficient when you have nerve trauma or nerve compression or for an injury, but it's less likely to be protective in conditions when you don't have such injury, such as with the bottom, you can see chronic pancreatitis or pregnant women.

This haplotype is especially relevant for conditions when you have nerve trauma or nerve injury.

The problem with genetic association studies is that although they identify a potential or relevant gene, they do not tell you where, how and when it participates to pain. So to do that, we

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used a strategy with various transgenic animals so that we could study where the pathway is engaged after nerve injury, as well as gain and loss of functions, to confirm formally its role in pain.

Here, the first slide here, I show results with GCH1 promoter mouse that expresses the GFP below after the GCH1 promoter. So that's when the cells want to engage GCH1 production. They will be fluorescent.

Using those animals, we found that in the DRG, whereas we could not detect anything, as you can see in the top panel, in a naive state, after nerve injury, several sensory neurons will become positive, meaning that they upregulate the GCH1 enzyme.

Perhaps more surprisingly, when we looked using this unbiased approach in different tissues, when we looked at the sciatic nerve, the site of injury, what we found was that, well, we could not see anything at the baseline state, basal state. After nerve injury, we found a lot of little signals in the nerve. When we looked more closely

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at it, we found that next to the axons from the neurons that upregulate GCH1, we detected a lot of non-neuronal cells, and we identified those as being activated microphages that infiltrate the injured nerve after injury.

In these two slides, we confirmed that GCH1 activity was upregulated and that was leading to an overexpression of BH4 in those two tissues, and these experiments allowed us to identify two target tissues where BH4 plays a role after nerve injury and, also, two cell types that involve this pathway.

Next, we decided to do loss of function studies, and to do that, we used animals that are conditional knockout for the GCH1 enzyme. So these mice can be crossed with various Cre drivers you can specifically remove GCH1 in a different subset of cells.

Mice that are knockout for GCH1 do not have any GCH1 activity, and when we looked at pain hypersensitivity-like symptoms in mice, there are conclusively knockout for GCH1 only in sensory

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neurons. We found that those animals developed less mechanical allodynia after peripheral nerve injury in the SNI pain module reminiscent to what we found or can observe in patients after nerve injury, the ones with the protective haplotype.

Perhaps more interestingly, we found that if we measured mechanical allodynia in animals that are inducible knockout for GCH1, we found that all the animals developed neuropathic pain at the beginning, but then when we induced the knockouts, we found that only the mice that lost GCH1 and, therefore, lost the ability to produce BH4 sensory neurons had an improvement in their mechanical sensitivity after nerve injury, indicating that the BH4 pathway does play a role in the development of pain hypersensitivity after nerve injury, but that reducing this production in sensory neurons was sufficient to prevent and also reverse the pain hypersensitivity.

The interesting thing is that we found that those animals that do not express BH4 is sensory neurons had normal, unaffected nociceptive pain

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responses, meaning that we tested several pain modalities and we found that those mice without BH4 and sensory neurons are capable of detecting and reacting appropriately to a noxious stimuli, so that we were capable of removing some of the maladaptive pain while keeping the normal nociceptive pain intact.

So then the challenge was to try and find therapeutic use for this pathway and how to target this pathway at the systemic level to reduce pain. GCH1 was not a very good target for drug development because it is the rate limiting enzyme for the production of BH4, meaning that it directly affects the amount of BH4 being produced and if you block this enzyme totally, then you cannot produce any BH4, which will likely promote the development of side effects.

Instead of GCH1, we focused our attention to sepiapterin reductase, SPR, the last enzyme of the BH4 de novo synthesis pathway. The reason is that studies have shown that in absence of SPR, cells can still produce minimal amount of BH4 in the cell

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through something known as a salvage pathway. This prediction, as shown in the de novo pathway, that it's sufficient so that enzymes requiring BH4 can still do their minimal function.

We used a structure-based approach to develop an inhibitor for SPR, and we used a scaffold -- when I say "we," that's Professor Julian Blagg -- were used as a scaffold an endogenous inhibitor for SPR, N-acetylserotonin, and modified it so that it would predict or fit better into the active packet of the enzyme and came up with this tool compound that we called SPRi3 as the third SPR inhibitor.

This compound we tested in vitro to confirm that, indeed, it was more potent than N-acetylserotonin and also in the DRG neurons in culture to confirm that it could reduce SPR activity in the target cell type.

Administration of this compound in preclinical models of neuropathic pain showed a dose-dependent reduction in neuropathic pain-like symptoms, and that was associated with the presence

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of the compound in two target tissues, the DRG and the sciatic nerve. That was associated with a reduction in BH4 levels in those two tissues.

We didn't detect any major side effects in various tests that were focused on which side effects we could have expected from BH4 deficiency.

Basically, in this first part of the talk, what I've shown you is our strategy, where we selected a clinically relevant pathway, notified through one gene, which is GCH1 and its metabolic outcome, BH4, and we took this pathway into animal models to perform mouse genetics to validate the pathway and define it better.

From there, we identified a different drug, which is not the gene that was the one we used to identify the pathway, but a more drugable target for which we developed a tool compound. That's where it was capable of reducing pain hypersensitivity in rodents, and now we are hoping that other compounds targeted against this enzyme could represent promising new drug targets that could hopefully be possible new treatments.

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In the second part of the talk, what I would like to do is use this BH4 pathway I described to you and this strategy we followed to propose a new potential target to illustrate how this pathway could be used for precision medicine type.

The current medicine, as we've heard many times this morning, is basically you have your first line of medications, a patient coming with chronic pain, and you try to -- basically, you're going to try most of those medications in patients and see what happens, and there's going to be a lot of variability, many side effects and a lot of patients that will drop out or ask to have a different treatment because they don't tolerate the treatment you gave them.

So precision medicine, the text I found on the White House website, proposes strategies to help clinicians to find new tools and knowledge and therapies to select which treatment will work best for which patients.

So going to take this hypothetical case of a chronic pain patient coming to see his doctor,

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suffering from pain for many months, the first thing you would need to do is to perform a diagnostic. That would involve, we've heard this morning, several questionnaires. Hopefully, more and more QST strategies that can really help tease out which type of chronic pain you're suffering from.

Also mentioned this morning, everyone is trying very hard to find new biomarkers that could help understand which disease states patients are suffering from.

Among those biomarkers, one thing that our studies taught about the BH4 pathway is that this is specifically involved in injured sensory neurons and also in activated microphages. We now have some evidence that also some aspect of T cell function is relying on the BH4 pathway.

That implies that if the patients -- you can have some biomarkers that can notify that your patients have signs of injured sensory neurons or activated microphages, it is more likely that this patient will be engaging the BH4 protection

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pathway.
We predict that disease state, such as peripheral neuropathic pain caused by nerve injury, inflammatory bowel disease, or different cancer pain types will be prime candidates for involving the BH4 pathway, which would place the patient as a potential good target for this treatment.
So that will help moving toward a mechanism-based diagnostic strategy. Once you know the type of disease, then you can suspect which pathway is involved and how you can try to reduce it.
The next step would be to use genetics, like we discussed about this morning, as well. It's a key factor for precision medicine, and we could use the same genetic tools we've used to identify the BH4 pathway in patients.
Here is the typical case. You could imagine having an interesting thing. If you have your patient that is a carrier of the GCH1 pain protective haplotype, that would suggest that blocking the BH4 protection pathway would not be

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likely a successful strategy, in which case you would have to move to other haplotypes and several other very promising adjuvants, like serotonin or period receptors, to find if there is more likelihood to have a good response to the treatment.
But for the vast majority of the population, 80 percent will have a normal GCH1 gene. If they have nerve injury or microphage activation, they will most likely have too much BH4, meaning that they will be likely responsive to a treatment that will aim at reducing those BH4 levels.
For the head [indiscernible] part of the treatment, the patients, the situation might be a little bit more complicated, but one could expect that they would potentially a poor responder for the treatment, and then you could predict that you would need higher or a different dosage regimen for those patients. But that could definitely help setting time in determining which treatment you could try.
One thing I would mention here about the

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GCH1 protective haplotype is a recent study a couple of years ago. It was very interesting. That showed that whereas this haplotype in European and Asian people is associated with less BH4 protection, in African-American patients, the same haplotype is actually associated with aggravation of pain response.
But this very elegant study looked also at the BH4 levels and confirmed that for some reason, in the African-American population, this haplotype is also associated with more BH4 protection. So whereas the haplotype itself is the same, what matters is the BH4 amount being produced.
So more BH4 is still associated with more pain, but if you have your patients, then it will be extremely helpful to understand that, because if you have African-Americans with chronic pain that have this haplotype, then they will become actually prime candidates for a treatment targeting a reduction of BH4.
So all together, that could really be a great help into precision medicine type of work,

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using those genetic tools to screen patients and select which ones are likely to have a highly protective GCH1 enzyme.
Then the final step would be to give a treatment to your patient. And in our study, we propose SPR to be a better target to reduce, without totally ablating the BH4 protection pathway. But then the next question will be what dose should we use for each patient to reduce pain, but without causing possible side effects. It's an extremely complicated question I guess you have for every medication.
To answer this question, then what you need is a biomarker for treatment efficacy. Here, I show you again the BH4 de novo synthesis pathway, and in light blue, you can see the two reactions that the SPR enzyme is carrying out under normal conditions. When SPR is absent, I mentioned that we have salvage pathways that can produce some BH4, and actually, this field is expanding, and we keep discovering novel salvage pathways. At the moment, there are two confirmed salvage pathways.

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I will bring your attention to the one in red, because in this pathway, the endogenous substrate for SPR, which is 6 tetrahydro -- not biopterin -- 6 tetrahydropterin can be processed by several enzymes and then lead to a metabolite that will not enzymatically be transformed into a compound called sepiapterin.

So this compound, sepiapterin, despite its name, is not the endogenous ligand for SPR, and it can only be seen and detected in a cell when SPR is absent, because if SPR is functional, it will take sepiapterin and transform it into BH4.

This sepiapterin is a very interesting compound, because it's extremely stable, which means we can detect it in various tissues. For example, we confirm that sepiapterin levels were increased in the DRG and sciatic nerve in our preclinical models in neuropathic pain treated with this compound, confirming that the enzyme had been targeted in those two tissues.

But surprisingly, we also found that this metabolite is, for some reason, secreted by cells.

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And here is a dosage of sepiapterin from supernatant of DRG neurons in culture. You can see that the more you block the pathway, the more you can find sepiapterin secreted by cells, and because it's secreted and it's stable, then it's detectable in plasma.

Here is a result from plotting the sepiapterin prediction found in plasma from the amount of SPR inhibitor the animals received. You can see a very strong correlation between the two, so strong actually that we were capable of spotting the samples from animals that had a dose that was not associated with pain relief, probably too low of a dose, from animals that had a pain relieving dose of the SPR inhibitor.

That means that sepiapterin, we think, can work as a very reliable biomarker for the efficacy of the treatment and precisely will tell you how much you have blocked the enzyme and how much it's associated with BH4 reduction.

So coming back to our patient, when he has validated all those criteria, meaning that he or she has too much BH4, and a strategy to reduce BH4 production with SPR inhibition, we predict that a simple test from blood -- and now we have some evidence that you can also detect sepiapterin in urine, so blood or urine.

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You could determine for each patient exactly how much they react to the treatment, and that will, we hope and we predict, that would allow us and clinicians to find the exact dose for each patient that will allow them to have sufficient inhibition of the pathway to have, we hope, pain relief, without reaching a level that will cause side effects. That will represent a very individualized or personalized treatment.

This morning it was said that individualized or personalized treatment is not the same as precision medicine. I would argue that it's not the same, but it fits within the precision medicine. So once you have isolated the patients that you think are going to be good responders for a treatment, being able to trace to follow for each patient exactly how they respond to a treatment, to adjust the dose very quickly to get to sufficient levels will be extremely helpful for the patients.

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On that note, I would thank everyone who was involved in this study. That took a huge amount of work and effort from many very skilled people, including, obviously, Clifford Woolf and Mike Costigan, the two co-discoverer of this pathway for pain, as well as Alexander and Nick, who helped a great deal for the biomarker studies.

I would thank, obviously, all the funding agencies, without whom it would have been impossible to carry out this work. And I would mention a disclosure. That is, Clifford, Nick, myself and other members of this story have equity shares in Quartet Medicine, a startup company based in Cambridge that is trying to develop new SPR inhibitors that will be more -- that could be applied hopefully into clinical trials. Recently, they have a deal with Merck Medicine which helped them a lot more to hopefully have some clinical trials in the coming few years, I think.

I would like to thank you for your

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attention.
(Applause.)
DR. KATZ: Thank you, Alban, for that elegant presentation.
So we have a couple of minutes if we want to take one or two questions now, and then we'll be able to do questions and answers for an hour at 3:30.
Yes, Shai.
DR. SILBERBERG: Just that was fantastic. I just wanted to ask a very kind of simple question. If I saw correctly, it seems like the whole range of the effect of the inhibitor No. 3 was threefold. It means you went from 100 to 300, you had the maximal effect.
DR. LATREMOLIERE: Yes.
DR. SILBERBERG: Comment on that. That's kind of unusual to have such a tight concentration dependence.
DR. LATREMOLIERE: The one thing I would start by saying is that we've been -- the maximum dose we showed here is the maximum dose we could

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get into the animals. We could not get higher because of solubility issues in the compound. So we don't have the full dose response of how much the compound could lead to even more effects, if that is answering partially your question. No, not really?
DR. SILBERBERG: There were two graphs. One had the bar graph. You had three concentrations where there was no more effect.
DR. LATREMOLIERE: Yes.
DR. SILBERBERG: You had already reached maximum effect. But the ratio to that point was a threefold difference in concentrate.
DR. LATREMOLIERE: Of sepiapterin, the threefold difference?
DR. SILBERBERG: Go back one. So you go from zero and obviously nothing, and then you have 0.1 and by -- well, here it looks like a 10-fold, it looks like, but at 1, you're at maximum already, right?
DR. LATREMOLIERE: Yes.
DR. SILBERBERG: Then the next figure, so

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you can clearly go from 2 to 10. You can go up to 10 micromolar, but in the next figure at 300, you're already at maximum.
DR. LATREMOLIERE: I agree with the point that we reached a ceiling effect of in vitro, and we've seen that the more we go into the whole animal, the real system, the less in vitro and the more in vivo we go, the less potent the compound is.
But here, for the in vivo aspect, the reason we could not get higher than 300 -- I could not say 300 milligram per kilogram is the maximum efficacy of inhibition. We were stuck for the in vivo part. That's the maximum we could give of this compound into the animal.
I don't know if you were to give 400 or 500 milligram per kilo, if we would have more efficacy or if we're at the maximum effect of this for the blockade of the enzyme.
DR. WOOLF: Just a further comment on the cell-based assay. If you go back, when it's an in vitro assay, just at the enzyme, you get a

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perfectly normal curve. Cell-based assays are very different. It's all the problems of uptake of the drug, all its exclusion or inactivation. There is a dose response, but it's not the same as you get when you look at the activity of the enzyme.
DR. KATZ: Let's go to Troels, who had a question, and then Verru, and then we'll have to move on.
DR. JENSEN: Just a brief question. So I understand that BH4 is involved in inflammatory pain, involved in neuropathic pain and even in dysfunctional types of pain.
Do you consider this mechanism as a sort of basic mechanism driving pain? Because, for example, mechanisms of neuropathic pain is quite different in terms of underlying mechanisms from inflammatory type of pain. But since it's involved here, do you think it's a sort of a background type of thing?
DR. LATREMOLIERE: I would say no, because although it's involved in the two types of pain, it's through different cell types. At least

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neuropathy pain, you have a very strong neuronal involvement and, also, on top of that, some microphages that participate. But in inflammatory pain, what we found is it was only from microphage the effect. So there was no neuronal GCH1 of production.

The BH4 upregulation, this pathway is not the same as saying that it's a pain pathway. It's involved in different types of pain, different cell types involved.

DR. JENSEN: But if I understand, in the very first study by the investigator in the Nature paper, you looked into the low back pain group, and you showed that it played a role here. So this is a clearly -- I don't know what it is clearly, but it's certainly not pure neuropathic type of pain.

DR. WOOLF: A further factor is something that Alban hasn't mentioned, that in the middle of the study, we read a paper in Nature Chemical Biology conducted by Kai Johnsson, who subsequently became an active collaborator of ours.

What he did was he did at least a three-

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hybrid screen. Instead of the usual test in the pharmaceutical industry where you have a target and you throw drugs against, he started with a drug and looked for the target, and the drug that he looked for were drugs where there's known efficacy in patients, but no known target. One of them was an anti-inflammatory drug called sulfasalazine, and the target he pulled up was sepiapterin reductase, reinforcing its involvement and its use for rheumatoid arthritis and inflammatory bowel disease.

So we think they are acting in different ways, but it may mean that hitting this pathway could be beneficial in any pathological situation where there's an abnormal increase in BH4.

DR. KATZ: That last question for Veeru.

DR. GOLI: Thank you very much. Great information, new to me. So I'm trying to understand the concept.

If you have nerve damage and excessive production of BH4, then you have pain, and if you have nerve damage and no production or less

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production of BH4, you don't have pain?

DR. LATREMOLIERE: You have less pain, yes.

DR. GOLI: So is this generalizable to all pain conditions that if you have pain and nerve damage, do you have to have a marker, biomarker? Isn't pain itself a biomarker in that sense?

Does that make sense? I'm just trying to understand if the effect is generalizable with respect to the presentation.

DR. LATREMOLIERE: Yes, we need to do more studies to confirm exactly which conditions are susceptible to the increase of GCH1 in sensory neurons, for example. But so far, what we've looked at is that, indeed, when you have nerve injury, you're going to have increase of GCH1 in sensory neurons, in which case, in all those conditions, we predict that reducing BH4 production will be associated with less pain.

So yes, it would be, and that's why the biomarker. That's why in the second part of the talk I was saying that initially, you can find if patients have neuropathic pain, I would suggest

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that they're likely to have BH4. Then you can check on their genetics to see how much they're likely to produce more BH4, in which case we predict they would have less pain if you reduce those levels.

DR. KATZ: Thank you, Alban.

DR. LATREMOLIERE: Thank you very much.

DR. KATZ: I'd like to introduce now Simon Tate. Welcome up, Simon.

As probably all of you know, Simon was leading the pain program at Convergence and now is leading the pain program at Biogen. He reminded me earlier that he's been doing pain drug development since 1992. So he's been at this for a while.

He will be speaking about preclinical aspects of development of precision medicine for sodium channels.

Thank you, Simon.

Presentation – Simon Tate

DR. TATE: Thank you very much, Nat, and thank you to the organizers for inviting me.

It says preclinical. It's kind of more

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translational, actually, and I will touch a little bit on clinical. I think there were three main themes that I want to bring out here.

The first one relates to the sodium channel itself and the advances made there. The second relates to the molecule. I think precision medicine requires a thorough understanding of the molecule, and I think I'm going to show that to you with one of the molecules that we've been developing, that the more you do to understand the molecule, the more chance you've got at matching it to a particular patient. Then I'll mix in, as the third theme, the actual indications themselves.

We've had channelopathies mentioned, but actually, channelopathies are rather an amazing group of ion channel mutations. There's a quote here that comes from a guy, William Harvey. Many of you will know the William Harvey Institute in London that was founded by Sir John Vane, the inventor of aspirin and the mechanism of action.

It's actually a really nice quote, because essentially what he's saying is that by studying

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the rare forms of disease, you can learn a lot, and that's essentially what we've been doing in some of the pain area by studying really rather rare pain disease states, such as erythromelalgia, which I will talk about, and trying to generalize that in the future to other pain states. I will discuss that a little more.

As I said, channelopathies are really interesting, and when you look at them -- and this is probably not the most up-to-date review, but it's from a couple of years ago. It's nice that somebody actually took the effort to pull this together.

You'll see there are 79 phenotypes in nervous system channelopathies, many relating to various forms of epilepsy, as I'm sure you know. What you will see is that 16 of those 79 relate to pain and/or sodium channels, and I'm going to focus on the sodium channel because it's what I know most about. But I think some of these channelopathies really help to gain an insight into disease.

So the structure/function of channelopathies

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has really led to a lot of the tremendous work that's been done, particularly by Steve Waxman at Yale and his group in sodium channelopathies.

I'll show you a slide here that is the amino acids diagram, the polypeptides chain of the Nav 1.7 channel. What you see here is the channel, and you'll see these circles, which are amino acid mutations, in the Nav 1.7 channel, whether in erythromelalgia, which are these red ones, or small fiber neuropathy, which are the gray ones.

The first interesting thing is that they do cluster into interesting areas for the function of the sodium channel. So in the intracellular loops, which are probably involved in regulation, in activation of the channel and also in the voltage sensing regions of these repeat transmembrane domains.

The two pain areas which are of most interest here are erythromelalgia, which I will talk about, and, also, more recently, small fiber neuropathy, where many of these sodium channel mutations have also been found. I'll explain to

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you how I think we can go about this from a precision medicine direction.

Like perhaps many speakers, I'm a little bit mixing personalized medicine with precision medicine, but I think it helps to set the scene for how we can go about getting the right drugs to the right patients.

Back in 2010, we reviewed a lot of placebo-controlled trials in neuropathic pain that had been run with what we call sodium channel blockers. Actually, one of the themes I want you to take away is when is a sodium channel blocker a sodium channel blocker, because these things often do many other things. We call them sodium channel blockers, but what I want to show you is that when we get into the more detailed mechanism of action studies, it's how they actually block the voltage-gated sodium channel that may be the most important component.

I think we're fortunate to have so much ability with voltage-gated sodium channels to look at the biophysics of the interaction between the

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potential drug and the channel, which we don't have in some of the other mechanisms that we're taking forward in pain. We do have it for some in some of the enzymes that we've just seen in the previous talk, allow that really detailed structure/function analysis to be done.

But initially at least, and this is a pretty broad-brush approach, but looking at all those neuropathic pain studies, you can see that approximately half showed some signals. These vary, but what you can say is that when you take a subset of peripheral nerve injury, lumbosacral radiculopathy and trigeminal neuralgia, then there is an increase in the success, perhaps indicating that there's something about these indications. There's something about the pathophysiology of these indications that lends them towards the positive future clinical studies.

Of course, we all know very well now the Nav 1.7 story. I'm not really going to exemplify very well I'm sure. You've all heard it where there are mutations that you saw on the previous slide which

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give rise to a gain of function, and on the flip side of the coin, there are patients who have a gene knockout, a loss of function of the channel and an inability to feel pain.

So that's a really nice starting point. If we didn't know that sodium channels were already involved in pain, this would have really have accelerated the target.

So back in 2012, I put this slide together, which was how are we going to find out if Nav 1.7 inhibitors are actually going to work in chronic pain, and I'll come on to the molecule in a moment. But it's absolutely essentially to have a molecule that's going to test the hypothesis. Too often in the pharmaceutical industry, we have actually taken molecules into clinical development. We should not allow those to test the hypothesis.

The one part of this which some of you may notice is that I've added CNS penetration on. I actually think this is really important. Even though this molecule is largely in the periphery, I think access to the CNS, access to the first

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sign-ups in the spinal cord to where the peripheral nerve goes into the spinal cord and the dorsal hole, I think is actually very important and very important for efficacy.

Phase 1, of course, we want a high quality molecule. I know in terms of the proof of concept here then there are three potential themes here. The first one, which I just mentioned, which we've completed in our phase 2 study, is the pharmacologically validated condition.

So I think perhaps most of us know that trigeminal neuralgia is particularly well treated by carbamazepine or, also, oxcarbazepine and predominantly through a sodium channel mechanism, and I'd like to show you how we believe that's true from preclinical data.

Then you can look at the combination of inferred pharmacology from sodium channel blockers that are used in lumbosacral radiculopathy as a compression neuropathy, where we believe we have some of the electrophysiological types that lend themselves, again, toward sodium channel block.

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Finally, the more precision medicine side, where you actually gear your drug therapy towards a patient that already has a defect, an increase in function of the particular channel that you're targeting.

What you won't see here is you won't see diabetic neuropathy or PHN, because whilst sodium channel blockers have some activity there -- and I think we're going to hear about a very nice study that was run in 2014 from the next speaker, with looking at the irritable nociceptor, it's very clear that there's a very heterogeneous and perhaps not the best first indication to go in with a sodium channel blocker unless you can subset your patients.

So I mentioned the molecule. I just want to take you through some of the pharmacology of the molecule, because it is important to understand this, and I think I want to show you how you can differentiate over the existing drugs that we use.

First of all, with respect to Nav 1.7, this molecule that we have tested is not specific for

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Nav 1.7. So that's not the only channel it hits. I actually think that's rather important, because whilst genetics leads us to Nav 1.7, it is not the only sodium channel that we have in our bodies.

The pain pathway is transmitted through the spinal cord to the cortex, for example, and so there are sodium channels doing other things there. Maybe they're quite important and those are the Nav 1.2 and Nav 1.6 channels.

What we have here is a molecule that is selective. It has a 10-fold selectivity over the predominant channels in the CNS, 1.2 and 1.6, and a much greater selectivity over Nav 1.1. I'm going to explain that, and that's actually very important why it has selectivity over Nav 1.1 because of its role in descending inhibition.

So really I think this is a very key slide to explain how understanding the mechanism of action allows you to tailor a treatment. So what we have here is a train of pulses, a train of action potentials, if you like, in a frequency dependent type of paradigm. So you elicit 10

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pulses, and then you look at the block. We're comparing our molecule, BIIB074. Changed its name when we were acquired by Biogen. It used to be called its longer name, so I'll just call it BIIB074 from now on.

What you'll see is as the train develops, the block develops rather rapidly with BIIB074. So you have a small amount of block on the first pulse, that's your tonic block; a much greater amount of block on your 10th pulse, that's your use dependent block.

With carbamazepine, as you can see, you have a small amount of block, which gradually develops, but you haven't got a large amount of block. What does this mean? This means that in order to be effective, you're going to have to give a much higher dose of carbamazepine. Of course, we can't give a higher dose of carbamazepine because of the side effects of that molecule.

So already this drug looks different. It looks different to any other sodium channel blockers with respect to this particular mechanism,

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and it also has frequency dependent block at all the channels. So as you increase the frequency of stimulation, the block increases. That is very good from a perspective of if you have a train of action potential, high frequency firing, burst discharges as you do in those compression neuropathies that I was talking about.

So this is tailoring the drug to the patient in terms of mechanism of action. Then you're going to actually potentially have a beneficial effect, as well as potentially beneficial on the side effect profile, because you don't want to be hitting these channels necessarily tonically, which I think is what's more happening with carbamazepine. Carbamazepine has a very nice use dependent block, actually, frequency block. It's Nav 1.7, but not at the other channels, and I think that may underlie some of the toleration issues that we see with carbamazepine.

I won't dwell on this, but it's really important to do the tissue pharmacology, as well. As you've seen earlier from Clifford's talk, this

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tissue pharmacology is potentially going to be moving toward human IPS cells. So we can do that in the human state.

What I can tell you is that -- I haven't got a slide to show you -- we have also studied the effects of this drug on human DRGs. So from a collaboration with a company in San Diego called Anabios, who seems to be very good at getting donor human DRGs, we performed electrophysiology on human DRGs and showed that the pharmacology on human DRGs was the same as we'd seen on rat DRGs.

That's not trivial. There are many mechanisms where there's species differences, and an example is TRPA1. There are great species differences between mechanisms. So for TRPA1, there are human versus rats versus dog, for example. You see a lot of difference in species pharmacology. That makes drug development more difficult.

This is just showing that we get a nice frequency dependent inhibition of firing in rat DRG neurons, which can be washed out.

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Then before moving to talk about the genetic studies, I also want to show you something around tailoring the molecule to the patients, as well. So there's quite a lot on here, but essentially what this is showing is that for the proposed doses that we're carrying out in clinical development, either BID or TID doses in trigeminal neuralgia, or painful, there's a P before it now. Biogen liked the P. Painful lumbosacral radiculopathy.

This is a simulation of the PK in terms of TID or BID dosing, and this is the extrapolated equivalence, human exposure to get either full reversal of hyperalgesia in an animal model or the minimum effective dose.

You can see that there is a C trough here. Where you're at the C trough, you still have coverage of block of your -- you have PK coverage, coverage of the exposure that's required to get full reversal of the hyperalgesia. This is translation really, but it's really important to understand your molecule and be able to show that before taking it into a human clinical study.

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Finally, I mentioned that how do we know that carbamazepine is working in trigeminal neuralgia because it hits Nav 1.7? This is more translational data, again, and what we've done here is basically to pick one particular physiological paradigm. You can pick any you want. So long as you're consistent, you can work with this.

So we looked at the amount of block in looking at exposure of carbamazepine, BIIB074 at two doses and the lamotrigine to look at. You can see that there's quite a lot a wide PK with carbamazepine, but you can see against Nav 1.7, you can get up to 38 percent block here, very high block at Nav 1.2 and 1.6, probably too high, which I think leads to the side effects.

You can see with the doses that we're proposing to study in the clinic and have studied that we have a nice high block of Nav 1.7, a slightly lower block of these others because of the selectivity.

But look at lamotrigine, and lamotrigine, whilst it has some efficacy in trigeminal neuralgia, it doesn't have anything like the efficacy of carbamazepine. I think you can see from here from doing these sorts of studies and you can test other drugs as well that we've looked at, they're pretty weak when you actually study the clinical concentration that's used in the clinic and look at the Nav 1.7 block.

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So let me move on to -- and I think so that was really to tell you that you've got to get the right molecule and you've got to understand the molecule very, very well. I think it's a key part of precision medicine.

I think erythromelalgia has become very well known by the pain community because of the Nav 1.7 genetics, and it is a pretty debilitating disorder. It is actually very refractory to drugs, and so what we do know, though, is about 15 percent of erythromelalgia is caused by mutations in Nav 1.7.

So here's some precision type of work that we've done in collaboration with Steve Waxman. So we're continuing to study more mutations, but here are four mutations that we've studied, V400M, 1234T, S241T and F1449V.

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What I'm going to go on and show you, the summary is here, is that therapeutic concentrations of BIIB074, there is much more block against cell lines expressing these EM mutations than there is in wild type. So we didn't actually know before we did this experiment whether we'd get more block or less block. Some of my electrophysiologists were actually predicting we might get less block than against wild type.

What we actually saw was a lot more block, which we don't see for carbamazepine. So that's very encouraging. We're actually seeing a differential effect versus this drug that we understand the mechanism of action for than we're seeing with the drug that's used in the condition.

Now, this is a very busy set of biophysics slides. I don't propose to go through them all with you, but I just want to try and show you what we've actually got here. So the black bar here represents where we have the clinical exposure, because there's no point in looking at these graphs

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unless you map onto it the clinical exposures.
What you'll see and what you really need to look at here is in the box, the red line here, for example, is against the mutation and the black line against wild type. So you'll for each mutation that the clinical dose against the mutation is more efficacious than against wild type in each case.
This one is the most extreme here where you can see the green line here is the mutation and the black line is the wild type. So different mutations also show different sensitivities to the drug, which we would expect, and that's good to see.
What I wish I could show you is the clinical study, but we're starting that. We're in the middle of getting that clinical study off the ground and hope to have the data within the next year.
So just to summarize then, what we can see on this graph is, for example, for this mutation I've just shown to you, S241T, and what you can see is carbamazepine. You'll see really very little

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difference here, whereas with the BIIB074 drug what you can see is much, much more activity. So more activity against all of the mutations with BIIB074 than we see against wild type, and carbamazepine shows no difference.
Other groups have been working on this, as well. This is a very recent paper from Cao from the Pfizer group in Science Translational Medicine where they looked at a study in four or five erythromelalgia patients, and they derived, as Clifford described earlier, sensory neurons from white blood cells that were taken from these patients.
There are changes that are observable in these IPS cells. So these are the donors D1 to D4 without the mutations, and what you can see is essentially there's less -- this is a trace up here. There's actually less spontaneous activity is IPS cells derived from normal donors than from those derived from erythromelalgia cells.
We might have expected this. Nav 1.7 is involved in the run current, and you expect higher

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spontaneous activity. But it's nice to see that in IPS cells.
The other thing that you can say, there's a trend here where this is looking at firing frequency, slightly higher firing frequency in the erythromelalgia-derived cells than there is in the donor cells.
So again, it's a nice thing to see, and I think what was quite impressive about this paper is seeing an effect on heat. As we know, patients with erythromelalgia are usually incredibly sensitive to heat, and so what this slide shows here is when you do a run up to 40 degrees, for some of the EM, for three out of the four EM cell lines, there is a differential response to heat, an increase in heat than there is in the wild type donor cells that you can see here, a differential response to heat.
So they're kind of activated by heat in this in vitro situation, but again, that's nice data to have and nice to be able to show that that is blocked by your compound.

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In addition, one of the pre-reads for the meeting from Paul Geha, who works with Steve Waxman, looking at the very mutation that we've studied, as well, S241T, showing that carbamazepine can decrease the firing frequency, which also affects increasing the temperature of this mutation. Now, this is carbamazepine, which we've already shown doesn't have a differential effect particularly against Nav 1.7 channels in the mutations, but at least it's nice to see that this drug does show some efficacy against this patient.
The reproducibility is not great here, but in terms of looking at these two patients, what Paul and Steve did was to look at some of the key features of this disease in terms of duration of the pain, in terms of awakenings at night, for example, and showed a beneficial effect with carbamazepine. So again showing that this is good for the development of our drug, because carbamazepine, which we know is moderately effective in some of these patients, we believe that by taking a drug that's more potent, we should

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have more activity against these mutations. So again, that's tailoring the study.

So we are currently getting this study up and running in several of -- in as many erythromelalgia patients that we can get manage who have mutations.

Actually, how long do I have left, Nat?

DR. KATZ: You have 7 minutes, including any questions.

DR. TATE: Okay. Well, just very quickly, I just wanted to show you that we have more confidence in this molecule and from the study that we have performed in trigeminal neuralgia and, also, the study in painful lumbosacral radiculopathy. Just to mention trigeminal neuralgia, you are very familiar with this condition. Again, a nerve entrapment, you can see the theme with the personalized medicine here.

But just to show you the impact that the drug had on these patients, you saw Mike actually outline how common this kind of study design is becoming, the enriched study design, the randomized

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withdrawal design. Very briefly, we had all patients on drug for three weeks of open label, and they had to have a 30 percent decrease in the number of attacks or the duration of the attacks to be randomized onto study drug.

What we found was that -- and these patients were obviously all having paroxysms and pain. They're largely carbamazepine entering the study. What we found was that of the patients who completed the study to open label, that was just over 70 percent, and the pain reduction was 60 percent. So 70 percent of patients had an average 60 percent. They all had greater than 50 percent reduction at this point.

Just to show you really diagrammatically how the study looks, so we have placebo in red and drug in blue. Obviously, the first three weeks are open label. So you can see a nice reduction here during the open label period and then this nice separation between drug and placebo in the double-blind period.

You'll see very nice p values and pain

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reductions dependent on whether is BOCF or LOCF. This is just a post hoc analysis. You can see two and a half points on our NRS scale where -- what's nice to see is that most of these patients responded, and so that's your kind of the precision in terms of picking the right indication for the right molecule, the theme I mentioned at the beginning.

Just to mention that we actually had favorable efficacy outcomes on all endpoints in the study. I've listed them here, but in terms of treatment failure, the Kaplan-Meier analysis and PGIC and SGIC. So you can see when a molecule works, it tends to give you very nice clinical data.

Related to the mechanism of action of the molecule, the safety and toleration profile that we saw was a good one. It was very well tolerated, and, in fact, in the double-blind phase, the profile of CNV802 BIIB074 was similar to placebo, and we haven't seen any significant changes in labs or blood pressure.

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So how do we build this together? So how does this come together as kind of an integrated development plan, taking the precision medicine side and taking the more personalize approach on the top? So we're moving this forward in trigeminal neuralgia.

I call this sciatica. This was more of a commercially focused slide. This is the lumbosacral radiculopathy study.

Then we are investigating, as I mentioned, erythromelalgia and plan to initiate a study in small fiber neuropathy. We're just working to define that study at the moment, because actually in small fiber neuropathy, as many as 20 or 30 percent of small fiber neuropathy patients may have a mutation in their Nav 1.7.

So we'd like to run a study in small fiber neuropathy, of course, genotype all of the patients, and then we can move ahead and ask the question, do those patients carrying an Nav 1.7 gain a function mutation have a preferential response to our drug.

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Then, of course, that would open up the question of where next in terms of how do you develop a companion diagnostic or whatever else you need to do to go to the next phase of personalized medicine.

I will finish there. I'd like to really thank these guys who have been with me for many years in a small company moving forward on pain assays in a very focused way, and, of course, our collaboration with Steve has led to the erythromelalgia work. So thanks.

(Applause.)

DR. KATZ: We do have time for a couple of questions if anybody has any.

Go ahead, Ralf, please.

DR. BARON: So we all have learned that trigeminal neuralgia is a paroxysmal disease, but we now realize that there are two types of trigeminal neuralgia, one with ongoing background pain. Did you distinguish between those groups in your study?

DR. TATE: No, we didn't. We didn't

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actually ask the patients for their ongoing background pain. We selected the patients as kind of type 1 TN patients. So I think looking and talking back to the investigators, some of those patients did have ongoing pain, because --

DR. BARON: So they should do it in the future.

DR. TATE: So in the next study, then I think we need to actually ask those questions. I agree, Ralf.

DR. BARON: What was the primary endpoint of your trial? So I saw BAS or something.

DR. TATE: No, no. The primary endpoint was the treatment failure endpoint. I actually had the Kaplan-Meier plots, which I went through quickly.

DR. BARON: You did show those.

DR. TATE: Yes.

Clifford?

DR. WOOLF: Convergence is not the only company that's been looking at this target. Pfizer have had treatment failure. Could you comment on

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at least why you think that may be so?

DR. TATE: Well, obviously, I haven't looked in detail at the results from that clinical studies. I've seen what they've presented, but I know their molecule reasonably well. Their molecule is highly peripherally restricted. I think it really is important and I think several groups have now shown, including ours, that having a molecule that accesses the CNS is really important.

Actually, when you -- experiments have been done actually by several groups now to show that if you take these highly selective Nav 1.7 molecules and you study them systemically, they don't work very well in chronic pain neuropathic pain models, the rat models, but they will work if you inject them intrathecally.

I think for one reason or another, it seems important to get those molecules into the CNS, or maybe just by the fact that the molecule can get into the CNS, it can also access the site much better, so it can actually get across the nerve

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barrier and get to the molecules. So I suspect it's entirely molecule-related, not target-related is what I should say.

DR. WOOLF: I have a second question. John Wood has recently come out with interesting data on the involvement of proenkephalin in the congenital insensitivity to pain and with the loss of function mutation, which is obviously a big surprise, if true. Do you have any comments on that?

DR. TATE: No. I mean, obviously, we haven't looked very much into John's finding of the proenkaphalins and the kind of central hypothesis revealed. So it's kind of based on one or two patients, I think, and I think we need to do more work on it, Clifford, really for me to make a -- I haven't actually done our own work on that, that mechanism.

DR. KATZ: Let's do one final question.

DR. ANDREWS: You had a pain readout, which was positive, so you necessarily didn't need to investigate on one -- my point was if the compound hadn't shown positive effect, analgesic effect, how

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would you have prosecuted the analysis of that? Because it's difficult with ion channels of sort of biomarkers, as you mentioned. Everybody thought --

DR. TATE: Halfway through the trigeminal study, we were seeing patients who were going to no pain and no paroxysms, and we, at that point, decided to do a protocol amendment and genotype all patients in the study. So I can tell you that there are very few patients who have Nav 1.7 gain of function in the trigeminal neuralgia cohort, but they have some very interesting other mutations that I can't talk about, but obviously will do in the future.

I think that we do genotype all of our studies, and so we've genotyped the studies that we're performing at the moment. We will retrospectively go back and look at response against genotype, and, of course, that's the great thing about all the basic research that's being done. We can then go back and look at responders against particular genotypes.

But because we picked what we believed were

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the best indications to go after for the mechanism, I think that was the important component here. I think in the future, of course, we'd love to get into diabetic neuropathy, but we have to find the right targeted way in. That perhaps would have been a better example to do the sub-genotyping.

DR. ANDREWS: I was focusing on what sort of measurements can we make when targeting ion channels.

DR. TATE: Oh, I see.

DR. ANDREWS: Maybe it's for the end of the --

DR. TATE: Yes, I think that's a long discussion, but I don't think we can use threshold tracking. But I think we can discuss.

DR. KATZ: I see that we have three people who want to ask questions, but I don't want to keep Troels waiting because he endured a long and arduous journey to join us today. Before he falls asleep, I'd like to get him up here to talk to us about phenotyping in clinical trials.

(Laughter.)

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DR. KATZ: I apologize, and I look forward to hearing everybody's questions during the discussion later.

Presentation – Troels Jensen

DR. JENSEN: Thank you very much, Nat.

Thank you to Bob and Dennis for organizing and for inviting me to come to this very interesting meeting on sodium channels, which is something which has interested me for a long, long time.

Now, you want to pay your attention to this slide here which is from Ramon Cajal, a famous Spanish anatomist who in 1913 presented this one, what happened if you have a complete injury to a nerve or a partial injury to the nerve. Then there are a lot of changes there, and we know from people who have neuropathic pain conditions that this can be a generator site for development of many types of pain, including neuropathic type of pain. We want to treat that as good as possible, and I think that sodium channels is one of the very good examples of that.

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Now, being a neurologist, we have used one of the most classical sodium channels for a long, long time, which is phenytoin, and we still use it. In fact, when patients come in with very intractable trigeminal neuralgia to our clinic, we, in fact, give them an intravenous infusion of phenytoin with the same doses that we use for patients that are in an epileptic status. The pain goes away immediately after loading them with phenytoin, and that's a very good example that you can, in fact, kill the pain immediately by a sodium channel blocker.

It's still used. Now, phenytoin is not used very much anymore for treating epilepsy, but it's a very good drug in that sense. Now, it has many side effects, and we will also see that many of the other drugs have side effects.

I'm going to talk about sodium channels as targets here, and I don't want to repeat what Simon has just told us here. But we know quite a lot about how these ion channels work, and we also know that there is more than one. Now, you heard about

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Nav 1.7, but there are obviously nine isoforms here. Some of them are involved in pain.

Here, you can see the sodium channels and their relevance to sensory processing and where they, in fact, are distributed. You can see their genes, their distribution, their response to tetrodotoxin. Some of them are sensitive to tetrodotoxin, and others are resistant to tetrodotoxin.

Those that are interesting in terms of pain are those in Nav 1.7, 1.8 and 1.9. I won't say that some -- that these ones are not interested in pain, for example, Nav 1.3 and Nav 1.6, they may be also interesting in terms of pain. But these are important, and we know some of the mechanisms by how they may influence sensory processing and nociceptive processing along the nerves.

So I made this cartoon about the ion channels involved in the processing of nociceptive information, and this is a nociceptive primary afferent here coming in with the endings a specific injury here and the transmission to second order

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neurons here in the spinal cord.

There are different types of ion channels that are involved here. For example, these non-selective ion channels, the TRPV1 is one example of that which can be activated, for example, by heat and also by acid here. The Nav 1.7 and 1.8 are just examples here that may be expressed here out in the peripheral terminal, and that can also be activated by various types of stimuli.

We know that at the site of injury, there is also change of ion channels here. There may be an upregulation of certain channels and accumulation of channels at the site of injury. We know that there may be even abnormal expression of ion channels that were not formally present here at that site.

The sodium channels are not the only ones that are involved. We also know that a whole list of different potassium channels involved also in driving the action potential here.

At the central site here, we know that, for

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example, the channels also may be involved, in fact, indirectly in driving the posttraumatic potential here. We know that, for example, release of glutamate, which may in fact be done by calcium channels here, act on NMDA receptors. We know also that substance P released also from the presynaptic terminal may act here on NK1 channels . So sodium channels are involved along just from the periphery and into the central site here.

Just also to mention that they are involved also, myelinated, that sodium channels are involved also in the transmission of action potentials along the myelinated fibers.

We know that the saltatory reduction of conduction velocity here takes place here at the Ranvier nodes here where there is a large expression of sodium channels in the node itself, and in this juxtaparanode region here, there is an expression of potassium channels here.

For example, following injury, there is this up-regulation of sodium channels, as we should see later, which also play a role.

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I will not go more into detail on this, but this is to just set the scene about the sodium channels and that they are clearly involved in nociceptive processing.

So just allow me to give my own personal view about precision medicine. I think I have very much difficulty in distinguishing between precision medicine and personalized medicine. I think the two phenomena, in fact, go hand in hand. You cannot have personalized medicine unless you also have precision medicine and maybe also vice versa.

So what is precision medicine? This is my very simplistic view about it. So when we have a patient coming into the clinic, he or she has a pain, and then the ordinary thing that you do in the clinic is that you try to -- you know that behind that pain, there is an etiology, there is a genotype, and there are also exogenic factors that may play a role here.

We try to dissect into this by establishing clinical phenotypes. We do various types of diagnostic measures, and based on this, we, in

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fact, come up with some proposal for a pathophysiology for that and then try to apply a rational treatment to that.

Now, if we look at it in terms of sodium channels, how does this precision medicine then look like? Well, almost the same. So we have an etiology which is then specific for sodium channels that there may be also exogenic factors here that are specific. We can, in fact, and sometimes we can find irritable nociceptors by the clinical examination.

We can do QST measure examinations, or we can do skin biopsies and try to identify something which we would call irritable nociceptors. Then based on that again, we have an idea about pathophysiology and apply a rational treatment.

In terms of sodium channels then, the choices we have are phenytoin, as I said, but it's also carbamazepine. It's oxcarbazepine. It's lidocaine, which we'll come back to in a moment. Then these are the types of specific sodium channel blockers, and there are the drugs as well, which we

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shall see.

So why may precision medicine, in fact, be difficult to apply? This is things that I find myself that makes it difficult to really apply precision medicine. I think one of the main problems, and I think this is something we have been struggling with for many years and we're struggling with it -- that there is no gold standard for neuropathic pain as, for example, for cancer, which we discussed before. Neither based on history nor examination, we cannot come up with something and say this is neuropathic pain.

There is low specificity, a variety of symptoms and signs. Some have better specificity than others. There is no specific sensory profile for sodium channels, for example, what we called irritable nociceptors, as we shall see in a moment.

The existing sodium channel blockers are very unspecific. They have other mechanisms, and, for example, the tricyclic antidepressants is a very good example of that. They have a sodium channel blocking property, but their main action is

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working on the monoaminergic uptake transporters. They're also working on NMDA receptors. They also have an opioid action. They also work on choline receptors, et cetera, so very dirty type of drugs.

Another point is that the neuropathic pain disorder caused by a sodium channel abnormality may, in fact, drive other pain mechanisms and comorbidities that are unrelated to sodium channel. That is, for example, many chronic pain patients have other conditions such as comorbidities which may not have anything to do with a sodium channel blocker, but what we are recording in the clinic is, in fact, pain intensity which is a very crude measure and which does not necessarily reflect anything which has to do with a sodium channel blocker. We need to be better in doing that.

So let me give you some clinical approaches for targeting sodium channels, and I will just talk about two things here. I will talk about identifying potential responders, so-called irritable nociceptor, and I will also talk about changed target by altering the administration, that

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we can, in fact, get to the target by making a different administration of a particular drug.

So we do know something about how drugs work at the present time. For example, we know that here just looking at the dorsal horn of the spinal cord, if there is a presynaptic neuron and the postsynaptic neuron and a descending modulation or an interneuron here, we know some of how drugs and where they, in fact, work. For example, on primary afferents, we have also the tricyclic antidepressants because they have sodium channel blocking properties. They act here.

We know pregabalin, gabapentin work probably on some of these presynaptic calcium channels. We have oxcarbazepine. We have phenytoin. We have oxcarbazepine. We have carbamazepine. We have lamotrigine. We have lacosamide, topiramate, levetiracetam. They all have sodium channel blocking properties.

Now, these three are not used anymore for treating neuropathic pain, at least not approved for it, but we also know that there are other

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drugs. For example, opioids may act segmentally on the postsynaptic site. We have the tricyclic antidepressants. They may act here, because they act on, for example, monoamine receptors, and they also have an NMDA blocking property. NMDA antagonists also work on this site here. There may be descending controls.

Already at this point, we do know something about where drugs work.

So if we look at how we can treat patients with sodium channel blockers, there have been studies in which you, in fact, apply a topical lidocaine to the skin. Here, you can see a state in which there has been injury to both small fibers and large fibers. There are degeneration and regeneration going on.

So there is probably a lot of abnormal activity bombarding the DRG neurons and the second order neurons, so we generate this thing called central sensitization phenomena here in the spinal cord. Then, of course, if you then apply topical lidocaine here to the skin, you may, in fact,

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reduce some of this and normalize this central sensitization, so you have a normalized or at least a less aggressive output from the dorsal horn.

One of the first studies was done in Ralf Baron's lab, with Gunnar Wasner doing a study, which was lidocaine applied to patients with postherpetic neuralgia. This was, in fact, one of the first ones, maybe the first one where you try to identify something called a sensitized state or a irritable nociceptor.

So patients were divided into what is called sensitized nociceptor or an impaired nociceptor based on the QST and histamine flare and an axon reflex following histamine. There was a lot of faith in that study and hope that this would, in fact, give us some new information. But unfortunately, what happened following this study was that if you look at these individuals that had nociceptor degeneration and those that had nociceptor sensitization, there was, in fact, no effect in the patients.

They didn't improve better those patients

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that had the sensitized nociceptor. In fact, it was the other group that benefited best from the treatment. So this was sort of disappointing at this time, but again, you have to understand that these were patients that had an application of a patch that may not get necessarily to the target that you want.

Now, this has been improved better because the German Pain Network has developed this concept called the Quantitative Sensory Testing type of approach in which a series of phenomena are, in fact, measures for cold, for warm, for mechanical stimuli. You can get what you call a sensory profile for an individual patient or a sensory profile for a group of patients suffering from a specific condition.

Now, we defined in a study that was done within the IMI, which was this consortium in Europe where we did a large randomized controlled clinical trial and tried to describe patients with neuropathic pain and divide them into a group with so-called irritable nociceptors. Now, that was

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based on patients that had normal cold and warm detection threshold. They also should have dynamic mechanical allodynia or increased mechanical pain sensitivity or reduced cold or heat pain threshold. So these are a lot of different type of things that you are asking for here.

In the non-irritable group, these patients were individuals were characterized by a normal thermal or mechanical detection threshold and no thermal or mechanical hypersensitivity. So this is an example how it may look like if you have an irritable nociceptor. So there is a high sensitivity to heat and pain and cold pain and also to mechanical stimuli and a normal response of reduced response here. In those with non-irritable, they have a loss of function to many of the stimuli applied.

So this was used, this concept, in two studies, one in which there was a topical application to patients suffering from nerve injury of postherpetic neuralgia which was published last year. It was a peripheral lidocaine patch that

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there was a hypothesis that a peripheral lidocaine patch will, in fact, block spontaneous pain and hypersensitivity.

It was a randomized, double-blind, placebo-controlled study of two to four weeks' treatment period and with lidocaine 5 percent versus placebo. Here you can see the results of pain was reduced slightly by lidocaine, and lidocaine reduced pain in patients with the irritable nociceptor. That was mainly those patients -- and that was on what is called deep pain and paroxysmal pain.

So the conclusion from the study was that it had a weak effect only on active and certain types of neuropathic pain, and it was, in fact, more efficacious in patients with the irritable nociceptor type, as you can see in this figure here.

Now, another study which you have heard about is the study in which we used the same principle, and patients were then given oxcarbazepine or they were given placebo. It

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turned out that in this study here that there was a better effect of oxcarbazepine in those patients that had the irritable nociceptor. Based on the numbers needed to treat, it was much lower than it was in those patients that had the non-irritable nociceptor.

It's important to note that a lot of patients, in fact, went out of this study because they couldn't tolerate, probably for the reasons that Simon also talked about in the previous talk. We'll come back to this in a moment, that there are, of course, many side effects, which is, of course, a limitation of using these types of drugs.

Now, another way of looking at these things, so we can either -- we had talked about how we can, in fact, use topical administration or we can do systemic studies, and I just want to demonstrate here that by varying the administration of a particular compound, we can, in fact, get more insight into the underlying mechanism.

So the question here is will a peripheral nerve block, will a sodium channel blocker, will it

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remove spontaneous pain and allodynia? We carried out a study where we, in fact, asked the hypothesis that by blocking input from the periphery, lidocaine, then can we also abolish some elements of central sensitization? Can we also block the spontaneous pain in these individuals?

So what was done in this particular study here, and I'm just going to demonstrate it by a couple of examples of patients. There were two groups of patients that went into the study. These were patients with peripheral nerve injury, or they were patients with diabetic polyneuropathy. It was not a big study, seven patients in each group.

What was done was that these patients were given a peripheral lidocaine block and also an infiltration in order to block all input from the periphery, and then we monitored not only their pain but also their response to warm stimuli, to cold stimuli, to pinprick stimuli in order to see will all phenomena go away.

Then after that, they also went later on into a study in which they had this lidocaine 5

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milligrams per kilogram intravenously in order to look at the systemic effect.

So here you can see the response. This is the peripheral lidocaine block, and you can see, this is pain, this is cold sensitivity, pinprick and brush sensitivity. The block is given here, and then the pain goes immediately down. So within 10 minutes, you're down to zero. At the same time, cold sensitivity, pinprick, and brush sensitivity is also completely down.

Now, here, you can see the kinetics of the study. So this is the measurement of lidocaine in the plasma of these individuals. This is following the nerve block, and you can see there is very little lidocaine here in the plasma.

When you give IV lidocaine 5 milligrams per kilogram, you can see there is absolutely no effect at all, yet the concentration of lidocaine is more than 10 or 5 times higher. So in this particular study for this particular patient ,which is a 67-year-old male who had an injury to his left tibial nerve with pain in the foot and an NRS score of 7,

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we know, in fact, we make the conclusion that the pain this patient has is completely driven from the periphery and also the sensitization phenomena that you see is also driven from the periphery and not done by a central effect.

But there were patients also with diabetic polyneuropathy, and here we did see -- in fact, the picture was a little bit different. We could also completely block the pain from where the peripheral nerve block here in the foot and also sensitization phenomena, and we could block warm sensitivity, cold sensitivity.

When we gave lidocaine intravenously, there was an effect on -- which is a little complex in this particular picture, but there was an effect also on the pain response. This comes out in this graph in which you can see that following the nerve block, there was a complete abolition of the pain both in patients that had nerve injury and those that had a diabetic neuropathy.

But in those patients that had IV lidocaine, there was an effect in patients that had

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polyneuropathy. So that suggests that the etiology itself may, in fact, also play a role for the treatment response. So the thing is not that simple.

Now, this concept that lidocaine may have an effect more centrally has, in fact, been shown previously, and we were interested in it many years ago based on studies from Jean-Claude Willer and Daniel Le Bars in Paris that developed this model called a nociceptor flexor reflex, which is a central mediated reflex in which you stimulate the sural nerve and then record from the biceps femoris.

There is a correlation between pain and pain sensitivity and the magnitude of the reflex. So it's considered as a marker, if you will, an objective marker for pain response. We could show that, in fact, lidocaine could block this nociceptive flexor reflex without having any effect on sensory processing for thermal stimuli on the hand and foot before. So lidocaine may, in fact, have also a central effect at least in diabetic

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neuropathy.

We have used this idea about IV lidocaine for other types of studies, and it may be that it is a crude model for looking into mechanisms. But in this particular patient, you can see, for example, she has had an amputation and now suffers from spontaneous pain and allodynia and hypoesthesia, which is, in fact, blocked when you stimulate with a von Frey here for a 60-minute period with lidocaine.

I think it may, in fact, have something to do with an effect at central sites, and this is suggested by a study which came out last year, in which it was suggested that systemically applied lidocaine may have antihyperalgesic effect through its metabolite and through glycine by increasing the spinal inhibition of pain through a specific transporter, the glycine transporter 1.

So at least it's open for discussion that lidocaine, in addition to having a peripheral effect, also may have a central action where this is related to some of the sodium channels that are

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expressed in the central nervous system, such as Nav 1.3. That I don't know, but it is a possibility.

The other point here is that the etiology of nerve injury may, in fact, influence the response to sodium channels. We know that there are structural and functional changes following nerve injury with development of irritable nociceptors.

Some injuries may give rise to a selective injury either of large fibers or of small fibers. In some cases, there may be injury to both the large fibers and small fibers with degeneration and regeneration. In some cases, there is a specific cut, and the output from this in the dorsal horn may, in fact, be different in these different conditions. So one injury is not necessarily the same even if it's out in the periphery, and the crush may also have different effects.

The final thing I just want to suggest is that structural changes perhaps also can be used to identify responders to sodium channel blockers, and this is a slide which I got from David Bennett

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based on his study that Annina Schmid did in patients with carpal tunnel syndrome.

What you see here is it's a triple-stained nerve fiber, where you can see the green is myelin basic protein and red is Caspr, which is, in fact, an indicator for contactin-associated protein, and then there is also the blue staining for sodium channels.

What you can see here is that there is this elongation here of the node and with an increased expression of sodium channels here in these types of nerve injuries here.

So then the question is can we, in fact, address this by blocking input there, and this is from a case that had a neuroma. He responds very much to lidocaine, but not to placebo responses. He had later a removal of these neuromas here.

Together with Waxman, we did a study years ago where we, in fact, could demonstrate that there was an upregulation in some of these neuromas, both Nav 1.7., 1.8 and 1.3. We, in fact, also went on, there was also an increase of map kinases, but we

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won't talk about this now.

But we went on and, in fact, gave to these individuals and tried to see how lidocaine would work in these individuals. It's a very small study, and it's a very confusing study. But patients were given either an IV infusion of lidocaine or an IV infusion of saline.

Here, you can see their pain responses. This is the percentage change of pain, and some of them had, in fact, an increase of pain. Only a few patients, in fact, had a reduction of their pain with lidocaine.

So I'm not indicating that this is the way to go, but it may open up for a possibility that we can, in fact, also use the structure in way one or another. It may be skin biopsies in the future to see if we can, in fact, predict a response to a sodium channel blocker based on specific findings.

So are there any caveats here in targeting sodium channels? Well, the point is that the sodium channels may also act at other sites than the periphery. As Simon Tate said, it was

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important that these drugs, in fact, also have the possibility to enter to the central nervous system, but that may, in fact, also pose a problem, because then they may have side effects, these drugs. Some of them, in fact, do have a narrow therapeutic window, which can be illustrated by looking at the numbers needed to treat and numbers needed to harm.

I just wanted to show a slide in which we have looked into painful polyneuropathies, numbers needed to treat and numbers needed to harm, and I just want you to pay attention to numbers needed to treat here for oxcarbazepine. These were studies that had been done previously in diabetic neuropathy.

Here, you can see you have a NNT value about 5, 5, 6 or something like that. Now, if you look at numbers needed to harm for oxcarbazepine, the abscissa here is different from that one, but it's also close to 5. Now, that means if you look at the ratio here, numbers needed to treat versus numbers needed to harm, it's almost clear to 1, meaning that every time you have an effect, this

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person is also going out of the study.

This was not what we, in fact, quite saw in the study with oxcarbazepine on the irritable nociceptor, but it does tell us that the therapeutic window is very, very small and we need to work on that. And that's possible that the new sodium channel blockers may come into play here, because they have much less side effects.

These are the final slides. How should we, in fact, move forward from here? So now I just want to show you that we are now going into a study, where we're doing studies on diabetic neuropathy and painful diabetic neuropathy.

We have the possibility now to look into 7,000 patients, all with type 2 diabetes, where we try to identify these individuals in a very simple way with a screening tool, the Michigan Neuropathy Screening Instrument.

We will do a BPI and a DN4 and just to find out who has diabetic neuropathy with these very simple questions. In fact, the questions are just out right now.

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Then 10 percent random of these patients will then come in for more additional examination looking on neurography and clinical examination, and we'll do QST, et cetera, cold, heat, et cetera. We'll do CCM measures, et cetera, in order to see how these patients look like, and then end up with maybe other patients that are very much more detailed, examined.

You can then do randomized trials on these individuals, but you can also do them on these and these. You can, in fact, later on, go back and see how good are we to predict, for example, development of neuropathy or painful neuropathy just following very simple measures if you go from various different types of levels here.

I just want to mention that this is, in fact, exactly similar to the suggestion that Clifford and his group has suggested just recently, that what you try to do is you, in fact, identify the pain state by very simple procedures, you go on, try to identify the mechanism. Then you find your target, and then you do your randomized

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controlled clinical trial with that.

So I think these are examples that you also, on a larger scale, in fact, can do something which gets closer to a precision type of medicine approach with this one.

Thank you very much for your attention.

(Applause.)

DR. KATZ: Thanks, Troels.

If we start taking questions now, we will have no break. So let's take a 20-minute break, and if everybody could try to be here promptly at 4:00, we'll have a 30-minute discussion at that point.

(Whereupon, at 3:41 p.m., a recess was taken.)

Q & A and Panel Discussion

DR. KATZ: Welcome back, everybody. I'd like to ask everybody to find their seats. We have a compressed discussion time, so I'd like to get it jump started. If Troels and Alban and Simon could please have a seat at the front.

Why don't we begin with -- since we didn't

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have specific question and answer after Troels' presentation, why don't we begin with any questions for Troels based on his presentation, and then we can carry on to the other speakers.

Does anybody have any questions? Actually, there were a few people. I thought there were a few people that had questions for Troels that we cut off.

Yes, Clifford, go ahead.

DR. WOOLF: Troels, one of the outcome measures you looked at for the irritable nociceptor was dynamic mechanical allodynia, but wouldn't you agree that's more likely to be low threshold mechanoreceptors rather than irritable nociceptors?

DR. JENSEN: You're absolutely right. I think the measures that were used here were sort of crude measures, and to what extent -- I mean, you may ask why would a sodium channel blocker work on something which is mechanical allodynia mediated by A beta fibers. We always would consider that this is a central sensitization phenomenon.

But then again, if you have an irritable

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nociceptor which is blocked by a sodium channel blocker, then you're also blocking the input into the CNS, and then by that token, you would have a reduction. But you're right, it's not an example of it.

DR. KATZ: Does that answer your question, Clifford?

Yes, Paul.

DR. DESJARDINS: Paul Desjardins. Just a question. When you administered the local anesthetic, especially in the lower extremity, were you administering that close to the site of the previous injury or was that through a popliteal block, or how much proximity to the injury?

DR. JENSEN: No. There was given a direct block of the particular nerve, and then there was also done an infiltration in order to really block all sorts of input there. So you were sure that there was no external input from that site. There was both a block of the nerve proximal to the injury, and then there was an infiltration at the site.

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DR. KATZ: Paul, why did you ask that question?
DR. DESJARDINS: The question really becomes if you can block the impulses further upstream, is that equally effective to having it directly where you would expect the neurons would be functioning differently?
DR. JENSEN: The thing was that in some patients, the nerve block proximal to the injury was not sufficient to block everything. Now, that may be due to the person who gave the blockade, but he was from Denmark, so it'd probably be better here.
(Laughter.)
DR. DESJARDINS: Blood beetles and all that. Thank you.
DR. KATZ: Bob and then Ursula, please.
DR. DWORKIN: This question is for Troels and Simon. Would you have any -- is there any reason to think that a sodium channel antagonist, whether selective or relatively unselective, would have efficacy in non-neuropathic pain? So kind of

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chronic musculoskeletal pain associated with osteoarthritis or axial low back pain.
I think most of what you both were talking about was within the neuropathic pain world. But like in Alban's talk, is it possible that a sodium channel blocker could have more promiscuous efficacy?
DR. TATE: From the preclinical data, you would say yes. From the clinical data, I'm less sure. What I can tell you about, Bob, is the radiculopathy study that we ran. The primary endpoint related to the neuropathic pain, the pain radiating below the knee, and we had a statistically significant signal on that.
When we looked at low back pain, 94 percent of those patients had concomitant low back pain, as well as the radicular low back pain, then there was really no effect. So it almost looked like at least this molecule is selective for the neuropathic pain against the non-radicular low back pain those patients were receiving.
Whether some of the other indications will

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be different, like osteoarthritis, is possible actually. Certainly, we've looked more recently, started to look mechanistically in some of the OA models as the MIA model becomes slightly better, if you like, slightly more developed. Then we do see activity of our sodium channel blockers in some of those OA models.
Again, I think it will take a brave person to take a molecule into OA, but I think it might be one of the places to go rather than low back pain.
DR. KATZ: Troels or Alban, any other comments on Bob's question about efficacy of sodium channel blockers for --
DR. JENSEN: I'm not aware of studies that have been conducted for oxcarbazepine or carbamazepine. I would say that some of the early studies were based on not very good classification of the patients. For example, in diabetic neuropathy, there might have been patients that just have diabetes and pain. So they might have just an additional musculoskeletal type of pain.
There was, what, three studies and two of

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them failed to work in diabetic neuropathy and one study was positive, oxcarbazepine.
DR. DWORKIN: It's the same box score pretty much for lacosamide, oxcarbazepine, topiramate and lamotrigine. Three negative, one positive or two negative or one positive right across the board.
DR. KATZ: Ursula.
DR. WESSELMAN: Ursula Wesselman, University of Alabama at Birmingham. My question relates to time of diagnosis, length of symptoms, and drug treatment, and also QST testing.
Specifically, actually for Troels, have you observed a changing target basically? Because we often see that in clinic, that a patient might respond to a drug well, but later on doesn't. So do you see the QST profile changing over time, as we see it, for instance, for cancer treatment?
DR. JENSEN: I don't have data to answer that question, but I will say that in this very small study with the 14 patients, seven with nerve injury pain and seven with diabetic neuropathy, what was really surprising was that many of these

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patients have had their pain for 5, 7, 10 years, and the pain went completely away. That was sort of encouraging.

DR. TATE: I can add that in our radiculopathy study, we looked at time of disease against effect, and we didn't see a correlation. So if the patients had only their radiculopathy for six months versus some other patients who'd had it for greater than between 5 and 10 years, there wasn't a difference in the effect in the patients who had it for longer versus the patients who had it less.

DR. KATZ: I'll add a comment to that. Just having looked over the course of the 20 years at countless clinical trials, it's very common to look at whether the duration of pain has an impact on the difference observed between drug and placebo. I don't think I've ever been impressed by any observation like that.

It's very common for people to worry about that and try to exclude patients who have their disorder for over some arbitrary length of time,

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but I've never actually seen that make an appreciable difference in the analysis of a clinical trial. I don't know why.

Andrew.

DR. RICE: Andrew Rice. Troels, I wanted to ask you about whether we should be looking at other aspects of sensory profiling to try and define sensory gain. I'll give you two examples, because the DFNS protocol is obviously highly validated and is a lot of data, but most elements of it are threshold measures rather than quantitative measures.

One is a rather peculiar phenomenon called paradoxical heat sensation, which the German Network originally included in its definition of sensory gain, and then we've been more uncertain of it recently; the other of which is something we see in quite a lot of patients with HIV neuropathy, for example, that they have profound sensory loss to temperature until you get to a certain temperature and then they get effectively what's a hyperpathia. But you have to go above the recommended German

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levels usually to about 52 rather than 50.

Those seem to me other sorts of sensory gain that we could be bringing in to this equation. So I just wondered if you had any comment on that.

DR. JENSEN: I think that's a very good question, and I think the DFNS concept is a very good starting point. But from now on, we need to refine it and try to tie it very much to presumed mechanisms. For example, as you say, some of the sodium channels, in fact, have an effect. Tell me better about that, but seem to work on the gain of function.

If you have something which has to do with a gain, for example, the slope of the stimulus response curve, then you should try to -- if you have a job working on that, you should try also to mimic that by your QST method, which we can. I mean, we can do things like that.

DR. RICE: It's one thing that we've discussed before. I'm not going to take credit for it, because you actually came up with the phrase, which is "perhaps we ought to be designing our

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sensory profiling measures to be hypothesis-specific." So there's some things you might look for, for certain drug targets, other things that you might not look. At the moment, we use a fairly standardized set of measures.

DR. JENSEN: For example, heat, now we heard that, for example, sodium channel blockers may also work on heat, and that is part of the irritable nociceptor definition. But you would also say that, for example, heat is also mediated by TRPV1 receptor. So how do you explain the two?

If we can target it more specifically, that would probably be better.

DR. KATZ: Ralf, do you want to add anything to that discussion? I thought you might.

DR. BARON: Well, thank you.

It's absolutely true that we are not capturing this upper threshold to stimulus response curves in our protocol, but I think we discussed this extensively many, many years back. But we thought it might be even more difficult to do all these different tests and clinical routine than it

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is already now.
If you would like to do more and more extensive testing, then it contradicts, in my mind, that we'd all call for bedside testing at the moment.
DR. KATZ: Yes, Shai.
DR. SILBERBERG: Nick was waiting to talk.
DR. KATZ: Oh, excuse me. Go ahead, Nick, and then Shai and then Clifford.
DR. ANDREWS: I was actually just going to -- may I ask that question again that I asked before when we went to the break? So targeting ion channels is difficult, and we know that.
Targeting ion channels is very difficult, and one of the difficulties is actually when you get a failed trial. You are obviously very fortunate that you got some efficacy, but how would you have understood that you reached the target, that you engaged the target without the biomarkers to accompany it? Have you got thoughts about how to follow that with ion channel targeting?
DR. TATE: Yes. It depends on the ion

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channel, of course, as well, because there are -- for example, Clifford mentioned retigabine earlier, and if you're doing clinical studies on retigabine, then threshold tracking works particularly well.
Electrophysiology on humans where you've got large fiber involvements, then you can use retigabine, and it works actually very, very well. I mean, studies have been done. Martin Koltzenburg has done studies looking at retigabine and threshold tracking.
So there you can actually do a biomarker measurement in a human and show that your drug is onboard and having an effect. So potassium channel, potassium channel openers, I think there is a way forward.
With sodium channel blockers, it's a little bit more difficult, because you're at the mercy of the fact that other than looking at side effect measures, which is one way. You can increase the dose, and if you have a CNS penetrant molecule, at some point you'll have enough engagement of the CNS

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sodium channels to show dizziness, headache, et cetera.
That's using an old fashioned way, but it actually does work. You can push the dose and start to see some of those side effects.
But as I said, it's channel dependent, and for voltage-gated sodium channels, there would not have been a straightforward way to show that we were getting into the CNS, for example, remaining in the CNS or also having an effect on peripheral nerve function.
We have considered looking at -- obviously, Jordi Serra has done his microneurography, and, of course, that's a very low throughput. This is very difficult. There may be people here who have looked at microneurography, but it's very difficult to maintain the recordings for long enough to get a drug onboard to show the action of a drug.
That's one potential way that we thought might be possible to look at sodium channel function, microneurography, but we are scratching our heads a bit to find good biomarkers for

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voltage-gated sodium channels.
I don't know if Troels has any wisdom on that front.
DR. KATZ: Shai was next and then Clifford.
DR. SILBERBERG: So my question is to you, Simon. I was curious. You had four mutations in very different areas of the protein, but you have the same outcome with the BIIB074. Could you comment on what is the molecular mechanism of action, and are those four mutations leading to similar channel behavior that it would make sense, or is something else going on here?
DR. TATE: Yes. All of those four mutations cause a hyperexcitability. The threshold for firing is reduced. So what actually happens in all of those individuals when we study the electrophysiology is that despite the fact that they're in different parts of the channel, they're all in parts of the channel that relate to the functioning of a voltage-gated sodium channel. So the inactivated state is likely affected from the regions therein.

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What happens is that, essentially, you need a lower threshold to activate the channel, and then that's why in disease states -- maybe heat is a potential example in erythromelalgia or exercise is another one -- then the channels just become more active.

Now, as you've seen, our drug becomes more active as the channels become more active. So there is a perfectly reasonable hypothesis that we're continuing to build that the more active the network becomes, the more active the drug becomes. So although they're in different places on the channel, there is a sort of overriding hypothesis which is actually quite news, because if only one or two of the mutations showed that, then perhaps our goal of having precision medicine targeting Nav 1.7 -- let's say there are 35 mutations when we get some whole genome sequencing of Nav 1.7 across some of these big pain cohorts that have been talked about today.

If the vast majority of those are responsive to a sodium channel blocking drug such as ours, we

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could envisage some form of precision medicine where you have a chip in the future, where you have some companion diagnostic, and you can predict whether you're going to respond better to a sodium channel blocker or not.

So it's only four. We're building that set, and I think it could certainly be many more.

DR. SILBERBERG: If I understand correctly, that means that the BIIB074 is an open channel blocker, no?

DR. TATE: Not an open channel blocker. It targets the inactivated state of the channel. So it essentially stabilizes the inactivated state so it takes longer to get back to the open state again. We can have a biophysics discussion later, but it takes longer to get to the open state again.

DR. KATZ: Clifford, you were next, and, Michael, I'll add you to the list.

DR. WOOLF: I just wondered mechanistically what you and Mike and Ralf consider the irritable nociceptor to be. Is it a sensitized nociceptor where the TRPV1 channel is altered in terms of

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expression level or membrane insertion or post-translational state so that it requires a lower temperature to activate it or is it a situation where there's a non-ectopic activity, but spontaneous activity from the peripheral in some way which is sodium channel dependent or whether it's a spectrum that covers both of those?

DR. JENSEN: I'm not the right -- I don't think I can answer that, but I would assume, as you said lastly, that it is probably a combination of different type of things.

The area where you probably -- and Mike can probably answer this better. The condition where you see it most characteristically is probably in postherpetic neuralgia, where you really have the division of patients that are more dominated by having signs of sensory losses and other signs and then also with hypersensitivity in another group.

But, for example, in diabetic neuropathy that I see quite a lot at the present time, it's the degree of hypersensitivity is minimal. For example, allodynia, I know it's written in the

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textbook that it's supposed to be a very common phenomenon. It's not. It's a very rare phenomenon in diabetic neuropathy.

So that condition is mainly dominated by sensory losses --

DR. KATZ: Mike, did you want to --

DR. JENSEN: -- leading to small fiber function.

DR. KATZ: Do you want to add something to the discussion of the irritable nociceptor identity?

DR. ROWBOTHAM: As we originally were formulating it, it was doing some deafferentation of the PHN at one end of the spectrum, and it's a spectrum rather than an all or none and irritable nociceptor at the other end. It was a profile on allodynia and thermal thresholds using QST, and then we added to that with the capsaicin response test, this tremendous aggravation of pain in a very abnormal way from just putting topical capsaicin on the allodynic, the pain skin, as being the components.

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Now, it's defined in a way that's more around the clinical profile than a sensory profile. So I'll leave that to Ralf to comment on.

DR. BARON: But to your question, Clifford, I think it's a spectrum, and I think you have to distinguish. If it comes with spontaneous pain, this is due to the ectopic phenomena in the neurons, and if it comes with the evoked type of thermal hyperalgesia or heat hyperalgesia, then it's the peripheral sensitization. Both are phenomena you can find in the irritable nociceptor type.

DR. JENSEN: But I think we have to realize that it was a concept that really came out from one condition, postherpetic neuralgia, and does not all apply to all neuropathic pain conditions. I think that's a --

DR. KATZ: Troels, I have a follow-up question for you on this point. In the two studies that you mentioned with Demant as the first author, at least we saw the beautiful curves showing that the impact in the irritable nociceptor patients is

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substantially larger than in the non-irritable nociceptor group. The method for defining the irritable nociceptor group was kind of complex, I think.

Did you explore the data to look to see whether there was a more parsimonious method for separating the population of oxcarbazepine responders from oxcarbazepine non-responders?

DR. JENSEN: The primary outcome measure was whether there was an effect on patients that had the irritable nociceptor. It was the outcome measure. That was your -- not any post hoc analysis.

DR. KATZ: Okay. Thanks.

Back to the list, Veeru, you were actually next.

DR. COLLOCA: Luana Colloca. For Professor Jensen. You published with Lene Vase that lidocaine can produce a different peripheral and subjective response when it's given in open versus hidden way, Pain 2012. Would you mind commenting on this and maybe say something about

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the role of this kind of effect in precision pain medicine or personalized pain medicine?

DR. JENSEN: This is a post doc working in our group and working on placebo, and they used the concept which has been developed by Benedetti in Italy, and that is this concept of open and hidden administration in order to look into mechanisms of placebo.

In that case, the lidocaine was used as a tool to determine the role of the hidden and the open administration. It was just considered as a tool.

DR. COLLOCA: Well, I understand it is, and I'm familiar with Fabrizio Benedetti who worked on the open/hidden, and published together with Fabrizio. My question is more related to the fact that --

DR. JENSEN: Now I know you. Sorry.

(Laughter.)

DR. COLLOCA: -- the peripheral responses. We have been studying a lot at the level of brain mechanism, but I love your study because you show a

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peripheral change and not just some occurring in our brain. So that is the reason why I would elicit your comment why a drug should show a different response or so peripherally and not just in the premise of a subject's outcome?

DR. JENSEN: I'd have to go back and look, and then we may have to talk to Lene Vase about that. You know her very well, I know.

DR. KATZ: Veeru, you were next and then followed by Luda.

DR. GOLI: Yes, Veeru Goli from Pfizer. Just a basic question. Dr. Jensen, you mentioned that when there's a sodium channel abnormality, there's also abnormalities in other mechanisms. I like that concept, because it's a very dynamic process, and I'm sure there's no one single mechanism that's involved.

Logically, what would be the other mechanisms that would work synergistically to target along this sodium channel abnormality?

DR. JENSEN: I think one of the answers lie in some of the meta-analysis and the systematic

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reviews that have been carried out. You know the drugs that have the lowest NNT value are still the tricyclic antidepressants, and the reason for that is probably also that this is the drug par excellence that has the largest amount of different effects. We call them dirty drugs, but they're not dirty in the sense. But they are working on different mechanisms.

I think we all believe that there are different mechanisms coming into play, at least in many chronic pain patients, but we want to dissect it further, and that's why it's so interesting now that we're having very specific drugs.

This is the way forward. It's not the way forward not to give the tricyclics.

DR. GOLI: Thanks.

Following the same train of thought, when there's nerve damage, you're going to have upregulation not just of Nav 1.7, but also 1.8 and 1.9. Would that be fair to say that?

DR. TATE: I think you do get upregulation of other channels, maybe Nav 1.3, as well as we've

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seen from Steve Waxman's work. I think that's why when I presented, I deliberately presented a selected molecule, not a specific molecule, because there's an awful lot that can happen.

These patients with Nav 1.7 gain of function mutations, some of them exhibit symptoms in childhood, like in erythromelalgia. The sooner that you see the symptoms, usually the more severe the disease. Some we don't see until patients are much, much older in either erythromelalgia or small fiber neuropathy. So there are other things happening. It's not just about that channel.

Whether it's other channels, whether it's epigenetics, there's just so many reasons why that could happen. So I think it's important when we're targeting some of these molecules to understand how to target them, and I think by having something that's more selective against sodium channels and not hitting some of the other mechanisms that the current drugs hit, that allows us to get a higher block against those sodium channels, because you've got a better therapeutic window against the sodium

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channel block.

With amitriptyline, by the way, a lot of people talk about amitriptyline as a sodium channel blocker, and it is. So you can show that amitriptyline blocks sodium channels, but if you do the translational experiment of saying what is the therapeutic concentration of amitriptyline that's used in pain, then you back-translate to the amount of sodium channel block you really expect in a patient, and it actually gets small.

The amount of sodium channel block is pretty tiny. So it's probably unrealistic to expect that amitriptyline is actually working via sodium channel blocking mechanisms, I don't think.

DR. KATZ: Luda and then John Farrar.

DR. DIATCHENKO: Luda Diatchenko, McGill. There is a known polymorphic non-synonymous change in the sodium channel 1.7 that has been associated with a few conditions, but maybe in one paper.

I'm curious if you use it -- okay. Let me have who wants to bite. So from non-pain common diseases, there is -- people know that usually the

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genes in which you have genetic variants associated with the risk of the disease, usually they're also a good drug target. If the variation has changed activities substantially of the gene, then you'll have a different response in the different diabetic variant carriers, right?

So the simple question, do you look at this polymorphism response in your patients?

DR. TATE: We haven't really had the opportunity to do that yet, Luda. I understand the question, and we have started to look much more widely at the Nav 1.7 gene and just look how polymorphic it is, if you like, with SNPs and so on. But to take each one of those and --

DR. DIATCHENKO: There is one which already has been shown associated with the risk of the neuropathic pain.

DR. TATE: Yes, yes, and we haven't -- I know the one, and it's one that was shown in a PHN study actually. It was looked at in a PHN study by the Xenome group actually, and functionally it doesn't do a lot, which is interesting. So that

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particular SNP doesn't actually really cause much of a change in Nav 1.7, but I think we have to study it a couple of ways.

First of all, we need to do the induced pluripotent stem cell route to get it in more of a native setting rather than just expressing in H2k cells. That's why I think that technique is really powerful for precision medicine is going to be a big component of what we do in the future.

Secondly, we have started to look in some of our studies at that particular SNP, but we haven't really seen an association in the wider pain studies that we've looked at. But we need to do more work, because I think there may be others, as well.

I think we just need to do more work, and I think we will open up our studies, as well, so that we can get more people working on them, because we have quite a lot of data that hasn't been mined yet. That's something that I'm very keen that we do get all the data mined from our studies, especially where we've got genotyping of the

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patients.

DR. KATZ: John, it looks like you get the last question, since we're running out of time.

Sorry, Ajay.

DR. FARRAR: All right. The obvious second component to all of this is actually access to the necessary site of activity, and clearly, different drugs are going to have different abilities to get to where they need to go. I was impressed with the slide that Troels showed about local injection of lidocaine into the nerve is obviously going to work differently than an IV administration of lidocaine. I'm not even sure where an IV administration of lidocaine is implementing its effect.

Obviously, the biggest problem with the Nav 1.7s has been the problems with the sympathetic ganglion and blood pressure issues and so on, and I'm just wondering how you sort of try to deal with those issues when we're trying to think about personalized medicine or when we're trying to think about how to develop new drugs that are targeting things that, if they get to the wrong place, are

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going to have a bad or inappropriate response and how you've been looking at that.

DR. JENSEN: I think we have to think along these lines that we can administer drugs in a way which is different from the systematic way, because most of the drugs -- all the drugs that we have looked at and used in neuropathic pain all have CNS side effects.

As you saw from the NNH and NNT values here, you're getting very close. The therapeutic window is so small in many patients, with getting older, that have cured cancer from patients with diabetes, et cetera. I think the problem is just going to be bigger with the CNS side effects if we don't find something where we get rid of the CNS.

DR. KATZ: Well, with that, we'll have to bring this very stimulating discussion to an end. I'd like to thank the speakers for their presentations and for their handling of their questions and answers.

(Applause.)

DR. KATZ: Now, just a few housekeeping

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announcements. John Markman has an announcement, don't you, John?

DR. MARKMAN: It's more than just an announcement. My name is John Markman, with the University of Rochester.

About two months ago, on behalf of the American Academy of Neurology, I had the distinct privilege of being part of the group that awarded Mike Rowbotham, who's here today, with the Mitchell Max award, and as you heard from Clifford's discussion this morning and a few others, the presence of Mitchell Max looms large over the work that we've discussed today.

In inspiring this award which Mike received, I can think of no more appropriate discussion than today's, and Bob Dworkin generously sponsored a champagne reception to mark this occasion. The award committee noted that pioneering work that Mike did in sensory profiling. So again, it's very appropriate that we recognize this today as we discussed that very achievement and look to its next realization.

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We also cited his work in clinical trial design, the development of topical lidocaine and other therapies.

Mike's passions obviously extend beyond the laboratory and his clinical practice, where you've heard of his prowess earlier today, and I'm sure you'll hear about it more in a moment.

He has many close collaborators, including Dr. Peterson, with whom he's embarked on many of life's most important projects. His beautiful family was there earlier this year in Vancouver when he received this award.

He has many wonderful collaborators, many of whom are in this room today, and you will hear from a few of them in a moment.

The first recipient of the Mitchell Max award was the gentleman you're about to hear from first, and then you'll hear from Dr. Woolf, Dr. Baron, and Dr. Dworkin, obviously, three of the most eminent leaders in this field whose legacy will live long beyond any of these meetings

(Video played of Dr. Fields.)

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DR. FIELDS: "Hi, Mike. Congratulations on the Mitchell Max award. I'm sorry I couldn't be there in person, but I'm delighted to have the opportunity to send you my greetings.

"I can't really think of a more deserving person for the Mitchell Max award. I want to start with a quote from Bette Davis, who said, 'Growing old ain't for sissies.'

"Well, there are actually some nice things about being a senior person, and one of them is seeing how your colleagues and your trainees have been successful. So this is a great occasion for me.

"I have really over the years appreciated your evolution from trainee to colleague and now an internationally known and revered clinician/scientist. This is fantastic.

"I think what people may not know is that you're also an amazing clinician, that not only a compassionate doctor, but a gifted clinical thinker. I think you're exactly, in my mind, what the Mitchell Max award was intended for, the type

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of person who should get the Mitchell Max award, and I'm sure that Mitchell Max would agree. If he's up there, he's certainly smiling now.

"Reflecting on our longstanding relationship from the time that you arrived at UCSF fresh out of your neurology residency in Boston, it's been a wonderful ride, and your success really, in retrospect, should not have been a surprise. You have that winning combination of intelligence, integrity, and commitment to excellence. You never really did anything halfway. I think this is really one of the underpinnings of your success.

"I think everybody would agree that academics aren't always the easiest kind of people to be around. On the other hand, all of your skills and talents and accomplishments have been wrapped in a package that's pretty easy to take.

"You have a wonderful bedside manner. You get along well with people. You have this kind of laid back surfer mentality which covers up really a pretty intense individual, but well disguised, and it's really been a lot of fun to include you not

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only as a colleague, fellow scientist, and a respected person for me to talk to, but it's also just been fun being your friend and having wonderful meetings, enjoying fine wine, cross country skiing, going to the beach, hiking in the mountains. Just all of that has been tremendous fun.

"In addition, Mike has always been dressed in a very stylish way, casual elegance, so to speak, and I've picked up quite a few tips and improved my own wardrobe, thanks to Mike.

"So one more quote, this one from Leonardo da Vinci, who said, 'Poor is the pupil who does not surpass his master.' And I think I can honestly say that I've been incredibly lucky to have had people like Mike in my life that have been trainees, but from whom I've learned as much as I've taught, and who have gone on to surpass me in a lot of ways, as tough as it is for me to say that. That's Michael, and so I'm just going to have to sit back and enjoy his success.

"Well, I'd have to say I'd love to take

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credit for some of Michael's success, but as tough as it is for me to say this, I think I was just in the right place at the right time and have been very lucky to have had somebody like him come to use UCSF and work with me. Anyway, I want to just sign off by congratulating Michael, and I want to thank John Markman for giving me this opportunity to extend my regards. Bye."

(Applause.)

DR. CLIFFORD: I trust Howard to use 10 words when one will do, but he's left me with precious little to say, other than Howard is your mentor and, in an indirect way, he was mine, too. He was actually my PhD examiner when I was in South Africa. He examined me remotely by mails. This was pre-Internet days. And when I finally met him, he was an inspiring character, and I continue to be in close contact with him.

Then in the late '80s, I think it was, I happened to bump into him, and he said, "I have finally found it, the real thing, a clinician who understands science, someone who's going to really

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make an impact, someone who understands what this is all about."

Who was he talking about but Mike?

I was just looking through Mike's publication record to remind myself he hit the road running, but there was a little bump. He did some early work on cocaine addiction, which somehow you managed to wean yourself off and get into pain, and that has changed the pain field.

I would like to join everyone here to congratulate you. You really have made an impact, and it is truly this combination of being an outstanding clinician and someone who's delving into the mechanisms and using clinical trials as a way of not just endlessly repeating trials, but as a means of understanding pain. It's been wonderful.

(Applause.)

DR. BARON: I was asked to speak some words as well, very brief. So the first time I came to listen to your talks and your papers was in 1989 when you just published the first irritable

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nociceptor paper in Postherpetic Neuralgia, and we tried in Germany to replicate this with some other tools like QST.

I don't know why, but we only found degenerative postherpetic neuralgia patients, not the irritable ones or the other ones. I just phoned you and said, "Well, there's something wrong with your concept. So we do find the other things."

You said immediately, together with Howard, "Well, come over to San Francisco, and we'll solve the problem."

So I applied for a Humboldt stipend, as you know, and, in fact, Pat Wall was the reviewer of this application. So I got it, and I went to San Francisco in 1998 for one year. We did some experiments. We did a nice paper where we described at least three subgroups of patients which we can identify from the degeneration types of the irritable types.

So I think this was the foundation for the clinical phenotyping things, and, in my mind, you

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are the founder of the clinical phenotyping of neuropathic pain. So, therefore, I'm very grateful, and congratulations to your award.

(Applause.)

DR. ROWBOTHAM: Thank you all. I'm blushing.

DR. DWORKIN: I get the last word. So sometime last year, my wife and I binged watched the TV series, "Fringe," and for those of you who have never watched "Fringe," it's about this universe and an alternate universe. And so I thought one way of kind of summarizing Mike's contributions is for us to just spend a moment thinking about an alternate universe where Mike had never been born.

So the first thing in this alternate universe where Mike has never been born is we wouldn't be having this meeting, because there wouldn't have been irritable nociceptors and precision pain medicine would not be advanced enough to have held a two-day meeting on it. In fact, what we'd probably be talking about is

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visceral pain, because that is something that we've considered.

So there wouldn't be irritable nociceptors, and there wouldn't be this meeting in an alternate universe where Mike had never been born. There wouldn't be topical lidocaine as a treatment for neuropathic pain and the development of gabapentin and opioids showing efficacy in neuropathic pain and tricyclic antidepressants would have been delayed. I think it would have occurred, but it occurred much more quickly because of Mike's contributions in the clinical trials he did.

There wouldn't be, in the alternate universe, the heat-capsaicin sensitization model that Mike and Karen developed, and we'd also know, in the alternate universe, much, much less about the transition from shingles to PHN, which is another one of Mike's major contributions.

Finally, this alternate Mike-less universe would have Fiji with less kind of lower quality healthcare, and I think maybe that's just as important as the pain medicine contributions are

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the contributions that Mike and his colleagues have made to healthcare in Fiji.

So I'd like us all to toast to our universe where Mike was born and to feel bad about the alternate universe where he wasn't.

(Laughter.)

DR. DWORKIN: So cheers, Mike.

DR. ROWBOTHAM: Well, I do feel like I had a screen test here. I've been flushing for hours or days.

So I've been also in the right place at the right time. Getting a chance to kind of transition away from doing human psychopharmacology in drugs of abuse, which is an interesting topic, and working with patients with substance abuse problems has a lot of parallels to working with pain patients, but it was really an eye opener to come back to San Francisco after my training and work with Howard.

I remember he pulled up these papers and said, "We should take a look at this disorder called postherpetic neuralgia."

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He hadn't really seen too many patients with it and I was just getting started and really, the publications were really just our observations of patients in clinics.

I've gotten a chance to collaborate with many of you over the years and have certainly -- it's been two-way learning. It's been a great ride, and some of the things I'm learning nowadays about cancer biology and biomarkers and cell culture models and other things, of cancers I think will cycle back around, and hopefully have some impact on the pain field in the future as we kind of move towards more and more of a precision medicine approach for pain.

So I want to thank you and thank you to John for all this work and putting this together. You caught me completely by surprise.

(Laughter.)

DR. ROWBOTHAM: Especially the videotape from Howard. So thank you all very much.

(Applause.)

DR. KATZ: Dinner is at 7:00.

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MS. THOMPSON: Dinner is in the same place.

DR. KATZ: All right. Thanks, everyone.

(Whereupon, at 4:45 p.m., the meeting was adjourned.)

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