ACTTION - IMMPACT-XIX

Accelerating the Development of Precision Pain Medicine

June 4, 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

Saturday, June 4, 2016
8:06 a.m. to 3:50 p.m.

Westin City Center
Washington, D.C.

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:06 a.m.)

DR. TURK: Good morning. Good morning. Please take your seats. We want to get started. We're hoping to get out of here by midnight and we've got to get started now.

Hope you all had a pleasant evening. From the conversations that I sort of milled around and listened to, it sounds like we stimulated a lot of discussion, which is perfect, exactly what we want these meetings to do.

It's not so much just what goes on in the formal presentations, but really what goes on over the coffee exchanges, at dinner, and collaborations of things that people work on. We, Bob Dworkin and I and the organizers are delighted to see that you're doing that.

A couple of housekeeping details just before we get started. As a reminder, this is being recorded and transcribed. So when you ask a question, when that comes about, please say your name, even though you may have said it several

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times already. It helps the transcriptionist so that she's able to do that.

The other housekeeping details are on there. There is a sign-up sheet on the desk back where Valorie and Andrea are for taxis.

So if you are looking at taxi times, sign up. There will be plenty of taxis. It just gives them some advanced warning so they can make sure that they have things out there.

Check-out time is at noon. There's a break at 10:30, 10:40 or something like that. So either you can decide that you want to check out then or you can wait until noon if you want to. We can put stuff in the back of the room or you can go to the bell check-out.

If you have a cell phone, please, as you did nicely yesterday, make sure that they're not going to be going off during the meeting itself.

Remember the microphones, you speak into them. I noticed yesterday when some people want to talk to somebody on the side, they turn like this and we lose you from the microphone. So even

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though you're talking to Mike Rowbotham, you've got to talk directly in front of or move your microphone if you will.

Any concerns, questions, or logistical details that I can handle, I'm happy to try to answer them. But Valorie and Andrea can do most of that.

As far as your stipends and things that kind, they take care of all that. So if you have any questions about that, anything about flight problems, anything like that, definitely check with them, room problems or what have you.

Any concerns, questions, things that people want to know? There will be a break and then there will be a lunch period that will be in the same facility where we were at yesterday.

Anything else people want to know, want to worry about?

(No response.)

DR. TURK: Okay. Then let me introduce John Markman, who is going to be the introducer for the morning sessions. John, when you have an

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opportunity.

Dr. Markman is from the University of Rochester. Many of you heard him yesterday. And hopefully all of you were here for the congratulations to Mike Rowbotham for the Mitchell Max Award. We were delighted to do that and thank John for arranging that.

DR. MARKMAN: Good morning, everyone. It's a true privilege to introduce our next speaker in a quartet of distinguished speakers, Dr. Katz.

Nat Katz and I have a personal relationship. He was my first teacher of pain medicine when I was a resident. So it's a true privilege to introduce him.

He is professor at Tufts University and, also, I think, one of the most distinguished thinkers about clinical trial design. And he's going to be speaking to us about COX-2 inhibitors and NGF antibodies as sort of illustrations of the potential for precision pain medicine.

Presentation – Nathaniel Katz

DR. KATZ: Thanks, John. Hi, everyone.

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I was asked to take on this topic of presenting to you what's known about phenotyping in patients for the prediction of the outcome of treatment with nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, and NGF antibodies.

I could probably just wrap up my whole talk right now, because the bottom line is that nothing is known about that.

I have not been able to find any published clinical trials where there was some attempt to phenotype patients at baseline based on the sorts of phenotyping that we've been talking about at this meeting, and look to see whether that mediates the efficacy or actually the safety of either cyclooxygenase inhibitors or NGF antibodies.

So that's my presentation. Thank you very much. We can chitchat for 20 minutes.

(Laughter.)

DR. KATZ: Of course, not only do you have to fill up the time, but you actually have to go over your time, don't you? So I had to find

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something to talk about.
What I thought I would do is look through the literature and look to see whether there were anything close, are there any examples even how you might think about phenotyping patients in a way that would be informative to the job of predicting outcome of treatment with cyclooxygenase inhibitors or NGF antibodies.
So that's what I did. I'll show you what we know now and then hopefully, you or others like you, will go out into the future and do the kind of studies that we need to see going forward.
It's been interesting for me to listen for the last day in this conversation about phenotyping, because it seems like everybody's using that word in a somewhat different way to refer to somewhat different things. And so I thought I would at least tell you how I'm going to be using the word for the purpose of the next 20 minutes or so of my presentation.
I'm thinking of the word "phenotype" as some kind of stable patient characteristic that might

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impact either the safety or the efficacy of the treatment.
The two sorts of phenotyping approaches that I'll be focusing mainly on, because I think that what most people in the room are interested in, are the so-called sensory profile: how does the person's nervous system process sensory stimuli, in general or painful stimuli, in particular; and then are there any biomarkers that might help categorize the patient in terms of their proclivity to respond positively or negatively to the treatment?
The biomarkers can be about different things, as well, but the biomarkers that I'll focus on are biomarkers that would seem to characterize what subtype of the disease that the patient has, a biomarker for osteoarthritis, or painful diabetic neuropathy, or postherpetic neuralgia or something like that.
Now, we've been using the word "phenotype" pretty broadly, in general, and that could refer to any patient characteristic that might impact the outcome. And so for the purpose of this

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presentation, I'm going to ignore things like does age predict the outcome of a treatment, or gender, or medical comorbidities, or psychiatric comorbidities.
I think anybody who works in the clinic understands that these things can have some impact in outcome, but because I think it's not what we're really focusing on today, I'm going to ignore those things.
I'm also going to ignore patient characteristics that I think are kind of more methodological in nature, that relate to the integrity, the quality, or the informativeness of data you get from that patient. So things like whether patients can report their pain accurately I don't think is really relevant to this presentation or whether they might be more prone to responding to placebo.
I'm ignoring, for the purposes of this presentation, all these methodological patient characteristics, if you will.
I'm also not really going to focus on

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clinical diagnosis. I think we all recognize that low back pain, for example, is a syndrome that consists of a lot of very different clinical subtypes. Neurogenic claudication is entirely different than lumbosacral radiculopathy or disc herniation, but I don't think this meeting is about that. So I'm not going to talk about that.
I'm also not going to talk much about PK phenotypes. I think we all understand that the degree of exposure to the drug impacts the outcome. That's not a new concept.
There's a lot known about different variants in pharmacokinetic subtypes of patients. I chose to ignore that, as well.
One other kind of conceptual issue before I get into the material itself, I think there's also a lot of confusion about people saying things like, "Oh, so-and-so is a responder to drug X and we want to know how to predict whether so-and-so is going to be a responder to drug X."
In order to know whether somebody is truly a responder to a certain drug, you need to study that

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in a particular way. You typically need to do these multi-period, within-patient, crossover designs to challenge and re-challenge the person with the same drug, and there are no such studies, as far as I know. I'm not talking about predicting whether a specific patient is a responder to oxycodone versus morphine. And the reason I'm not talking about that is because there's no data on that.

Instead, what I'm talking about is group characteristics that act as effect modifiers. And I want to dwell on that point for one second, too, because the only thing that I care about is whether the phenotype predicts the difference in response that you'd see if you gave that patient an active drug versus if you gave them a placebo.

Open label studies that just say, "Oh, here's my patient subtype, and I gave them open label drug, and here's how they did," that's, more or less, uninformative, because you can't distinguish in that study design whether your patient characteristic is just predicting the

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natural history of the disease versus the response to the therapy.

That design does not distinguish that. So I'm ignoring all literature that has that type of a design, because it's uninformative for the meeting that we're having today. So I hope that helps. I hope it doesn't create more confusion and helps maybe decrease some potential confusion.

I'll just take this one slight step further, which is that the design that answers the question of interest is this kind of design, where if you want to know does a phenotype modify the effect of a treatment, you have to do something like this, where you take patients and you do randomized, double-blind, placebo-controlled trial, you give them either your drug or placebo, if that's the comparison of interest, or some other active drug, if that's the comparison of interest, and then you prospectively divide your patients into different patient characteristics you're interested in, whatever those might be, whether it's the German Neuropathic Pain Network profile or it's some

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biomarker or whatever.

Then you have your difference between drug and placebo in the first group, you have your difference between drug and placebo in your second group, and your question is do these differences differ.

That's really the only design that can inform this question. And as I already said at the beginning of my talk, which could have been the end of my talk, if I were smarter about it, there are no such studies doing that for either NSAIDs and anti-NGF antibodies.

That's kind of the take-home message for today if you want to check your email or something for the next few minutes.

(Laughter.)

DR. KATZ: Now, the rest of my presentation is going to be divided into the two classes of drugs I was asked to talk about. First, I'll talk about drugs that inhibit cyclooxygenase and what we know about patient characteristics that might mediate the outcome of those drugs.

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The first question that you might ask yourself is, is it even theoretically conceivable that there could be patient-level characteristics that could impact response to nonsteroidal anti-inflammatories, for example.

The answer to that question is yes, actually. There are a variety of factors that characterize nonsteroidals, that actually -- I don't practice anymore, but when I was in practice, I used to think of all the NSAIDs as, more or less, the same. And then we have the COX-2inhibitors. That was kind of interesting.

Now, it seemed like we have two, more or less, categories. But the fact is that they're all actually quite different one from the other in ways that not only where the drugs themselves might produce different responses, but at least in theory, they could potentially interact with individual patient characteristics that might make them perform a lot differently between one patient and another.

These are just some of the factors. Of

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course, COX-2selectivity is the one that everybody talks about. They do differ between one and the other in the degree to which they penetrate, not only penetrate into, but stay in inflamed tissues. That seems to be mostly related to the acidity of the moiety, but probably other factors that other people in the room know much more about than I do, protein binding, rate of absorption, rate of elimination, penetration into the skin.

This a very funny thing, because cyclooxygenase inhibition probably occurs in the central nervous system, as well, from nonsteroidal anti-inflammatory drugs, but there's not really not known, at least not a lot I know about the extent to which the clinical effects that we see with these drugs are actually mediated by central nervous system effect versus effect in the periphery.

You'll read textbooks on pain medicine where the NSAIDs will be put in the book chapter on peripherally-acting analgesics as opposed to the opioids, which are billed as centrally-acting

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analgesics.

But that seems actually to be quite untrue and that the NSAIDs do, to one degree or another, have central actions. And you can imagine that individual patients might differ on factors that confer NSAID effects.

This is all theoretical. Yes, it's possible that people may differ in these important ways. Has anybody actually ever looked at whether there are such inter-individual differences that could interact with these factors? And the answer to that is, yes.

There are maybe -- I was able to find two studies, I think, in the literature that looked at inter-individual differences and factors that interact with this pharmacology.

This is one of those from -- this is actually from Garret FitzGerald's group at Penn, where he did a study actually on 50 -- it's a crossover study on 50 patients, so not a tiny study, where they brought people into the GCRC.

Let's see if I can read this myself. They

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gave them either placebo or rofecoxib or celecoxib. And as I think probably everyone in the room knows, we do have biomarkers for the activity, for the salient features of the activity of nonsteroidal anti-inflammatory drugs.

In this column here, we have a biomarker for the inhibition of COX-2; this column here, we have a biomarker for the inhibition of COX-1; and, here are some biomarkers that I won't go into detail on.

Usually, when you see these things reported out, you see just the averages right there. The average COX-2 inhibition produced by rofecoxib, the average COX-2 inhibition produced by celecoxib, which is what you see here in this graph. And you see that rofecoxib and celecoxib in this study produced, more or less, the same degree of COX-2 inhibition, on average, compared to placebo, which didn't do much.

With COX-1 inhibition, you again see that there was a little bit more COX-1 inhibition from celecoxib compared to rofecoxib, compared to placebo, on average.

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But what they did here, which makes this study unique, in my mind, is here is every single patient, and here is every patient's individual degree of demonstrated inhibition of COX-2, demonstrated inhibition of COX-1, et cetera.

If you didn't have this bar graph up here to see that the averages were different, you'd be hard-pressed to see that with the naked eye. It just looks like a cloud.

It looks like the inter-individual variability is much larger than the difference in the between-group averages, which is actually what they found.

So individual patients can differ enormously in the extent to which they have COX-2 versus COX-1 selectivity. And nobody to my knowledge has ever looked to see whether that mediates the outcome, either efficacy or safety.

How many years have we been spending hundreds of millions of dollars on huge safety studies for COX-2 inhibitors, for example, as well as huge efficacy studies?

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Yet, inter-individual differences, as far as I know, have not been looked at as mediators of outcome. And if someone else knows more about it than I do, which would not surprise me, I hope that in the discussion you educate all of us on that.

What's the bottom line here? The bottom line here is that there are important inter-individual differences on factors that might impact the pharmacological outcome of these drugs, but it just has not been looked at.

Another thing that these same authors in this same paper looked at was genotypes for metabolic subtypes. Different people have different genes in terms of the metabolism of cyclooxygenase inhibitors and, also, different genes for isoforms of the cyclooxygenase enzymes themselves.

Without going into the details, since I don't really fully understand it anyway, I will just say that they matter, these genes. So if you're in a genetic subtype that has a different COX-1 isoform, you will show a different degree of

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Cox 1 inhibition and since that seems to be the main thing that produces salient side effects of NSAIDs, that could be important. And that held true for both celecoxib and rofecoxib. Of course, the people who metabolize it more poorly have higher plasma concentrations which is not a surprise.

So inter-individual differences based on SNPs for different genes that relate to both the pharmacokinetics and the pharmacodynamics of NSAIDs do seem like they have the potential to matter. But they've just not been looked at in clinical outcome studies, to my knowledge.

That's kind of all that I was able to glean from the literature on inter-individual differences and how they relate to cyclooxygenase inhibitors.

Now, the next question that I'll attempt to deal with is we've been talking a lot in the last day or so about these sensory profiles and do they matter in terms of the outcome of analgesic treatments, particularly the efficacy outcome.

As I said in my introduction, there's no

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published study looking at whether sensory profiles predict the outcome of NSAID therapy, but there is an unpublished study that I actually did that we've been sort of perpetually packaging up for publication, and I'll just show you a little bit of data from that.

This was a randomized, double-blind, placebo-controlled, crossover study funded by Astellas.

It was a methodological study just to look at performance of different endpoints, et cetera, et cetera. One of the things that we looked at was -- we had already previously developed what we call a bedside sensory testing kit to see if we could evaluate sensory profiles in patients with different disorders, and we developed it actually for use in patients with osteoarthritis of the knee. We had a little publication about a year ago that described just the development of this little kit.

I think about it as kind of a dumbed-down version of the German Neuropathic Pain Network for

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people in multisensory trials who are only going to spend 10 minutes in doing this, what can you do to generate reliable data.

We showed that we could generate reliable data using this bedside approach. Then in this study, we wanted to see did the classifications that this simple bedside sensory testing approach generated predict the efficacy of naproxen in the treatment of osteoarthritis of the knee. That's what the study was.

This was just a picture of the stuff that's in the box, so when you get it. The main things that we focus on are we used a pressure algometer to measure pressure pain thresholds in the arthritic knee.

Then we also used pressure algometry in the knee to do a DNIC test or a CPM test, whatever word you like, and we used that with ischemic pressure in the -- ischemic pain in the forearm was the conditioning stimulus.

We tested for cold allodynia over the knee, which didn't really yield anything. We tested for

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using Von Frey filaments for light touch threshold at the knee, which also didn't really yield anything. And those are the basic components of what's in this kit.

Here are the results. What we did is we divided patients into three categories based on the results of this test. The first test was did they have what we considered primary hyperalgesia, which was based on pressure algometry in their arthritic knee.

Then we looked at what we called secondary hyperalgesia, which was pressure algometry at the elbow, non-affected area. Then the third thing we looked at was DNIC, whether it was what we considered to be intact or dysfunctional based on a pre-specified cutoff that we introduced.

So if you have three tests and you have two different outcomes for each test, that gives you eight mathematical permutations of all those three tests. So this is just the eight possibilities.

I'll just draw your attention -- for a small study, we had 51 patients. To have eight subgroups

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in a small study means that you're not going to be able to analyze a lot of your subgroups. That's just math.

What we did was we focused on three groups. This top row is the people who everything was normal or at least what we considered to be normal. And that actually was the largest subgroup, 19 out of 51, almost half.

Then these people down here, everything was abnormal. That's the other extreme. There were only seven so it's a small group. And the rest of these people had a mishmash where some things were normal and some were abnormal, and we ended up just combining them.

Now, we have three subgroups and the question is did that have any impact on the outcome of NSAID treatment. So we looked at this in four different ways.

I know this is a complicated table, but I'll just try to draw you to the highlights. The first approach was to look at all of the different tests that we did, and that was basically this here

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collapsed into two groups.

If you look at the patients -- and the endpoint that we looked at was a standardized effect size of therapy and the endpoint was the WOMAC Pain Subscale, the standard endpoint in osteoarthritis clinical trials.

Standardized effect size, the difference between drug outcome and placebo outcome divided by the pooled standard deviation. So the normal meaning of standardized effect size.

You can see that the people that were all normal, their standardized effect size was 0.44, which is kind of what you'd normally expect from naproxen in a study for osteoarthritis in the knee.

The people who were all abnormal had almost double the standardized effect size, which was the opposite of what I predicted now probably four years ago when we started designing this study.

The second way that we approached it was just looking at the DNIC test, which is these groups here, and forgetting about this hyperalgesia measure. Again, we looked at normal versus

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abnormal.

You can see here that in the normal, there was standardized effect size of 0.33, not so terrible, about double in the patients with abnormal sensory, all abnormal sensory function.

If you look at it just based on the hyperalgesia, which was the other component, again, the same pattern where the people who were all normal -- that was these people here, standardized effect size of 0.42; people all abnormal, again, these are only 11 patients per group, double the effect size, 0.80.

Finally, we also used the LANSS Questionnaire which is just a paper-and-pencil questionnaire. Many of you are probably familiar with it. It's one of these questionnaires that purports to divide patients into neuropathic versus non-neuropathic pain.

The neuropathic group are the people whose pain score is above 12. That actually turned out to be the best differentiator of all, which is kind of embarrassing, because I really wanted the kit to

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work better than the paper-and-pencil questionnaire. Otherwise, why would you bother doing the bedside sensory testing kit?

Actually, you had almost four times the standardized effect size in the people who are so-called neuropathic versus non-neuropathic.

Of course, I'm immediately rushing to remind everyone about the limitations of this study. It's small, it's unpublished, there's small cell sizes. I don't think any of these differences were statistically significant. I neglected to put them on the slide, because these are very tiny cell sizes.

But it suggests a pattern, no matter how you look at the data, that the patients with dysfunctional sensory profiling, if you will, no matter how you look at it, those patients had appreciably larger effect sizes of naproxen versus placebo, the opposite of what I was expecting for this so-called peripherally-acting drug.

As far as I know, this is the only study looking at sensory profiling to see if it predicts,

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in a randomized, placebo-controlled context, a difference between outcome of a cyclooxygenase inhibitor for any chronic pain syndrome.

Now, what I've learned over the years is that whenever I think I've got something innovative, the first thing I should do is look in the literature and I'll find that Lars Arendt-Nielsen has already published something on it right before I did.

(Laughter.)

DR. KATZ: I thought that this was the case, because just yesterday when I was just trying to update myself before today, I found that Lars had published a paper about a year ago looking at etoricoxib, which is a selective COX-2 inhibitor that's on the market in, I think, every country of the world besides the United States, for a variety of very interesting reasons.

He did the ideal type of study that I outlined at the very beginning, that conceptual paradigm where you phenotype everybody at baseline using all the millions of things that only he seems

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to be able to pull off and then did a clinical study, a clinical trial, where the patients got one month of etoricoxib and one month of placebo on a crossover paradigm with, again, as I mentioned, a lot of different approaches to phenotyping the patients.

I thought that I was going to be scoffed [indiscernible] when I saw this paper, because I thought that he was actually going to publish -- I thought he would do the obvious thing, which is say, "Okay, here is the difference between etoricoxib and placebo in phenotype A versus phenotype B." But for some reason, unless I misread it, his paper doesn't actually have that.

He just presents the open label results of etoricoxib, which is exactly what I said earlier, is the wrong way of looking at this kind of data. And so why he didn't present the etoricoxib versus placebo difference and whether the phenotypes mediated that difference, I have no idea.

I actually plan on sending him a note and asking him if I misinterpreted his paper or maybe

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he, for some reason, chose not to present it. And maybe he'll come out with some follow-up paper that presents what we really want to see.

This paper looks very exciting. It looks like he has the data, but it actually does not address the question at hand, because of the way he, I think, presented the data.

That's what is known. That's the world's literature on phenotyping to predict effect mediation for cyclooxygenase inhibitors for the treatment of pain.

I see I'm already over time, so I think what I'll do is just carry on to say a word or two about antibodies to nerve growth factor.

You're all familiar with the pathophysiology, so I won't go over that. We all know that these drugs work for pain. They're not approved yet in any jurisdiction for a variety of interesting reasons.

There are uncommon, but very severe safety problems associated with this class of drugs, the main one being what's so-called the rapidly

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progressive osteoarthritis.
But there's also this issue of peripheral neuritis or peripheral neuropathy associated with these drugs. Most of it is transient. People just get tingling of their fingers and their toes that goes away after a few weeks.
But I've spent a fair amount of my own personal time reviewing cases from one of the programs that I was involved with to see are these always transient or do some of these cases of peripheral neuropathy actually go on and on and on. And it seems to me like they are not all transient.
It has not gotten as much attention as the rapidly progressive osteoarthritis, but it is actually an issue.
Here, if there were some phenotype or some biomarker that could predict either the efficacy or the safety of these products, that would be a very good thing, because once you give someone an antibody, you can't take it back. And if they end up with this complication, it's too damn bad. So you would like to predict that in advance so you

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could just give the drug to the people who you could predict would benefit or would not get the safety problem.
There are multiple companies right now in phase 3 clinical development with these drugs. They are going to be -- each company will end up with more than 10,000 patients in its database.
So you might ask, well, what are people doing to try to phenotype patients at baseline to figure this out, and as far as I know, nobody is doing any phenotyping to predict efficacy.
I had the opportunity to speak with people from these companies in advance of this presentation and I'm still not aware of anyone doing anything for that.
Now, I know that some of these companies are represented in this room. So if anybody, during the discussion, wants to raise their hand and say, "Oh, no, actually, we are doing something," that would be great.
There is some work going on to try to develop biomarkers that predict safety. Who's

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going to get rapidly progressively osteoarthritis? And I want to thank Rosalind Arends from Pfizer who is managing this program at Pfizer.
I also want to thank Morten Karsdal, who is a consultant at Nordic Bioscience in Denmark, who apparently is Mr. Biomarker and is working with everyone to try to help figure this out. He was kind enough to share some slides and some information with me about this, as well.
There are a lot of biomarkers that purport to represent bone pathology, bone metabolism. There's literature on this and there is some work being done to determine whether any of those bone biomarkers could distinguish the patient destined to get an anti-NGF-induced rapidly progressive osteoarthritis from patients who are destined not to get an anti-NGF-induced rapidly progressive osteoarthritis.
This is a slide from a presentation that Rosalind just gave a few weeks ago somewhere. This has not been published yet. I'm not going to go through it in detail, because it's not my work. I

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don't really understand it.
But the bottom line is that they are looking at ways to model sensitivity and specificity of different predictive algorithms resulting from combining these biomarkers in as intelligent a way they can think of to try to do this prediction.
It seems like some of the performance of some of these algorithms actually looks pretty good, although we're talking about, obviously, a very small numbers of cases, 30 cases of this and 50 cases of that.
That's all I want to show just to give you a sense that this work is going on and that's really all I have to say about it for today.
This is actually my final slide. My conclusions from exploring this literature, as well as the very small amount of work that I've done in this area, is that there are actually -- considering that nonsteroidal anti-inflammatory drugs have been used since the time of Christ in the form of willow bark extract for pain relief, we know virtually nothing about

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who's going to benefit and who's not going to benefit, which is kind of shocking, I think.

It's now 2016. So after 2000 years of using these drugs, in the last four or five years, we're starting to see some emergence of a literature on whether we can predict what your outcome is going to be, whether it's from a safety or an efficacy endpoint, using both soluble biomarkers, sensory profiles, et cetera.

With the anti-NGFs, it's actually very important for us to do that and even that work is really still in its infancy. So that's what I was able to find out, and I do think it's an area where further research would be beneficial.

Thanks for your attention.

(Applause.)

DR. MARKMAN: In the interest of time, I think we're going to hold off on questions. Our next speaker is Dr. Staud, from the Center for Musculoskeletal Research at the University of Florida. He's a professor with the international leadership on thinking about fibromyalgia and

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central sensitization.

Today, he's going to talk about the potential to affect descending inhibition and how it might inform our future research in precision pain medicine.

Presentation – Roland Staud

DR. STAUD: As we heard from the previous speaker, the identification of phenotypes in precision medicine will be or is a very important part.

What I'm going to do in my talk here is to give you some information regarding the current state of the knowledge that's available in identifying phenotypes and, also, how it can be used for precision medicine.

What we know and what I'm going to talk about is that endogenous pain modulation, which is the focus of this talk, is highly variable in healthy individuals, as well as in patients. This is, to some degree, determined by genetic and environmental factors.

The pain inhibitory function, generally, in

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many publications, has been found to be inefficient in chronic pain disorders. The question here is now if this function can be used for characterizing individuals that may respond either to particular drug classes or to particular individual treatment response.

Again, to the question about phenotypes, phenotypes is an approach that has been begun, but is definitely not complete. And much of these phenotypes are just hypothetical phenotypes, as for example, mentioned here in this particular slide.

When it comes to pain modulatory phenotypes, to separate groups of individuals into either so-called normal phenotypes compared to the pain facilitatory phenotype, as well as, here, to the pain inhibitory phenotype and saying that or hypothesizing that the pain facilitatory phenotype is these individuals at higher risk for pain disorders, whereas individuals with a predominantly pain inhibitory phenotype are protected for pain disorders, as well as pain.

Now, if we use pain modulatory function for

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the characterization of phenotypes, this has precedence here. For example, this is Irene Tracey's approach to identify endophenotypes just based on neuroimaging here.

From her work, her suggestion is that when functional brain imaging, as well as structural brain imaging is used, phenotypes can be described according to activation of certain areas either in the pain inhibitory system or activation of limbic system, as well as the nociceptor system, and that even changes in brain morphology can be used to identify subtypes in pain.

What I have done, and I have really no proof for a clear definition for this phenotype, is in terms of pain modulatory endophenotypes, as a suggestion here, the different possibilities that are available here. So in terms of pain modulatory function here, it is do you use temporal summation as the pain facilitatory phenotype, as well as the response to chronic pain stimuli.

Then the analgesic phenotypes here, in particular, the response to context-related or the

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occurrence of context-related analgesia, response to spatial summation, offset analgesia, conditioned pain modulation, and then the stress response in general.

What I'm going to focus mostly is on the top-down approach from mostly central factors to more peripheral factors in pain modulation.

So the pain pathways are relatively well established. Pain is signaled to the spinal cord and the central nervous system and results in a response that is, to some degree, well delineated, often with activation of, here, the periaqueductal gray, the RBM.

This has a direct effect on dorsal horn neurons, usually in the presynaptic and postsynaptic fashion. And many of the mediators are known, particularly opioids, norepinephrine and, to some degree, serotonin.

Now, the effectors that change endogenous pain modulations are here, which are really due to mood-related factors, as well as to factors that are related to cognition and, in particular, the

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factors that relate to placebo analgesia.

What I wanted to point out here is that endogenous pain modulation seems to happen at every level of the central nervous system, from the brain, brain stem, the spinal dorsal horn, autonomic nervous system, and further down.

These systems seem to interact, at least to some degree, but they also have intrinsic pain modulatory function.

I wanted to demonstrate the pain modular function essentially from the brain in a caudal fashion and to start with placebo analgesia, which is one of the most important pain modulatory functions that is available. Placebo is a generic term which is really used essentially as a control for a usually active treatment condition.

Placebo entails the placebo effect, which is here shown on the right side, which is an effect that is due to expectations and learning, due to influence from multiple factors here.

But what, in clinical trials, is often important are these factors here that are very

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poorly described, generally speaking, in clinical trials. So the combination of all these factors entails the control that is used and it includes the placebo effect.

We know a lot about the activation of certain brain areas associated with placebo effects. We know that it's an active process that leads to activation particularly of prefrontal areas, the cingulate cortex, as well as the insula, as well as some of the basal ganglia.

But particularly, as important, the projections of these particular pathways then to clearly well-known areas of pain modulation, like the periaqueductal gray, as well as the RBM, then here, again, from these areas, either directly or indirectly going to the dorsal horn, where they influence activation of the dorsal horn neurons.

The brain imaging, which is part of what I frequently do, is able more recently to show more difficult-to-approach details of the central nervous system, like the brain stem, as shown here.

This is the brain stem and you can see, in

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terms of placebo analgesia, that during analgesic response is that activation of the PAG, the RBM are visible or detectable on brain imaging.

More recently, we have started to do imaging of the spinal cord. This is not our work, but we are also able to identify activations within the spinal cord.

Here, this study by Eippert, has shown -- this is the spinal cord here and the activation, you see this little dot here. That's how small the activations in spinal cord imaging are.

Over on this side shows the difference in activation. So here, in the control, there is a large amount of activation. In the placebo condition, shown here, there is essentially no activation. And this is just the contrast, so showing the area in the appropriate location that is affected by a placebo mechanism.

The molecular mediators of placebo analgesia are known, to a large degree. Many of them are opioidergic and involve these particular areas

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here. And then I want to just place your attention to the dopaminergic pathway. There are also pathways that are involved with cannabinoids.

The particular interest that we may have in terms of early trials, as well as in terms of interventions, is that placebo effects can be effectively modulated.

I showed you here this meta-analysis of, I think it's at least 30 studies, which show the effect sizes, here on the right side, of different interventions.

Here, for example, verbal suggestions that increase the placebo effect, we can see that they have moderate-to-strong effect sizes; and, then here, changes in conditioning, which also has moderate effect sizes; and, then here, changes of placebo analgesia due to looking at images.

Overall, the overall effect size is moderate and some of the effect sizes are relatively strong. So you can imagine that this is important for clinical trials, but it's also important for clinical care that placebo effects can be effective

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or could be effectively included into a treatment armamentarium.

I was thinking here in terms of the placebo effect in precision medicine. The important factor is that placebo effects are really highly reliable when they are executed in a similar environment and in a similar context. You can really repeat this really well.

The second part, which is well known here, is that when placebo interventions are repeated, they usually seem to increase the placebo efficacy. It is possible that with the identification of placebo responders, that this can inform trial design and benefit treatment of individuals.

Going further down in the central nervous system, I will focus now in temporal and spatial filtering of pain as a potential indicator for precision pain medicine.

Temporal and spatial filtering of pain relates really to offset analgesia and conditioned pain modulation. These factors are usually brain stem and spinal cord-related but they have, also,

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influences from brain areas.

The mechanisms of some of them are well known; others not so much. For example, offset analgesia, which is a method of increasing pain sensation through a -- increasing and then a constant stimulus, which is followed by a small increase in the intensity of the stimulus.

Here, in this particular situation, it's heat. And then after about five seconds, the temperature or the stimulus intensity drops back to baseline.

As you can see, under these circumstances, the initial increase is relatively small, but the subsequent change results in a strong decline of pain reporting, and this is called the offset analgesia effect.

The brain activity to offset analgesia is shown here, and this is the brain activity of offset analgesia on this side. I will talk about the brain activity of CPM later on.

Again, as you can identify that brain areas become activated due to offset analgesia, but,

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also, it involves brain areas that become deactivated, here in blue.

Red areas are activated. Blue areas become deactivated. And it is not quite understood what the particular meaning of these particular deactivations is, if it's a direct effect or an indirect effect.

I just want to point out some of the areas here which seem to be important, as the interior insula.

The pharmacologic characterization of offset analgesia has been attempted here, for example, to look, with opioids, if it can modulate offset analgesia.

This is a relatively small study, where the individuals are shown here and the mean changes are depicted at the bottom here. And you can see there's a very small and non-significant change of offset analgesia detected after individuals received hydromorphone.

To look at offset analgesia in the context of NMDA receptor antagonists, like here, ketamine,

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it also has been shown that the ketamines do not seem to affect offset analgesia. So we really don't know exactly what the mediators of offset analgesia are at this time. But this is a field that's relatively new and a lot of work is currently being done.

But what's encouraging is at least in this one study here is that the reliability of offset analgesia seems to, at least in the hands of these investigators, be very, very high. This is an interclass correlation coefficient of 99, which is suspiciously high.

(Laughter.)

DR. STAUD: In terms of offset analgesia, what has it done so far in terms of phenotyping? It has shown that similar to other forms of pain modulation, endogenous pain modulation that patients' neuropathic pain seems to lack efficient offset analgesia.

The upside of offset analgesia, which is probably important for trial designs, is that it's easy to perform and, therefore, may become useful

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in the future as an evaluation tool, but much more work is needed.

For the last part of my talk, I just wanted to focus on conditioned pain modulation, formerly known as Diffuse Noxious Inhibitory Controls, where there's a large body of evidence available.

I will tell you something about the pros and cons, in particular, related to comparison between experiments of different investigators.

It started early out, conditioned pain modulation, in the last century. In the 1980s, Le Bars and VA started this in rats. They lightly anesthetized rats and they found that conditioned pain modulation is a bulbospinal event relating to these areas here. In those days, in those experiments, the effect was very, very short, lasting only several seconds after the end of stimulation.

This has now been modified significantly by many investigators. I think most of us will agree that what currently is described as CPM is not the same CPM that has been described by the original

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investigators.

How CPM is usually done, it's the pain inhibited pain condition that individuals receive a conditioning stimulus, usually either cold water or hot water, water bath, where they immerse one of their extremities while a test stimulus is applied to a different area of the body.

There's lots and lots of variations in this particular field. Some individuals apply or have applied test stimulant at the same time the conditioned stimulus is applied. Sometimes they applied it afterwards.

So kind of showing that in their hands, often the effect, the pain modulatory effect is long-lasting, because if the test stimulations are done afterwards, they take usually several minutes to complete, and still analgesia was to be detected.

The question here, which has never been really answered, is if stress-related analgesia, which has a much longer-lasting effect than CPM, may play a significant role in these forms of CPM

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testing.

Now, also, a lot of attention has been placed on the role of the conditioned stimulus for CPM, in particular, to the magnitude of CPM, because it is known that with increasing magnitude of the conditioned stimulus, the conditioned pain modulation increases. But there seems to be a ceiling effect, as shown here. This is a mild conditioning stimulus, this is a moderate conditioning stimulus, and this is a strong one.

You can see that the conditioned pain modulation seems to be unchanged when you reach a certain threshold in conditioned pain intensity.

As shown before, the imaging of this particular mechanism has been done. Here, it's the brain imaging shown just of the test stimulus and the important areas are really the brain stem, in particular. And this is shown here on the right side, here, where, in particular, the subnucleus reticularis dorsalis has shown decreased activation during CPM stimulation.

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The relevance of these test sets may be for chronic pain disorders, and there are multiple chronic pain disorders where CPM is either minimal or absent, most predominantly in disorders like fibromyalgia, irritable bowel syndrome, and so on, but, also, in disorders like osteoarthritis, for example.

Here in this meta-analysis of CPM trials, where the effectiveness of CPM was detected, you can see there are over 30 studies published where the effect sizes range from mild to moderate to, in several cases, very, very strong effect sizes.

This is for TMD, IBS, and migraine. And here is one effect where the test identified impaired, overly effective CPM in patients with stroke.

Again, the pharmacological evaluation of CPM here in terms of can it be improved with certain pharmaceutical agents as oxycodone, this is the effect on pain over time.

We have 180 minutes and just as a control here, temporal summation was used, whereas

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oxycodone had no significant effect on CPM, it was effective on temporal summation, which has been previously reported.

Similar findings have been obtained with hydromorphone. Again, this is a relatively small study and, again, only non-significant changes of CPM were detected.

The opposite, the inhibition of opioidergic pathways has been attempted by multiple investigators. The majority of these investigations showed no effect of naloxone, an opioid receptor antagonist, on CPM.

Interestingly, I wanted to show this to you, this one publication with tapentadol, which looked at CPM in patients with diabetic neuropathy. This was a placebo-controlled trial.

Here, an effect on patients, CPM with tapentadol, was obtained. This is a significant improvement of CPM. At the same time, the pain of these patients improved.

Similar effects have been done here with apomorphine, which is a dopamine agonist, again, to

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seem to have improved CPM.

As for all types of research reliabilities of critical importance and the evidence of reliability studies is mixed. There are several studies that showed excellent reliability of CPM testing, whereas a similar number of studies showed poor reliability.

This may be due to multiple factors, including the different forms of how these tests are executed by different investigators. As I will point out afterwards, standardization, it is of critical importance that we finally agree what the appropriate form of CPM testing is.

I just wanted to show you an interesting study that looked at the reliability of CPM in terms of sex differences. As I'm showing here, I'm showing here that the reliability of men, for some unknown reason, was much, much lower compared to women. There was no real explanation available about this.

The use of CPM so far as a predictor, as Dave Yarnitsky has shown, that it predicts

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chronic post-operative pain. In one of his studies, it has been identified as a predictor for opioid-induced hyperalgesia.

And the last and probably controversial line of evidence, the analgesic response to serotonin norepinephrine reuptake inhibitors -- and I want to briefly discuss this, because it seems to be an interestingly important topic, but it needs some further clarification.

So I just want to show you the way it was done. This was 30 patients with diabetic neuropathy. They received an open label intervention, first 1 week of placebo, followed by 30 milligrams of duloxetine, followed by 4 weeks of duloxetine.

CPM was tested before any of the treatments occurred and then right at the end, during the last week.

Now, it had an effect on diabetic neuropathy. The pain was significantly reduced. But interestingly, the efficacy of pain reduction was different or seemed to follow a regression line

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here that individuals with efficient CPM, which is shown here -- this is the reduction of pain with a conditioning stimulus -- that the efficiency negatively predicted the effect of the drug on neuropathic pain.

So the more efficient the CPM was, the less effectiveness of the drug was obtained. And the less efficient it was, the more effectiveness. And the important part of this trial was that these findings were reversed at the end of the trial, at this end of these 6 weeks, so that individuals who had inefficient CPM now had efficient CPM.

Here, it's the same thing shown here, that CPM before and after the treatment has significantly changed, and indicating that potentially the intervention, the identification of individuals with less efficient CPM are a predominant target for these particular interventions.

Let me conclude with pointing out that descending pain modulation is a critical part of acute and chronic pain relief and that decreased

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endogenous pain inhibition seems to be a characteristic of many chronic pain conditions.

It appears that CPM can be used to determine endogenous pain inhibition in groups and possibly even in single individuals.

The usefulness of CPM for offset analgesia in precision medicine will, however, require some more standardization of CPM and offset analgesia and, in particular, that prospectively controlled trials will be necessary before either CPM or offset analgesia can be used as a predictor for treatment response.

Thank you.

(Applause.)

DR. MARKMAN: Do you want to take questions?

DR. STAUD: Yes.

DR. MARKMAN: John?

DR. FARRAR: It's a fascinating area and certainly, we've known for years, just in clinical practice, that some patients sail through a serious surgical procedure, have relatively little pain afterwards, and do very well. Others have very

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significant problems.

I wondered, there have been some attempts to try and offset or to change basically the patient's expectation for pain after surgery with a variety of mechanisms, and I wondered whether you knew of any attempts to try and look at that in the clinical setting.

The prime example is where you test a patient with a heat probe. You then give them a drug. You test them with the heat probe again, but in half the patients, you use a lower heat so it "enhances," in quotation marks, the effect. And then you do the testing again later that's been done -- Irene and some others have done this with FMRI.

I just wondered whether you know of anything where that's been looked at in the clinical setting.

DR. STAUD: No, so far. I thought this is a very important part of evaluating the particular effect. So far, no attempt seems to have been made, at least to my knowledge.

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MALE SPEAKER: Yes, quick question. Thank you very much. Very interesting information. The CPM, is that a trait or a state in an individual patient?

(Laughter.)

DR. STAUD: Yes. This is like a question that has been interesting for many of us so far. But the long-term evaluation or the long-term characterization of this particular effect has not been done yet.

Clearly, there seems to be potentially some relationship to age, that as we know, that CPM seems to decrease with aging. There may be some or there is potentially some trait effect, but we can only speculate at this time.

DR. MARKMAN: One more question. DR. MARCHAND: I wanted, yes, to react to the -- yes, absolutely. We just finished the one study, I have the data here, I can show you if you want, where we tested it in young adults.

We tested the CPM now and after that, a day after, a week after and one month. Even at one

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month, it's really stable, I mean it's really, really stable.

But I agree with you. I will say it's a trait and a state. It depends. You have both, because if you compare a young and older adult, for example, you will see a difference, also.

Then age is clearly playing a role and sex in playing a role. Also, gender is playing a role. And there are other factors, for sure. But I think that at least if you compare it -- because if it was moving around all the time, it will be of no use at all, because if you measure it to see what's happening with a drug, for example, and you know that it's not stable over time -- but it seems to be quite stable, as a matter of fact.

DR. STAUD: Yes. I think one of the important work that needs to be done is with the context-dependence. For example, it is well known for placebo analgesia if similar changes also influence significantly CPM, and this awaits to be completed, this work.

DR. MARKMAN: As we're all, I think,

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probably mourning for Muhammad Ali this morning, with these talks, I think you're giving a sense of all the work to do. He said, "It's not the mountains ahead to climb that wear you out. It's actually the pebble in your shoe."

We're going to now switch gears to a different approach and a different mountain that's being climbed, which is through QST, with Dr. Baron.

Dr. Baron is, I think arguably, the world's leader in using QST to characterize patients with different pain conditions and try and think about a treatment response. He is professor of neurology at the University of Kiel. It's a pleasure to introduce him.

Presentation – Ralf Baron

DR. BARON: Thank you, John. Well, my task today is to talk about QST, as you have heard. I put always these pictures at the beginning of my talk, and some of you might know them, just to show you that many individuals are heterogeneous in their appearance, and I think this holds true for

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patients, as well. And I will talk to this a little bit.

This is the group or some of the group, I think, in Kiel, in Germany. They are doing all the work, as you know. You also know that neuropathic pain -- and we would like to concentrate on neuropathic pain today -- has many, many different etiologies, and I put together some of them. But just for this purpose of the talk, just imagine one patient with -- or two patients with painful polyneuropathy.

You see two patients and they come to your office and you ask them, "Please describe to me your sensory perceptions, what you feel." And again, it's the very similar etiology behind this. This is polyneuropathy.

One patient says, "Well, I'm suffering from thermal hypersensitivity," and pinprick you can measure and mechanical allodynia. And the other, patient's profile is characterized by burning pain, prickling, and shooting sensations and, in particular, numbness, and there are no evoked pains

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whatsoever.

This was the observation we had many, many years back. And we thought that if patients are so heterogeneous, there might be different underlying mechanisms and we might be able to identify this with the QST setting.

This leads me to the agenda for today. I'm calling this personalized treatment, but whatever, precision is fine with me.

I would like to show that classification of patients is possible based on these distinct sensory profiles, perhaps speculate a little bit with you about mechanisms -- because Clifford is here, I think we have to do this -- some words about genes.

We had some data on genes and I showed you this some years ago already; therefore, very briefly. And then the most important thing, can we use these profiling options and techniques to predict the treatment response.

I would like to give you three examples. One is on capsaicin, topical capsaicin treatment;

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very briefly, the oxcarbazepine study Troels already mentioned; and, then, something about tapentadol.

The tapentadol is, in particular, in the light of the talk of Nat because -- well, you will see why in a minute.

We think that the answer to all the problems we have with the many negative trials and so forth might be this concept, the mechanism-based classification or treatment approach.

This is my slide. You have seen many, many others from Troels and Clifford, but this is mine. We know that there are individual pathophysiological mechanisms operating in our patients.

This is the idea we have; that is, linked to genes, perhaps to etiology, and to the environment. And the treatment response is also linked to the mechanisms.

We have the problem that we are not able to look directly into the mechanisms in our patients, but this is much easier in people who are working

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in the animal world, but we can't. So we need to use surrogates to look, to have some ideas about the operating mechanisms. We think that the sensory profiling approach might be such a surrogate where we can identify some mechanisms and then identify in treatment responders.

In the first part of my talk, I would like to briefly share with you some data about QST, about the sensory testing protocol we have.

You all know, and we have mentioned this several times during this meeting, this is the DFNS QST protocol which we established in Germany 10 years ago now. We have many, many stimuli, 13 parameters all together, which we apply, mechanical parameter, like pinprick, Von Frey hairs, vibration. This is for positive signs like allodynia. We also use algometer and, obviously, the heat, the thermode [ph].

We have a variety of stimuli assessing temperature and mechanical sensation and assessing small fibers as well as large fiber functions. This is, I think, the important thing with the

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protocol.

Just to mention this briefly, the algometer is the only stimulus which is assessing deep somatic innovation, like muscle innovation. All the other stimuli are applied to the cutaneous tissues, to the skin. So we mainly have an idea about the innovation properties of the skin. This is the logo of the German network.

What we can do with all these data -- and this is now so-called sensory profile of one particular patient and you see here at the bottom are the 13 parameters, for example, cold detection, warm detection, and so forth. So here are the mechanical stimuli.

This is DMA. It's a little bit differently coded. Therefore, we have an extra part here. This is paradoxical heat sensation, so we talked about these phenomena already.

What you can see if you put data of one patient, like in this example, into the Z room, you can see on one glance if a certain parameter is normal because you have zero line and if you, if

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your value hit the zero line, then you have normal data compared to our normative database.

If you are in the upper part of the figure and, again, on function part, you have a hyperphenomena, a phenomenon like hyperalgesia, allodynia, and so forth, and if you are here in the lower part, you have phenomena to this particular stimulus in the hypo area, so hypoalgesia, hypoesthesia, and so forth.

We think that this might indicate a degeneration of fibers and this is in hyperactivity state, be it in the periphery or in the central nervous system.

This, again, is one patient and we did this now in many, many, many patients in our networks. We not only have data within the German network, but also within different European networks.

This is the so-called Neuro Pain Network. This was sponsored by Pfizer, with many, many centers across Europe. And this is the IMI Europain, as you have already heard, with many, many, many centers all over Europe.

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What we did in the last years is that we concentrated on neuropathic pain patients with peripheral origin, so peripheral neuropathic pain, and we excluded all the central patients we also have in the data on pain.

This is a little bit different from the approach we used some years ago and what you have seen in earlier talks from me. Here, we concentrate on peripheral neuropathic pain, because we thought that the mechanisms in central and peripheral neuropathic pain differ.

We excluded CFS from our database, because we, again, thought that CFS might differ in terms of underlying mechanisms. And we excluded trigeminal neuralgia, again, for the same reason.

We included in this particular analysis all the polyneuropathy patients, different etiologies, zoster, postherpetic neuralgia, and radiculopathy patients.

So if you just concentrate in these entities, we can come up with more than 1,100 patients now which are in our database. This

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is a very clean database.

The QST is standardized in all centers. All centers have to do training sessions. So they are trained. We have very strict quality assurance in place.

They send data to the central database and this is checked and so forth for plausibility and so forth. So it's a relatively clear database with these patients.

If you look in this a little bit more in detail, and I show you many, many different patients now which we analyze in this video, you can see that patients really are not the same. So they are heterogeneous. They have different sensory perceptions. And if you look at all the different 1000 patients, you can get this. I think I can convince you that some are here in the negative range, but some are in the positive range and so forth.

This is a variety of different perceptions and problems and perhaps underlying mechanisms.

To get some order in this seemingly

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heterogeneous picture, we used a statistical trick to do a subgroup analysis, a pattern analysis, and we also used hierarchical cluster analysis.

If we do this, apply this in this particular group of peripheral neuropathic pain patients, we could come up with three very stable different subgroup clusters, and these are the different clusters.

I'll show you the mean of these groups now in this particular graph. We call them -- the first one, the blue one is the group sensory loss, which we call sensory loss.

You see the blue profile, nearly all of the values are located in the negative area of the Z profile. So everything is indicating loss of function, degeneration.

The red one is thermal hyperalgesia. It's one-third of the patients in this group. This group, which you can see here, is mainly characterized by thermal hyperalgesia for cold, as well as heat. So the main hyper phenomenon is thermal hyperalgesia.

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The green one is very interesting. It's characterized by loss in the small fiber range. So this is warm/cold in combination with mechanical hyperalgesia for pinprick and severe allodynia, as well. And because this is dominated by those mechanical hyperalgesia problems, we call this mechanical hyperalgesia, and a quarter of the patients form this category.

If you look at these three different profiles, this is very, very similar to the original three profiles Mike identified in postherpetic neuralgia patients when we published this paper back in 1998. So this was really confirming for us that there might be some truth in these statistical approaches.

If you look at the values which best discriminate between all these three groups, because I think this is very important if it comes to use in clinical routine, this is warm detection threshold in mechanical pain sensitivity, which is the pinprick stimulus. I will show you in this 3D plot how the data really look like.

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The green one -- again, the color coding is the same -- is the mechanical hyperalgesia group; the red one, the thermal hyperalgesia group; and, the last group is in blue.

Obviously, you can see, if you see here, the values just for the two different parameters, one, detection threshold; and, the pinprick threshold. Pinprick is over here on the left side and this is the warm.

You can see, obviously, that there's an overlap in these three groups. But still, if you look at the centroids -- these are the centroids -- there's a clear discrimination between both of them.

I think if we just use the two parameters, we can, with a certain probability, allocate particular individual patients to one of these three subgroups, which I think is very important for the future if it comes to clinical trials.

We did a replication. So this is the original cohort and you see here, again, the three different subgroups and the profiles. We did a

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replication in the second cohort.

These are the patients who were included into the trials, Troels' trials, which he was discussing yesterday, this Demant trial with the lidocaine patch and the oxcarbazepine.

These patients were not in the original group and, therefore, we had access to this replication cohort. And you see a very, very similar structure as it comes to the profiles.

How is the distribution within etiologies with these three different subgroups? You can find, identify each of the subgroups in each of the etiologies, but there are certain frequencies and particular frequencies.

Perhaps this is important, again, for trial design. If you have a drug, for example, which is particularly active in hyperalgesia phenomena, you should look into these graphs, which classical clinical model you can choose for your trial. These are all the patients, the polyneuropathy patients.

Clearly, the most important profile here is

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the loss profile. And as Troels already mentioned, allodynia, mechanical allodynia, which is hidden here in the green one a is very rare phenomena in polyneuropathy.

This is radiculopathy, peripheral nerve injury, much more hyperphenomena in the thermal range, as well as in the mechanical range. For postherpetic neuralgia, this is striking. This is the most important, and the most frequent clusters or subgroups are these hyperphenomena. I think it's very interesting to look at these different distributions.

Some speculation about mechanisms now, so this link. Can we really look into mechanisms? And I think if we start with a sensory loss subgroup, I think this is pretty straightforward, we think that in these patients -- and you see the graph here -- the peripheral nerve fibers, the A fibers, the C fibers here, the spinal cord, these patients are characterized by a degeneration of all fiber classes, because we have losses in the small fiber range, as well as in the large fiber range;

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so degeneration here and here.

The pain might be produced perhaps in the spinal cord, in the spinal ganglion, those root ganglion, so ectopic problems in the dorsal root ganglion. Marshall Devor's work, I think, points to this direction.

Also, if there is a deafferentation in the spinal cord, the pain might be produced as a deafferentation pain spinally.

Another example, thermal hyperalgesia group, again, characterized by heat and cold hyperalgesia mainly, so what could be the underlying mechanism in this subgroup. We think this is then due to upregulation expression of some channels and receptors. And we talked about TRP V1, perhaps others, sodium channel expression.

And we can explain the thermal hyperalgesia phenomenon which we call peripheral sensitization and the spontaneous pain is produced by spontaneous activity in the surviving hyperactive fibers in this subgroup.

So perhaps I can convince you that there

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might be a link between the mechanisms in our specific profiles, and we call this peripheral sensitization.

Just one brief word to this link. Can genes influence the individual mechanisms and the phenotype? We collected DNA of many of the patients in our network and did a very classical association study where we looked for association between the QST parameter and profile, in particular, polymorphisms which we choose before.

I know this is old-fashioned and this is not replicated, but after all the correction procedures, and I think this is pretty straightforward, we could find one polymorphism. This is the A1 and the TRP A1 gene, which acts as a protection gene against cold hyperalgesia.

If you have this polymorphism -- and this is located here in the TRP A1 -- and you will get postherpetic neuralgia or diabetic polyneuropathy, you are protected against cold hyperalgesia. Perhaps you can get heat hyperalgesia or other spontaneous pain, but statistically, you are a

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little bit protected against cold.

The same holds true for heat hyperalgesia. Again, a protection SNP in the TRP V1 channel gene here, in this area it's located. Again, it's weak data, but just to show you for the whole story.

This is the main and most important idea. Can we use the profiling techniques to predict treatment response and to identify responders?

The first example is on topical capsaicin 8 percent. This is a small study. What we did in this study is we treated 20 patients with capsaicin topically.

We did the profiling before we initiated the treatment. So at the beginning of the trial, the profiling was done and then we did a post-hoc analysis, retrospective analysis, looking for responders and non-responders to this treatment.

This is the responder profile on the left side. On the right side is the non-responder profile, which we could identify. By chance, it was 10 and 10, which was nice.

If you look and compare both, we could

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identify significant differences in the baseline profile for cold pain threshold and for the mechanical pain sensitivities or the pinprick threshold.

That was really irritating for us, because we thought -- our hypothesis was that this might be something -- has something to do with heat, because it's capsaicin, but it was cold.

There's a co-localization of TRP A1 and V1 in many, many nociceptor fibers. Perhaps there is some underlying sense, I don't know.

If you combine both of these parameters, the cold pain threshold and the mechanical pain threshold, and you define a threshold, you can predict the response based on the data here retrospective with relatively good specificity and sensitivity values. So perhaps a hint that we can use these profiling to identify responders to capsaicin.

The second example is Troels' and this really is the first profile stratified trial. And I really would like to stress this. We know we

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came from the scenario that many, many sodium channels failed in phase 3.

You mentioned this yesterday. Novartis didn't get approved and so forth. So the question is, does it work in subgroups, and this is the title. And I really like the title, because there's everything in there, it's randomized, it's double-blind, it's placebo-controlled, and phenotype stratified, so the best that you can do at this point of time.

This is the data, how I show it. It's exactly the same data. If you now allocate the original profiles which Troels found in his trial for responders and non-responders -- so the stratification due to your things -- if you allocate this and compare this with our profiles -- so this is the 31, these are the profile, the mean average profile of the 31 patients you put into your group -- irritable nociceptor, correct? And the underlying shade is the profile of our statistical result of the thermal hyperalgesia subgroup. And perhaps I can

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convince you that it's very similar, except one here, but this is due to Danes, I think. So this is a difference in Danes.

On the other hand, they allocated 52 percent into the other group, non-irritable nociceptor group. And I underlay here the sensory loss profile of our cluster analysis and this, again, neatly fits. And again, there's a small peak, which is not correct, at the pain pressure threshold.

I hope I can convince you that there are some similarities of these two groups, the irritables in the Demant oxcarbazepine study and our groups, which we could identify.

Interestingly, we put into the European Medicine Agency CHMP qualification advice and asked them whether they are willing to use our QST certification testing for trials in the future.

We got a positive reply and this is the exact wording from the reply, that they think that our sensory profiling and subgrouping strategy is an adequate stratification tool for -- and

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particularly for phase 2 trials.

But -- and there's a "but" --this is phase 2 and I think we can implement all these techniques and things into phase 2, but we need something like a bedside testing, and we will hear more in a minute about beside testing.

We are doing some bedside testing things, as well. We tried to establish a bedside test which mimics as closely as possible the QST battery, because we have all the data from the QST battery.

If you see this part here, these are small metal pieces and these are exactly the same size as the thermode of the Medoc machine, and we can cool and warm them. I don't want to go into detail, I can't, I think. But this is an ongoing project, and we will really look for and validate this bedside test exactly against QST. Perhaps we would like to see what this will do.

Can I have five more minutes? This is the second example. I just wanted to share the data, because they are brand new and they are under revision now in the European Journal of Pain.

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We calculated a prediction model, a real huge prediction model in pain research. From my mind, I think this is the first really prediction model in pain research. We know all these prediction models from oncology and we heard a lot about oncology, but this is the first in pain.

This is in the cohort. These are data of a clinical trial with tapentadol in patients with back pain radiculopathy; so a huge group of patients, back pain radiculopathy.

I have to admit, these are data from an open label trial, no placebo arm. And I know what Nat is now saying and looking, "This is all rubbish."

(Laughter.)

DR. BARON: But I disagree and I would like to show that perhaps there is some sense in what we can learn from this. But, look, we had access to all the data of this particular trial of Grunenthal with tapentadol in patients with back pain radiculopathy.

There were 46 baseline co-variables, so all the baseline data which were assessed in this

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particular trial. We wanted to see whether some of these baseline characteristics may have a predictive effect on outcome.

Just briefly, demographic characteristics, you mentioned demographics briefly. Medical history, vital signs, so this is all the normal things.

Physical examination, but we also had the PainDETECT score. We used the PainDETECT questionnaire. I will show you the PainDETECT briefly in a minute. And, also, things like qualities of the pain, like burning, prickling, allodynia attacks and so forth. You can read this. And we had all the comorbidities available at baseline, sleep as of 36 EuroQol and HADS.

What we did with PainDETECT -- this is the PainDETECT questionnaire. It's a little different from LANSS and DN4, as you know. But we use them the capture neuropathic elements to the pain.

These are the seven questions we assess with the PainDETECT. Interestingly, and this is important, we have a grading in our PainDETECT

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questionnaire from 0-5. So we have some information about intensity of each symptom we would like to assess, which is interesting for the prediction model.

Now, this is more for the statisticians. I do not really understand this, but they say this is state-of-the-art prediction models; first, univariate, then multivariate analysis, all these correction things, over-fitting and so forth.

This is a very, very conservative prediction model, I have to admit, with all these correction things.

In every step, there are corrections and so forth. I think that what falls out of this prediction model is a relatively solid predictor for this particular trial.

These are the results and I think these arethe learnings we have. If we look for the primary outcome in these clinical trials, this was improvement of pain intensity on the NRS scale, which we discussed extensively, we couldn't find any baseline predictor for this outcome. But we

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also looked for different outcomes, because we had all the questionnaires also at the end of the trial.

We looked for the improvement of function, functionality, and the improvement of quality of life in this trial. Then we could identify some very stable predictors, and I put them together here. It's a low health state, a good mental state, and a high PainDETECT score, and a little bit male, which is a predictor of the physical function. And if it comes to quality of life, it's low depression, low anxieties, the classical comorbidities which we would think there might be; and again, a high PainDETECT score and few PainDETECTs. So if you have very few of these severely painful attacks, you have a good chance to be a responder in terms of quality of life and you have improvement of quality of life.

Also, always the high PainDETECT score. So many, many neuropathic symptoms. If you have many symptoms, burning and so forth, that is a predictor for a good improvement after the treatment with

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tapentadol, which might be in line with the mechanism of action of tapentadol with these additional NRI components. So we can speculate this.

We put this, the data from the model, into a formula. For example, for the quality of life response, you can calculate this formula. You can put in all these baseline values here and then you can calculate the predictive response in this particular individual based on the data and the clinical trial. You can also do nomograms and do this graphically and estimate the response of the patients.

I think what we can do in the future -- and scientifically, perhaps there's a problem. I will discuss this in a minute. But clinically, I think this has relevance, because even if this is not a placebo-controlled trial, it's open, it's relevant for daily clinical routine.

We can estimate from this prediction what change of quality of life we can expect in one patient who is sitting in front of you in the

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office.

Let's look at three different patients, and I've put this data of these patients into the formula. Back pain, a little bit of depression, but also with sunlight. So if you look for PainDETECT, 10 is relatively low; attacks is low and HADS is low.

Then the formula will calculate a predicted possible response of 30 percent increase of quality of life after the treatment of tapentadol.

I think I can talk to my patients and say, "Well, you have these values at baseline; you can expect 30 percent change, increase in quality of life."

There's another one huge neuropathic element. Your burning is really high and so forth. So PainDETECT is high, 21, no attacks and HADS is 4. Then the prediction will say, "You can expect a 50 percent increase in your quality of life after the treatment."

But this is interesting, because it's not only prediction of response, it's also a prediction

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of non-response in this model. If you have a patient with huge depressive symptoms, so HADS is really high, and severe attacks, these really intense attacks, he comes into your office with a PainDETECT of 8, it's low, severe attacks, and high HADS level, then the prediction says, "You have a decrease in quality of life after the treatment of tapentadol" and this is due to the -- I think the side effects are more intense than the benefit in terms of reduction of pain.

The patient in these trials will rate this as a decrease in quality of life. I have these data available in my office. I think I could choose perhaps tapentadol in some of these patients, perhaps. This is from the precision medicine.

There are many limitations to this approach and we discussed this. Nat said it absolutely correctly. There's no placebo arm, so we can't separate general predictive responses, effects. So these are effects everybody has with every medication.

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It's independent of the specific medication with tapentadol and the specific predictive effects, which really relate to the tapentadol treatment.

But I think perhaps the PainDETECT might be -- is likely be specific, although I don't know this exactly. But I think these approaches, even in open label trials, have some learnings.

What we learned is that demographic baseline data are not relevant. I think this is what we can say, even if this is open. There is no association between demographic data and response.

Gender has a minor influence, only in functionality and the prediction of functionality. Male are a little bit better in terms of function afterwards.

This is, for me, the most important learning. The alternative outcome parameters, like quality of life, functionality, seem to capture this better than the conventionally pain intensity measures. I think we have to think about this a little bit more in detail.

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These are my conclusions. I think we are on a good way that the personalized treatment becomes reality. This is what I've shown you and this is my vision on how we can translate this into the practice.

I think in the future, every medication has a certain prior profile and then we can profile a patient with QST. And this is the medication profile, one for example, and then you have to look whether your QST key is fitting into this profile. And you'll see this is not really fitting.

Then you have another profile. This is another medication you have tested already. It doesn't work. And then you have the right profile. The key is fitting and this the right medication for the right patient.

These are, again, a little bit into the future, where, at the moment, prediction analysis are calculated, are performed, which substances, with QST data.

I've shown you oxcarbazepine and capsaicin, but there are many, many more, where now, QST is

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implemented in particular phase 2 trials and others, PainDETECT, as well, and the NPSI of DD, Neuropathic Pain Symptom Inventory, as well.

I think companies did learn a little bit and the best step forward.

Then I would like to thank everybody, so all the people, patients who are involved in the networks, the German network, the European IMI, and the Neuropain Network.

These are all the academic partners in these networks. Many are here in the room, as you can see. And, of course, all the lab members and patients.

Thank you very much for listening. Thank you.

(Applause.)

DR. MARKMAN: To wrap up this first session of the morning, I invite Dr. Freeman, professor of neurology at Harvard Medical School.

I think we're going to hear more about how to take some of this attempt to improve treatment matching and make it more pragmatic and more

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applicable to everyday practice with some of the techniques he's going to talk about right now.

Presentation – Roy Freeman

DR. FREEMAN: Thank you. Thank you, John.

I'm going to go from the laboratory to the bedside, and it's a long trip. You've heard, I think, what I'm going to say in the next couple of slides about the trip from mechanism-based treatment of pain to sensory profiling and back again, and you've heard this from a number of different perspectives.

Let me give you my perspective on this, and that is that doing a clinical trial with a new chemical entity or even an old one or seeing a patient in a clinic is like being an old-style matchmaker.

You need to match the patient with the drug and you'll either be a successful matchmaker or it will be a mismatch. It's a challenge. Ralf, I think, showed it very graphically with his finding the right key to fit the lock.

You want to match the patient with the drug,

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which is to say that you want to match the pain mechanism with the drug mechanism. But the challenge for the clinical arena is to know what the pain mechanism is.

The hypothesis that underlies the mechanism-based treatment of pain based on phenotype is that the phenotype is a surrogate for the pain mechanism.

We then want to go back and there are a series of assumptions inherent to this that you will match the phenotype with mechanism, mechanism with drug, and then patient with drug.

Now, this is the challenge and in order to accept the challenge, you really have to, as Coleridge said in the 19th century, "Every movie-goer knows and every theatre-goer knows you have to suspend disbelief," as to the, as they said, implausibility of the narrative, because it really is a fairly implausible narrative. And I think all of us who are either believers or agnostic waiting to be convinced need to, for the moment, suspend disbelief.

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Now, it's not as implausible as all that. Why that is the case and why one might be willing to suspend disbelief is, I think, embodied in this series of serial nerve biopsies shown in EM.

These are patients who all have diabetic peripheral neuropathy and just for purposes of illustration, I want you to imagine that each one of them has neuropathic pain. I actually don't know whether they have neuropathic pain, but they could easily have neuropathic pain.

There is absolutely no question, when you go from the normal patient, perhaps a patient with impaired glucose tolerance, to the mild peripheral neuropathy, to the moderate to the severe, in which it's hard to imagine that there's even a large or small nerve fiber there, it is easy to imagine that the generators of pain in these different patients are very, very different and that it seems much more likely -- and here, one invokes the transient etiological approach to the mechanism-based treatment of pain -- it's much easier to imagine that what is more important in

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the therapeutic intervention is the mechanism and not, as is currently viewed by at least the American regulatory authorities, the disease.

Now, this has lent some support, and I'm taking you back to an older paper from the Danish group, because I'm going to begin to introduce the notion of timelines, this has given some support-- and I am sorry for the shift of data -- by a comparison -- this is much worse than it was in my computer -- if you can sort of imagine the non-DPN moving above this column over here, I think it's kind of clear, and the DPN coming down over there and that moving across over there.

(Laughter.)

DR. FREEMAN: Well, the theme is suspension of disbelief.

(Laughter.)

DR. FREEMAN: Of course, this is accurate, isn't it? I don't know what Ralf said about the Danes and what he implied by it, but there's something there.

But to get back to this slide. There are,

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apart from the one asterisk, non-DPN and DPN patients, in terms of symptoms, have actually very similar profiles. And this is not quite as bad, the same thing with clinical science.

I won't go into the details, but this formed the basis for a discussion that I had with Pfizer over a decade ago. And here, I want to introduce the timeline. I actually gave this talk, I think, three years ago to an audience just like this. In fact, some of you may have been there.

I had some -- I call them historical slides, Washington-based historical slides which illustrated the timeline, and I'm going to use those slides again in this talk.

Now, at that time, Clifford convened his meeting shortly after coming to the U.S. and had published that article he showed yesterday. Clifford and Mitchell Max had written that piece in Anesthesiology. The German network was up and running. And I was agnostic about the notion of mechanism-based therapy based on phenotype. But I said to Pfizer that, "Look, if this really is going

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to work, if this is true, we cannot do this based on having every clinician spend two weeks in Mannheim with Rolf-Detlef Treede, be trained by a German technician in a white coat, get a certificate."

(Laughter.)

DR. FREEMAN: And I don't wish to denigrate what happens in Mannheim. This is the gold standard. This is the BMW 7 Series. But I thought we needed to do something, I don't know, a litter greener, a little ecologically-friendly, a little shorter.

I proposed -- I don't know, the Prius, the new Tesla -- something that was a little shorter than the two-hour and $25,000-piece of equipment that is necessary to do the full German battery, which I think all of us will regard as the gold standard.

This was at the time when Bill Clinton was president and Obama was a community organizer, so quite some time back. So it took a long time. Clifford gave some well-needed support and

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eventually mission was accomplished. And that actually took place round about there when George Bush president, and this is, I don't know, an iconographic slide of mission accomplished.

Pfizer agreed to incorporate a relatively simple, quantitative sensory test battery in a clinical trial. As it transpired, they actually did it and more. And they also thought that a symptom inventory was a good idea and they agreed to incorporate the NPSI.

As many of you are familiar with the NPSI, this is a self-administered questionnaire, 10 different descriptors and you know them well, superficial and deep spontaneous ongoing pain, burning, squeezing pressure, brief pain attacks, paroxysmal pain, evoked pain provoked by brushing, pressure, and contact with cold, abnormal sensation in painful areas. And there are, in the questionnaire, temporal items which were not included in any of the clinical trials.

The QST battery that I proposed was one which looked at sensory threshold using the graded

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Von Frey hairs. It looked at static allodynia, dynamic allodynia, punctate hyperalgesia, temporal summation to tactile stimuli, cold allodynia and cold hyperalgesia.

This has changed somewhat over time. It's not exactly what we do at the moment, but this is what was done in the trials that I'm going to talk about.

What I call the QST method was proposed and presumably implemented in these trials, as well, which is to say the testing needed to be performed in a quiet environment, patient lying quietly, testing performed on the area of maximal pain, supplied instruments needed to be used, the test needing to be performed in the same area, and the exact wording needed to be used and so on.

I also want to say that in contrast to the $25,000-piece of equipment that -- at least that's what they cost in the U.S. -- that the German network -- and that is used for all our laboratories for QST -- all of the equipment was bought at Home Depot, with the exception for the

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Von Frey hairs, which cost a little bit more. But the rest of the equipment is less than $10.

So the QST method, and this is really how we do the sensory threshold determination, using an up-down method with the Von Frey hairs. I'll show you graphically. You start with 4.31. After the patient perceives it, you go down. If the patient doesn't perceive it, you go up.

When you go down, more than one trial was required, three trials, and we did this three times initially just to be sure that this was done well, and that the aim of this was really to assess the state of afferentation, and, of course, this is a large fiber measure.

These were the instructions and the instructions -- and even though this is bedside and simple, the QST method was important and the paradigm was important and the instructions needed to be identical. No, it was not translated differently when this was done in the various CROs that did the trials.

We looked at static mechanical allodynia

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evoked by the base of a Von Frey hair, as you see over there, for the 10 seconds, and the tester read the identical instructions to the subject each time.

Same thing with dynamic mechanical allodynia. There are the instructions. I won't go through the instructions in detail. And identical reading of the instructions.

I show this just because I want to make the point that there is not punctate hyperalgesia, that even though this is a $10-equipment and there is no training by Rolf Detlef, that we tried to make this rigid and identical across sites. I say tried, because this was at clinical trial.

Same instructions, temporal summation. This is the largest Von Frey hair, the 6.65. See the timer, approximately 2 hertz, same instructions and cold allodynia.

The rod is placed is cold water, cooled in ice. So using equipment available in any clinic and any lab, make sure that it's for 4 degrees Centigrade and applied.

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The biggest debate with these videos was whether we should use one of the male feet or a pedicured female foot, and the male one, as you see.

We are now at this point. Obama is debating John McCain. And I, to be honest, had forgotten all about this. I spent a lot of effort persuading Pfizer to do it. You know how long these clinical trials take. They did what they did and I was doing other things.

I was at one of Bob Dworkin's meetings, at the time when they used to have these things in Bermuda, and David Simpson comes up to me and he says to me, "Do you remember that cumbersome QST thing that you made us do in the HIV trial" -- David Simpson was the PI on the HIV pregabalin trial -- "what ever happened to that?"

I gave that gesture and we went to the people involved at Pfizer and said, "What ever happened to it," and as you may know, that was a negative trial, that pregabalin for HIV neuropathy was negative. But when -- and there was no pre-

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specified hypothesis at all, but when the data were examined -- and I'll underline it over here -- the treatment effects differed greatly in subjects with a greater sensitivity to pinprick at baseline, so the punctate hyperalgesia score.

Maybe I didn't explain. Other than with the sensory threshold testing, we do not test threshold, but we ask patients or subjects to rate the pain to the punctate hyperalgesia. So all of the evoked pain assessments are not done looking at a threshold, but are measuring an evoked pain.

So those that rated punctate hyperalgesia, and you saw how it was done, greater than 10, and this was a negative study, 2.14 greater improvement in pregabalin compared to placebo.

Now, Pfizer wishes that they said, "Okay, we, just as the EMA, may be moving in that direction," with their phase 2 and hopefully phase 4. Of course, it was a negative trial, but the punctate hyperalgesia group were dramatically different.

Where are we? Now, Obama is president and

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Bill Clinton looks like that. So there has been a change. And we have the results of what I'm calling the primary analysis trial.

What Pfizer did -- and they actually did this in four trials. Some of them were not as intensely trained. The first one or two, I was actually involved and people from my team came and trained the investigators really well.

One or two of them were not as well trained as I would've hoped, but Pfizer had the video and trained the investigators. The results of this actually have been reported in Pain. I'm not going to take you through the details of this, but this is the first paper which looks at the sensory profiles or the phenotype.

Here, you see the results of the clinical QST across all of the various measures, static mechanical allodynia, dynamic mechanical allodynia, cold allodynia. I can take you through all of them.

But there is a bottom line over here and that bottom line is actually very, very similar to

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the point Andrew made, and that is that, first of all, there are more similarities than differences; and, second of all, that the prevalence, the frequency of evoked pain in DPN and HIV peripheral neuropathy is actually rather low compared to the other groups.

What I would ask you to do is to focus on the severe, which is in blue. So if you look at the key to this, it's saying that a mild response to the stimulus, which is 0-3, is in red; a moderate response is 4-6, is in green; and, a severe response, 7-10, is in blue.

So there are subtle differences, but the message is that overall, in these three disorders, central post-stroke pain, HIV peripheral neuropathy, and diabetic peripheral neuropathy, there are many more similarities than differences.

In the same way, looking at the NPSI -- now, the NPSI was used in four of the trials, whereas only three QST were used -- you see very much the same, with the exception of -- here, I want to take you to the bottom row. Remember, the same key and

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as you see, there is somewhat more burning pain, electric shock, stabbing pain, pins and needles, and tingling in the peripheral groups, HIV and DPN, and less so in the post-traumatic pain. And this is the NPSI. But again, overall message, more similarities than differences.

What was really interesting, and I want you to focus purely on this rather complex figure, on the top panel, in which the QST is actually compared to the -- and it is a little hard to see, I know -- the QST is actually compared to the NPSI, what is really interesting is if you look at the somewhat darker blue -- and again, we're looking in the A, the top left panel -- what you'll see is that pain provoked by cold actually correlates reasonably well -- to me, the fact that there's any correlation is surprising -- reasonably well with the cold hyperalgesia and cold allodynia test and that the static allodynia, dynamic allodynia correlate reasonably well with pain evoked by pressure and with pressure pain and squeezing pain.

To me, this is, to some extent, internal

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validation of both techniques in that both the questionnaire and an evoked pain measure show acceptable correlations.

Well, what about pain phenotype as a response predictor? Pfizer actually did a fourth study or a fifth study, depending on whether you are counting the post-traumatic neuropathy study in which only the NPSI was done.

We now have data with what I call the primary analysis, which was the thesis, and then the confirmatory analysis study. These are the results of a multivariate analysis.

With respect to NPSI, moderate-to-severe pain provoked by cold, moderate pain provoked by pressure, and mild pain provoked by brushing, was associated with a significantly better response to pregabalin than placebo in both primary and confirmatory analyses.

Now, of these primary analysis studies, only the post-traumatic pain study was positive. All the other three were negative. If you look at the difference between the effects of pregabalin

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placebo, the mean value was 0.77. In the confirmatory analysis, the difference between the effects of pregabalin placebo, that was the spinal cord injury study, which was a positive study, the mean value was 1.40.

So some support to the notion that sensory profiling using a questionnaire can predict treatment response and, in particular, in a negative study.

What about the bedside QST? Here, we show severe punctate hyperalgesia, moderate-to-severe cold hyperalgesia, and moderate-to-severe temporal summation to tactile stimuli were associated with a better response to pregabalin in both the primary and confirmatory analysis.

It's important to note that the degree of afferentation or deafferentation made no difference at all. It was not a predictor.

The primary analysis showed a difference between the effect of pregabalin placebo using those criteria was 1.34. The mean difference, statistically significant, the confirmatory

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analysis 1.88.

Now, for negative studies, these are reasonable values and one -- again, these were not pre-specified hypotheses, but certainly formed the grounds for a pre-specified hypothesis.

This is what the punctate hyperalgesia looks like. As Ralf implied, the DPN, bottom right; HIV, bottom left; central post-stroke pain, top; and, all of them grouped together, there really does seem to be a difference between those patients that had a peripheral cause of pain and the central cause of pain.

Here's the temporal summation, not quite as dramatic, but still the same and still a difference between central and peripheral.

I want to just look at selected other studies. Now, I'm not going to refer to it -- it's been referred to several times -- the two Danish studies looking at sodium channel antagonists.

I'm going to look at the study by Jim Campbell using the alpha-2 agonist clonidine topically. This was a randomized, double-blind,

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placebo-controlled trial. They received 0.1 percent clonidine gel. The study was borderline negative.

But he -- by he, Jim Campbell -- and his group decided to look at nociceptor function by looking at the degree of pain evoked by 0.1 percent topical capsaicin applied in a 1-centimeter area on the anterior tibia.

Subjects who experienced any degree of pain to capsaicin or clonidine were superior to placebo and this showed more and more an effect the more pain subjects perceived. And it was only related to the capsaicin test. No other measure of sensory function showed this difference.

Here, you see the ITT, top left; the capsaicin, no response, to the right; capsaicin response greater than zero; separation, greater than 1; separation. And as you go from 2, to 3, to 4, to 5, the separation increases, so lending some support to the notion that some kind of sensory profiling could make a difference in the assessment of a response in a clinical trial.

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Here, you'll see the relationship between the capsaicin response, going from 0-7 on the X-axis, and the intraepidermal nerve fiber density, shown on the Y-axis. And the more intraepidermal nerve fibers, the greater the capsaicin response, so providing some structural support to the physiological test.

I now want to talk about this trial or this meta-analysis, a retrospective analysis, which comes from the Danish group. I see Ralf and Troels having a sidebar and I think it's important and I'd love to hear what the two of them say to one another, because this was a retrospective analysis. And the conclusion of the retrospective analysis was the following.

This post-hoc analysis of 8 drugs with mainly non-selective action on neuropathic pain mechanism, arguably, found limited usefulness of sensory phenotyping in pain as the basis for individualized treatment. And that was the conclusion of the paper.

I've left this area blank because I think

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that area is the [indiscernible] en bloc. You can see a glass over there which can either be half full or half empty or one of those figures, the old lady, the young girl.

Depending on how you look at this, the data can be interpreted differently. Here are the data taken from the trial and I'm going to focus just on one of these forest plots, one confidence interval and that is the -- this doesn't seem to be working anymore -- this is the one over here which looks at gain.

Sure, the confidence interval is rather large but -- and we are looking at pregabalin. As Rolf and Tony Dickinson said in their editorial, that the sample size was rather small, but gain does seem to be a factor.

I want to make a point over here. If we think back to the talk maybe given by many people, Clifford, Nat Katz, where they spoke about the many factors that go into a single individual's response to a drug, we are talking about age, we're talking about gender, we are talking about PK, we're

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talking about genetic factors, the sensory profile is just one of those factors.

When we are seeing a patient in the clinic or doing a clinical trial, you just want to give your therapeutic intervention an edge. You want to improve the likelihood that your intervention is going to be effective.

It seems to me that my interpretation -- and I'm not particularly a glass-half-full kind of person -- my interpretation of this is that the presence of hyperalgesia, of gain of function, call it what you will, gives you an edge and this, of course, is consistent with what we saw, without being specific, in those pregabalin clinical trials.

When I gave this talk three years ago, it was, I proposed a road map. That road map still exists and I said that we need a dynamic approach to sensory profile using QST.

This should be in specialized clinical centers, where I think we need to be dynamic in how we use these tests. We need to have international

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within-nation approaches to QST, laboratory-based QST and we need to begin to do the same in the community.

I also said that there should be obligatory phenotyping for all phase 2 and phase 3 studies. I think, then and now, I think one should still be critical or agnostic as to how valuable this will ultimately be. But I certainly -- and I was agnostic at the start -- am leaning in the direction that this gives an edge. This does impart some value. I thought it was an important opportunity for academia, industry interaction.

I thought this is the way, whether it'd be open label or double-blind, randomized, placebo-controlled, a way for pooling data across studies, because what we looked at was purely pregabalin. And I think we need to do the same thing with other drugs with different purport of mechanism of action.

I said then -- and remember this was three years ago -- that I hope this would be accomplished. This was three years ago. Before

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the circus that was the Republican nomination of 16 candidates and before we had any idea who was going to be the Democratic candidate, I said I hope this would be accomplished before our next president looks like this.

(Laughter.)

DR. FREEMAN: Well, times have changed and so I do need to say "or."

(Laughter.)

DR. FREEMAN: Thank you for listening.

(Applause.)

DR. MARKMAN: I want to take two questions and then we'll take break for about 45 minutes.

DR. COLOCCA: Yes, I have a question. Luana Colloca. Why Baron and Roy didn't talk about the bedside kit? I mean, it seems like they already had one very cheap, Home Depot. I wonder why, when the European Agency asked about money and the time, you didn't suggest, well, there already one in the literature or --

(Laughter.)

DR. FREEMAN: We can talk offline about

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this.
(Laughter.)
DR. BARON: Our approach is if it comes to bedside, that we would like to mimic our QST protocol as closely as possible. And if you look at your protocol, I think it's marvelous, and it's doable, and we see signals. I'm involved in this, as well. But there are some missing spots so you do not look for heat, I thought you said, at all.
DR. FREEMAN: We do now, but we didn't then.
DR. BARON: You didn't back then. And several other things. And, therefore, I think we need to do it a little bit more extensively than this which was proposed at this point of time and, again, to do it as closely as possible to QST.
DR. DWORKIN: I have a really related question. If our objective here is to make recommendations for accelerating the development of precision pain medicine -- and I'm going to be provocative -- shouldn't one of those recommendations be that Roy, and Ralf, and Nat, who also has a BSTK, that stands for bedside testing

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kit, all come together and develop one bedside approach, because having three different bedside QSTs available is going to do the opposite of accelerating?
That's going to impede the development of precision pain medicine, because if I'm a drug company or an academic investigator, I don't have a clue whether I should use Nat's approach, or Roy's approach, or Ralf's approach.
So just to be provocative, I would suggest that our article might have a recommendation that the three of you have to come to consensus.
DR. FREEMAN: I think it's not an unreasonable point.
DR. BARON: Perhaps one thing about this, we had the same issue with the questionnaires. Do you remember this? There was the LANSS question of PainDETECT DN4. And I was proposing a meeting where we met all together, with my aim, my vision to have one questionnaire with the best items. But due to many, many points, in particular, the many characters on board --

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(Laughter.)
DR. BARON: -- it was impossible with the questionnaires. But with the three of us, I think we could succeed.
DR. DWORKIN: We will make a commitment that if you guys guarantee us that you'll come to consensus and at the end of the day, there will be one bedside QST, we'll allow you -- well, we will fund you to have this meeting in Bermuda.
(Laughter.)
DR. DWORKIN: One way or the other, we will pay for the Bermuda subgroup --
(Crosstalk.)
(Laughter.)
DR. DWORKIN: But only if there's consensus at the end of the meeting.
MALE SPEAKER: Not just consensus. Bob, not just consensus. If you're going to make that effort to do this, then you really have an obligation to do it according to the guidance of the FDA for a drug development tool and validate both the questionnaire in the context of, in fact,

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the DDT requirements and this bedside testing.
If we're going to make all this effort, bring all these people together and get consensus, then it needs to be qualified. And that way, the companies will use it and, in fact, we might learn something.
If we don't do that, then the companies will continue to have -- well, maybe we'll use it, maybe we won't use it. But, in fact, this would be a real product that could really drive the development of this kind of effort to phenotype.
DR. FREEMAN: These are all points. I just want to make sure I understand Bob. Do we go to Bermuda in order to seek consensus or do we need to have consensus first?
(Laughter.)
DR. MARKMAN: We're about to take a break. Let's have Ian take the last word and then we'll stop there.
DR. GILRON: In the spirit of precision, Veeru raised a point that I think we need to emphasize in the recommendations, which is for any

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phenotyping, the distinction between state and trait.

A question for all of the speakers today and Troels, as well. As far as I could tell, I think that some of the patients that have had phenotyping done with respect to sensory testing may have been on neuropathic pain treatments.

Do we know whether QST parameters change on or off these different treatments and whether it's necessary, first, to answer that question? And secondly, do we have to have people off treatment when the phenotyping is done?

DR. FREEMAN: Yes. It's a very important point. It's a point that we've discussed several times with respect to the German network data, which I understand is acquired while patients are on treatment. They are not taken off treatment. Rob, correct me if I'm wrong about that.

I want to say one more point, and that is -- and this refers purely to pregabalin. I did not show you, but this was done at the beginning and at the end of the clinical trials, and the

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measures did not change.

The aim was to see whether, of course, pregabalin made a difference to these evoked pain measures. They did not.

DR. GILRON: At the end on treatment or the end off treatment?

DR. FREEMAN: Sorry. At the end of treatment. So the last visit, it was.

DR. GILRON: They were still on pregabalin?

DR. FREEMAN: They were still on pregabalin, yes.

DR. MARKMAN: Well, I'd like to thank Dr. Freeman, Dr. Baron, Dr. Katz.

(Applause.)

(Whereupon, at 10:22 a.m., a recess was taken.)

DR. MARKMAN: Our next speaker needs no introduction, so this is very easy. If everybody would join us to hear Dr. Turk, who will be speaking about Non-Pharmacologic Treatments in Precision Pain Medicine: The Rationale for Lumping Versus Splitting.

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Presentation – Dennis Turk

DR. TURK: Thank you. In listening to the presentations the last day and a half, when I first got interested in the area of pain, I got frustrated, because we were so dependent upon what patients tell us and their way of interpreting whatever treatments we're offering them.

I tried to get over that by switching into another area, I worked in diabetes for a while, and then I found out it wasn't any different. So we're in the same situation.

As I heard the presentations here, though, yesterday, I heard a lot about ion channels and different chemical agents and I started thinking about, well, there's another part of this. There are subjects, people.

Then I heard Nat this morning say he's not going to talk about that stuff, people thinking, oh, my God. I don't want to think about it.

But then I heard Andrew Rice yesterday talking about how the mice and the rats use their environments and respond in different ways when

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they're afraid of something.

So maybe we can't get away from the fact that our subjects do think, they're conscious, and maybe the problems that we keep running into is we keep looking for the very narrow, subtype people or animals on the basis of the physiology, or the neurophysiology, or the sensory processing.

Maybe that's an important part, but maybe it's not all. So I'm going to try something maybe a little different for some of you to help you think some of these things.

There's how birds see the world, and they see things differently than we do. There are two kinds of people in the world, those who think there are two kinds of people and those who don't.

(Laughter.)

DR. TURK: The first group we can call the splitters and the second group the lumpers. In listening to -- and the title of this presentation, the title of the whole meeting is really -- I think we all have a similar perspective on splitting may be important. We may want to be splitting in

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different ways. Now, you could decide whether the splitter is the bird or the target, that's up to you. But I think this is important because that's the whole purpose of what this meeting is.

There are a lot of different ways we might go about splitting or stratifying patients, and we've heard about a number of different ones, some of which we're going to pay attention to, some we'll not. We spend a lot of time on biomedical factors, most of the time on mechanisms. There's also symptom presentations.

We heard a little bit about that, that it actually could alter people possibly into subgroups based on their symptom presentations. It's possible we could also look at the etiology, whether it's the actual etiology or the perceived etiology that might explain it. There may be psychological factors that contribute.

We could possibly could end up finding ways to phenotype, stratify, psycho-type patients and it may be important to know something about those and that may explain why we see some of the results we

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do.

We could also look at response to treatments and are there differences in how people, how animals respond to treatments, and that goes to the subtype, and we've heard a lot about that in a lot of these discussions.

I'm going to focus on the bottom three of these, because we've heard a lot about the other ones. Mostly, I'm going to focus on these in a sequence, and, hopefully, these are related sequence.

We could think about it, as I said, as stratifying, subtyping, phenotyping people on the basis of the nature of their symptom, on the basis of the etiology.

The reason I said actual or perceived is because it may be that the perception of those subjects of how their symptoms began or what their symptoms are like make a difference. And whether it's the actual cause of their symptoms, it's a trauma of some kind, it was a disease of some kind is only part of the action.

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So just to show you some slides as I go along to illustrate some of these points. This was a study that we were involved with that looked at 569 patients who had fibromyalgia.

We asked them -- and a bunch of other things -- but one of the things we asked them was the perception of how their symptoms began, was there a trauma of some type, was it an accident, did something happen to you, was it an illness, was it just, who knows, I woke up one morning and had the flu and it just got progressively worse.

You can see that the percentages of patients who could be split here and those who thought there was a precipitating event, that was about 36 percent of the sample, and 39 percent who said there was no cause, they don't know, it just seemed to come on, it got worse over time, and eventually they had all these other things going on, and then about 21 percent said it was something else. So it wasn't our two. But if we just seem to split patients on the basis of their perception of their symptoms, does that make any difference and that

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will help us understand something about them? And can we be thinking about precision health care, precision medicine, not only on the basis of some of the things we saw for the last day and a fraction, but also for some of these other factors?

So we split those people in a study into those who said there was a traumatic onset and those who said it was idiopathic onset, or it's something else.

You can see that there's no difference on age, sex, high school education, marital status, duration of their symptoms. They didn't differ on those factors. So we were interested in what does differentiate these people.

Based on biomedical findings -- and we had a whole range of different tests, which I'm not going to go into -- we found that there's really nothing that we can find different between those who said their symptoms began following a trauma and those who didn't.

There was nothing different on the pain severity, nothing different on how much they said

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the pain interfered with their life, nothing different in the level of affective distress. So what's different about these people?

Well, we also want to look at these people. What about physical function? Maybe there's something different in their actual physical function.

I'm only going to show you one of many physical tests that we performed and these are by physical therapies and functional capacity exams. They found that they can find nothing different in these groups whether they had traumatic onset or not a traumatic onset based on physical function that they could do in these tests, not significant.

Then we say what about perception of disability. How did these people think about their circumstances and what happens to them? Does that differentiate among those who had a traumatic onset and those who didn't?

What we found that is, yes, in fact, if the patients said that they believe their symptoms began following a trauma, even though we have no

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evidence that there's anything different, they were significantly different in how they perceived their disability. We also looked at their quality of life and other things.

Those were things that they consistently seem to differ on. So it wasn't anything on demographics. It wasn't anything on physical factors that we could find. It doesn't mean that we couldn't have looked at other things, but at least we couldn't find anything.

Interestingly, we also looked at how were these patients treated by those who are clinicians in the room. If the patient comes to you with fibromyalgia, or to a practicing physician, and he or she says that they're diagnosed with fibromyalgia, what kind of treatment would they receive?

We found out that if the patients said they had a traumatic onset, there's no objective evidence they truly had, that this is the patients saying it, they are more likely to get nerve blocks, physical therapy, TENS or opioids. This is

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if the patient said it, not because they were different than anything.

What is the physician making the decision on why he or she is providing these different treatments? They're also interacting and responding to the patient.

Therefore, there's a whole social interaction that's going on that's also important when we think about this.

Let's switch gears to another sample, and I'll be looking at different kinds of populations.

This is a study that looked at people with whiplash-associated disorders. We had 108 patients. We're interested in seeing can we find differences among these groups that might be meaningful to understand how well people are responding to different treatments, how they're adapting to their condition, who goes on to develop these chronic conditions, looked at cervical range of motion, neck strain, shoulder range of motion, shoulder strength, elbow flexion-extension, grip strength, pinch strength, plain x-rays.

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We have neuropsychological tests that we did. Is there anything that's unusual about people who have mild symptoms following a motor vehicle collision and those who had more severe symptoms?

We have split the group based on the severity of their symptoms. What we found is there's nothing different among these people on the severity of their symptoms in any of the measures that we had.

Now, these are gross physical examination measures and neuropsychological tests, but we couldn't find anything different among these people.

So what might differ? Well, we were interested in patients', again, perceptions, expectations and how does that influence the perception of their symptoms.

I have to show you a measure we developed so you'll understand this. We had something called the Pictorial Fear of Activity Scale for the cervical region. There are 78 photographs of movements and five controls. They manipulate or we

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manipulated arm position, manipulated whether they were lifting something or not lifting something. We looked at the extent of the motion that they were engaging in. Was it extension, was it flexion, lateral bending or rotation?

We looked at the degree of exertions. So was it an extreme change or was it a minor movement about these individuals? We then showed these people photographs to ask them how much these activities would bother them, that would be distressing to them and cause their symptoms to get worse.

So just an example, this is a sample of one of the pictures, which is arms on the side, unloaded, left rotation, extreme. That's just showing you what we're manipulating.

I'll just show you another one. I won't read them off to you, just so you could get a sense of what we're asking the patient to do. So they're looking at this set of pictures and they're responding to how concerned, worried, fearful that they would be of doing this because it might even

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make them have more damage, more injury, or might make their symptoms worse.

We started saying what predicts pain intensity, what predicts the number of symptoms, what predicts the Neck Disability Index, which is a scale that's used in whiplash in the neck and shoulder area for disability.

What you can see is that age didn't matter, range of motion didn't matter, whether it was pain for severity it didn't predict, for number of symptoms for disability, but what it did predict was TSK, which is the Fear of Movement scale, and the Pictorial Fear of Activity.

Their concern and their worry about movement was what predicted the severity of the perceived reporting of their symptoms. Not a big surprise to you.

This is the same thing that occurred for each one of these measures. So that the subject, patient, is interpreting their own symptoms and responding to those symptoms, even though, on objective measures, we can find nothing different

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among these individuals.

We could also think about looking at maybe there's some psychological characteristics that are different. And Nat listed some of those quickly in his slide. Maybe we can look at some of these.

Bob Kerns is in the room, so I have to pull out an old measure he developed called the Multidimensional Pain Inventory, which, if you're familiar with it, has three different parts.

It asks about pain severity, interference, life control, affective distress, support from significant people, and the environment, how do other people respond to you when you experience pain, and what do you actually do with your actual activities.

So there's a 52-item, one version. There's a 60-item version of this questionnaire. So the question is, do these people respond differently. Can we subtype, psycho type, however we want to say it, for these individuals, stratify them in some way on how they respond to this type of questionnaire?

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What we looked at was one group of these individuals using cluster analysis. You've heard a bunch of things about one group identified. These all started out as people getting referred to a tertiary care pain facility.

So these are not your mild problems you see in primary care. We found that one subset of these patients reported high pain, high levels of emotional distress, low sense of control, and little activity.

When I looked at Ralf Baron, when he showed some of the patterns that he had, gee, a lot of pain, a lot of emotional distress, it sort of looked like this was important in the subtypes that he was looking at, as well.

Another group we referred to as interpersonally distressed, despite having pain severe enough to be referred to a pain clinic, what was most characteristic was they said they had low support from significant people in their environment.

People around them were very negative toward

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them, they didn't try to help them, they didn't try to distract them, and they never did things to help them out.

We use the term interpersonally distressed. So although they had pain, what was most characteristic was that they were interpersonally distressed.

The third group of people -- remember, these are all people coming to a pain clinic. So they had to have sufficient level of pain. Relative to the other groups, they were doing pretty well.

They were very low emotionally distressed. They felt some control, and they tended to be somewhat more active than the other populations. So these were three subgroups we identified in this initial early study.

That has been replicated, those three subgroups, across patients with chronic low back pain, with headaches, temporomandibular disorders, lupus, metastatic cancer, local cancer, and fibromyalgia. We see the same three patterns of adapting to having their symptoms.

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Now, interestingly, if you look at these, if you look across these, for the dysfunctional patients, the percentage of patients is different in these different groups.

For example, the back pain patients had a much higher percentage of people who are, quote, "dysfunctional," high pain, high distress, low activity levels.

For the lupus patients, that was a relatively small number. If we look at the metastatic cancer patients, interpersonally distressed group, they're pretty well, a pretty small group of these people.

If you have metastatic cancer, people tend to be supportive of you. However, if you happen to have fibromyalgia, these patients are saying, "We don't get attention, don't get support. People don't help us. We have interpersonal problems."

For the adaptive copers, it's quite variable, very few -- relatively small percentage in the low back pain samples and a much higher proportion in the lupus samples. By the way, the

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sample size is that these run anywhere from 300 to 400, 500. So these are pretty decent sample sizes.

Now, maybe what's different among these three groups is there's really something physically different about them. The people who are dysfunctional have a lot more physical findings that contribute to their particular problem. Maybe that's what's really important here.

So here, we are looking at a sample of people with temporomandibular disorders. We've used this MPI clustering procedure for that. We looked at pain duration, looked at symptoms based on examinations, muscle palpations our dentists have performed.

We have looked at intercisal opening, how much they can open their mouth, which is a characteristic of temporomandibular disorders, it's restricted. We looked at abnormal CT scans. We had CT scans in all these patients.

Interestingly, if you look at that, the dysfunctional, the interpersonally distressed, and the adaptive copers, there's no difference in any

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of those findings.

The findings that one might think would be related to having TMD, these groups don't differ, but yet they do differ on the things that I showed you earlier.

We also had another sample of patients that we've looked at who had -- this is chronic back pain patients -- no, this is a heterogeneous chronic pain sample.

And we looked at these three different groups, dysfunctional, interpersonally distressed, and adaptive copers. They don't differ on lumbar flexion, they don't differ on fingertips to floor, straight leg raising, cervical range of motion.

So there's something here that's potentially important for us to understand, in addition to whatever we know about them physically. And it may be that when we start thinking about phenotyping and genotyping, we may be thinking about psychotyping, if you will, and then maybe some combination of these factors are going to become important to us.

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This is a study that Kati Thieme did, who's from Germany. She looked at those same subgroups of patients that she identified, and this was –- I think this is fibromyalgia patients -- on fibromyalgia patients. And she said, "Okay, let me see on the MPI what subgroups do we find."

She finds dysfunctional, interpersonally distressed, and adaptive copers. Then she looked at measures of anxiety, depression, and without any kind of emotional disorder.

Each of these three different subgroups showed three different patterns of psychological distress; in particular, depression and anxiety.

You can also think about response to treatment and Nat, I think, gave us some ideas about thinking about response to treatment.

Well, this is my collection. As of 2004, I stopped, because I ran out of room on my slides. These are pharmacological treatments that are in the literature that have some beneficial effect and some symptoms for some patients with fibromyalgia. A lot of stuff.

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As a matter of fact, that's 57 different pharmacological treatments. But I'm going to prescribe something that works better than aspirin, but it costs a lot more.

We have a lot of new drugs and maybe we're getting better with the newer drugs. This was a study that was looking at a whole range of different treatments for fibromyalgia, duloxetine, milnacipran, pregabalin, and the others which I can't quite read from where I'm standing.

But the ones that are at the top are the ones that are approved by the FDA for the treatment of fibromyalgia. If you look at that, the beneficial effects that the patients are reporting with that is 50 percent pain reduction. It's not particularly great, even though we have three FDA-approved drugs for fibromyalgia.

All you know is because we've been hearing about this for every other kind of treatment out there, the range of beneficial effects we're seeing for the patients is 30, 40 percent, and those 50 percent, but rarely do we see it that high.

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Substantial numbers of patients are not getting better.

Is it because we just need to find subtypes of physical factors that might explain this or might it be the case that we should be thinking about other ways of subgrouping patients?

This is a paper that Henry McQuay reported. He looked at very interesting reductions in pain from duloxetine. He looked at the placebo response, and he looked at the drug response.

This is for fibromyalgia patients and what you see is almost a bimodal distribution both for the placebo and for the active treatment. He also did that for OA and for chronic low back pain and for DPN.

So we're seeing differential responses and now maybe there are subtypes of patients who will respond differently, as we heard about, based on the physical factors that we've been seeing.

But there are also a whole bunch of psychological -- or non-pharmacological, I should say, because there's a lot of non-pharmacological

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treatments. This was my list as of 2004. I ran out of room on the sides.

There's published studies as of 2004 that every one of these different treatments has had some beneficial effects for patients of fibromyalgia. By the way, they happen to be 57 of those, nice balance there. That's 114 treatments for fibromyalgia, all of which have some beneficial effects.

I really was kind of curious about what the physical mechanism are going to be to explain all those different -- and the treatments are extremely wide range, from ECT, electroconvulsive shock therapy, to hot baths, pretty extreme difference.

Now, the hot baths tend to be in Germany. My understanding is that in Germany, if you have fibromyalgia, you get several weeks in a spa and it tends to have very beneficial effects. If anybody want wants weeks in a spa, just go to Germany and say you have fibromyalgia.

(Laughter.)

DR. TURK: There are a lot of psychological

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treatments. There are other kinds of treatments out there that had some effects. But notice that the effects are still fairly modest that we're seeing. We're not seeing huge benefits to these different kinds of treatments.

Let me show you a treatment protocol that we did. It starts explaining some of the possibilities. It's because what we're doing is these are giving generic treatments to everybody. Every patient who comes in with that diagnosis, we lump them.

They have fibromyalgia, they have back pain, they have TMD, they have IBS, whatever that happens to be, we lump them together and we give them the same treatment.

Obviously, this meeting wouldn't have to go on very long, because all of you are the believers that that's the wrong way to go about it. So this was a study that was a rehabilitation-oriented study. You don't need to know the details but it was -- just in general, it was a six-week, three-hour sessions once a week.

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They had attention from a physician who talked to them about their condition, gave them reassurance about they weren't going to have a condition that was going to be terminal, and that they really needed to start taking control of their lives and get going.

They had physical therapy, aerobics, and stretching exercises. This is a heterogeneous group of patients. Occupational therapy, focus on pacing and body mechanics, and the psychologists focus on pain and stress management.

So that's what the treatment was and you don't need to know the details, but I want to show you this. What happens if we go back to those three subtypes of patients?

So we have dysfunctional, interpersonally distressed, and adaptive copers along the bottom. So at the bottom, this is where the patients started prior to treatment. Those are the patients in each one of those groups. Now, at the end of the treatment, what happens to these groups?

Do they switch? Well, we found out that

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62 percent of the patients who were dysfunctional turned out to look like adaptive copers by the end of the treatment. You can look at the other percentages.

If we look at the interpersonally distressed patients, they didn't do nearly as well. Now, remember there was nothing in this treatment that dealt with interpersonal problems, or family issues, or how you interact with people at all and that treatment didn't have nearly the same beneficial effect.

The adaptive copers didn't need the treatment. They were already doing pretty well already. We are wasting our time and their money and their time in putting them in this treatment.

But everybody got the same treatment, because they were sent to the rehabilitation program. So maybe that's not the way we should be going.

This is looking at another study that Kati Thieme did in which she looked at differential responses of patients. What kind of patients were

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these? I think they were fibromyalgia -- to an operant conditioning type of treatment, very behaviorally-oriented, reinforced the appropriate behaviors, ignored the pain behaviors, a cognitive behavior therapy type of intervention which focused more on thinking and an attention control, a relatively small study.

What she wanted to look at is what did the responders look like. So if some patients responded to all of these three treatments, are there any characteristics of who the responders were?

So she looked at the baseline characteristics and she found out that if the patients reported having higher physical impairment at baseline, greater pain, more pain behaviors, more negative responses from significant others, they were low physical functionally, they had more physician visits, and high catastrophizing, they did much better with the operant treatment that the other two treatments.

If, in fact, they happened to have high

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levels of affective distress, low solicitous behavior, low pain behaviors, and inadequate or poor coping on the scales that she was using, they did better with the cognitive behavior therapy. The same patients all going to the clinic for fibromyalgia, but they're responding differently to these treatments.

Interestingly, the attention control group, if they have a lot of negative support, they did well in a group treatment. They got to spend time talking to and being with other people who had the same kind of problem.

So even the people who got what she thought was her placebo treatment, there were some who got a beneficial effect, a relatively small number of people, but that's where the benefits were.

Let's think about what I very quickly went through. Obviously, all of you know there are predisposing and protective factors. We talk about genetics. You talk all the time about genetics, prior stresses, prior learning history.

We also could talk about precipitating

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factors. Is there a physical trauma, is there disease, is there an illness, is there some sort of emotional trauma, as I tried to show you with the patients in some of the studies we had.

You can look at perpetuating or protective and alleviating factors. It could be the symptoms, could be attitudes, beliefs, meaning, coping responses, social support, financial resources, behavioral responses, consequences.

Maybe one of the problems is that we tend to think of people at the time they come in for treatment. So it's so sort of a cross-sectional perspective.

So what we did was we were interested with looking at what happens over time with patients. This is extracting literature from some other areas. The age of onset -- this was a meta-analysis we did a number of years ago. [Indiscernible] was the lead author on this, in which there were no -- patients who go to pain clinics, what was the average age when they say their pain began.

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Interestingly or not so interestingly, it was when they were age 37. By the time they got to the pain clinic, that means they've had 37 years of history to be the kind of person they are.

But prior learning history, their genetic factors all preceded what happens to them at the time they say their pain began. We then say when do they actually get to the pain clinic.

The mean age of patients being treated in these 54 different pain clinics that they looked at was 44 which means that the patients have had had their pain seven years before they got to the pain clinic.

So what's happened in those seven years to these people? That's the current age of change or their changes in pathology. What's happened in that time frame? And they're going to live for 30 more years. To my knowledge, at least, since I've had black hair when we're looking for cures for people with chronic pain, those same patients who I saw 30 years ago are still waiting for the cure for their pain.

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I have a hunch -- I don't want to say this too loud, because you'll stone me, but if I come back in 30 years, I think we're still going to be looking for the cure for pain. We're going to find better treatments. We're going to find ways that we reduce the symptoms. But I'm not confident we're going to have a cure, at least definitely not in my lifetime. I'm planning on living 30 years, in case you were wondering.

Maybe we should also look at what's happening to them over those 30 years, because now their pain is maybe reduced, hopefully, but they're still not cured. So things have changed.

These people have a whole range of resources available to them. I mean, there's support, economic factors, the environment, the culture, all these things are going on around them.

Interestingly, we tend to forget that these people don't live in isolation. They live in social context, people around them. So if you take this perspective instead of just looking at the patient at age 44 when they come in the door and

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you're trying to figure out what's our best treatment going to be for them, you need to start thinking about what happened to these people before, both from their genetic composition, both from their learning history, in that seven years from the pain onset, what happened to these particular patients. What's happened to their family situations? What's happened to them along the way?

I need to always say this when I mention the word "psychological," because my non-psychological colleagues almost inevitably say, "Oh, you're saying their pain was caused by psychological problems." That's not true.

What I'm saying is that when you have a persistent symptom that continues over long periods of time, it starts affecting a lot of different domains of your life. So whatever the initial cause may have been, you now have a patient, and his significant others around him -- as I showed you on that NPI, there was one group that was interpersonally distressed, those significant

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others are, in fact, important, as well.

So as you're thinking about your patient, or your ion channel, or your particular sensory profiling, understand that you're looking at a point in time and there's a lot of history that may be important for you to understand and think about.

So maybe the question remains to resolve, can we improve clinical outcomes by matching treatments to patient characteristics or personalized health care, precision medicine -- we've heard those terms. And that's where we're all going to go toward, goal.

What I've tried to suggest -- I don't have to convince this group -- is that there's a value in possibly getting away from the crude diagnosis, fibromyalgia. There's subtypes of people with fibromyalgia. Back pain, there's subtypes of people with back pain.

If I read an article -- in the old days, if you'd read an article about we had a study about back pain patients, I haven't got a clue what they're talking about. It's a location for a

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symptom, but it doesn't tell me a whole lot about them. We've gotten better than that.

There are large variations in the adaptations to disease, response to treatment. Patients with the same diagnosis respond in different ways. You all know that. Everybody who's a clinician surely knows that.

Additional diagnostic classifications, the traditional diagnostic classifications are not comprised of homogeneous sets of people. We've seen that numerous times here.

Psychological factors maybe -- maybe -- are important to think about. It's not that we write them off as I'm not going to talk about that or that's complicated and let the psychologist deal with that or wait until everything else has failed, then bring in the psychologist to do some kind of an evaluation.

Maybe we should start thinking about this in a longitudinal perspective. And if you're seeing patients with that type of history of their pain problem, maybe you need to think about it sooner or

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the clinician does. And you need to match treatments to those patients perhaps.

Lack of attention to important variations has hindered our understanding in the treatment of patients. For these reasons, splitting may be essential in chronic pain.

However, maybe it's not so simple a dichotomy of lumping versus splitting, as I started this out with. But how do you split? What are the different ways you can go about splitting patients? We have heard about a number of different things.

I think we all agree that we probably don't want to split exclusively on the old diagnostic classifications but then we start thinking about, okay, what are the ways that we do want to split these people.

No single treatment eliminates pain for all patients with chronic pain, no question about it. Thus, we should be considering combinations of treatments. This one, I used to say this 10 years ago, it was a radical idea, every clinician knows it, but it was a radical idea to the research

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people. It was a radical idea to pharmaceutical industry. What do you mean? We want you to give you a treatment. What do you mean, this combination of treatment? What combination?

Then we have people like Ian who did some work to demonstrate the value of combinations of pharmacological treatments. Sometimes, 1 and 1 does equal 3.

It may be you'll get better outcomes if, in fact, you have more than one treatment. When you think of fibromyalgia, we have a symptom checklist and the mean of 38 items on our symptom checklist and the mean number of symptoms that the patients report is 22.

I don't know about your best treatment, but to think that you're going to take care of all the fibromyalgia patients with a single treatment, I don't care what your treatment is, you're probably going to end up seeing your 20 to 30 to 40 percent benefit on some symptoms for some of those patients. But you're not going to get them all and maybe we shouldn't expect it to.

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These should be matched to the patients based on whatever characteristics we think are important, whether we think it's genes, whether we think it's sensory profiling which may be affected by genes, whether we think it has some biological or psychological characteristics.

But we need to be thinking about splitting these patients apart and that maybe it's not -- is it a psychological treatment, is it a physical treatment, is it these two physical treatments, is it physical therapy in this drug?

But maybe what we're looking for is what's the combination of physical, biomedical factors, and psychosocial factors. And do we look for what's the best combination of treatments that'll match those patient characteristics?

I showed you just one slide and that made an important point. You've got to demonstrate –- it's one thing –- we can identify an infinite number of subgroups, no question. Cluster analysis will find something even if there's nothing there.

Replicating a cluster analysis doesn't

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always occur. But if, in fact, we find some differences that are meaningful, then we've got to test out, do the treatments match those patient characteristics, really make any difference.

Therefore, you're going to have to have treatments that are beyond what you expect to see with the placebo drug. If we start getting combination treatments, the reason that people shy away and get scared about this is the complexity of doing the research, because now you need a lot more arms to your studies.

If I got three subgroups based on psychosocial factors and three subtypes based on sensory profiling, so the number of possible treatments in your study is going to be pretty outside what you're going to be able to do.

That's one of the dilemmas when we talk about trying to match patients with different characteristics, is it gets to be very big and complicated kinds of studies.

So all I wanted to hopefully just do in the short time I had was not to say there's anything

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wrong with all the things we've been trying to identify, these subtypes of patients, the stratification of patients. But at the same time that we're looking at a range of those different biophysical factors, the genetic factors, we might also want to pay attention to that unfortunate conscious individual who is paying attention to what you do to him, and what you say to him or her, what treatments you're providing to him.

That may explain a great amount of what we see with every treatment having some beneficial effect, because we're not spending enough time with those individual patients and customizing, tailoring, matching the treatments with the patient characteristics.

Thank you.

(Applause.)

DR. MARKMAN: Question? [Inaudible - off microphone].

DR. TURK: Only an easy one. I won't let Nat -- Nat never asks an easy question. I can't see Dr. Katz. I think we need to be fair to the

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people in the back.
DR. KATZ: You can handle this one.
DR. TURK: Go ahead. I'm not sure.
DR. KATZ: Is there any data on the predictive validity of those three psychological subtypes for the outcome versus placebo or pharmacological pain treatments?
DR. TURK: Those three different subtypes, from my knowledge of them, have -- there's only been one pharmacologically-oriented study. All the rest of them have been rehabilitation, or psychological treatments, or physical therapy kind of treatments.
So there are good data on the difference of psychological treatments and physical therapy treatments. I don't know of -- I think of the one study and I think it was –- Mike Rowbotham, did you do that study?
There's one drug study and there was sort of modest effect, so I can't say that for the pharmacological treatments. I can say that there is pretty good evidence from a range of different

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studies across the world, a lot of them in Scandinavia, I should say, that have actually shown that –- there's also been some very interesting studies showing that baseline, the best predictors of who's likely to become disabled following a whiplash injury was not in the physical findings, but was basically the kinds of measures I always use, including the MPI, which is what that was based on. So I don't have an answer to the pharmacological, though.
Only easy question, Penney? Let Penney have hers, because she's been quiet this whole meeting.
MS. COWAN: I want to thank you for your presentation. What I want to say is that -- I mean, I've been listening to all of these presentations. What you're really saying is that it's about people and every one of them is going to bring something different to the treatment.
So no matter what research you find, you have to consider the individual. I think eliminating the pain is not something that most

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people with pain expect.
They know that there may always be some level of pain. It's about living with the pain. So we can't tell them to live with it. We have to teach them how.
The whole pain management is to improve the quality of life, increase function, and reduce the sense of suffering. But I think most importantly, we have to realize that these are people and they bring a whole bunch of stuff with them, the fears, all of the personal issues that are going on.
So while your treatments and your research may say this is what should happen, it may not happen because they're people. I think the provider needs to take time to find out who they are and what's really going on with their lives so that they can base the treatment on what the needs of that individual are.
DR. TURK: Not wanting to take up too much time with this. Thanks for the comment. And just to reinforce it, but I think most primary care types of physicians or practitioners actually do

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that to some extent, more so than we scientists who are trying to narrow everything down.
If I had you follow a physician around seeing their patients every day, they spend a lot of time trying to figure out what's the best combination medications, what's the sequence I'm going to do this, what do I need to refer this patient for. So they're doing that.
The trouble is they're doing it on their hunches and unsystematic ways, and the hope is that by some of the phenotyping approaches we're seeing, we may be able to give them some guidance about how to help them structure those combinations of treatments.
Penney are you --
MS. COWAN: I was just going to say it's a combination of treatments. It's never just about one medication, but they don't have the time to do that anymore. That's the problem, because payers aren't paying for their time. So I just wanted to say that.
DR. TURK: I don't want to get into the

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politics or the problems of the reimbursements of --
MS. COWAN: It would be lovely if they had the time, but they don't.
DR. TURK: Serge?
DR. MARCHAND: I think it's sort of important, because I will just tell you a very rapid story. My background is in psychology. I've done a -- I was a psycho educator, in fact.
DR. TURK: Oh, don't let people know that.
DR. MARCHAND: I know it's terrible. It's coming out. But I decided to go in neuroscience because it was more serious. I decided to study physiology, biology, neurophysiology and I've done that for a long, long time. I was really proud of myself.
I was talking to some people and when people were asking me, I would say I'm a neurophysiologist.
I will never say that I've done -- but the most important results that I got in my lab were psychological manipulation of what the subject is

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thinking about what was going to happen with their pain.
When I say that, it's measuring brain activities, spinal cord activity and all the shebang. But I think is we should, in the next publication, make an emphasis on that and I totally agree with you with psychotyping.
It's so funny how when you go and you give a talk, when you talk about placebo or psychology or whatever, it's so funny to see how much people would say, "Oh, okay, then it's psychological, okay, okay. Now, let's talk physiology," like it's not important.
I think we need to emphasize on that, because for the patient, it's a huge difference.
DR. TURK: Your comment would've been much stronger had you not started out by coming out of the closet and saying you were a psychologist.
(Laughter.)
DR. TURK: If you have said, I'm a neurophysiologist, then we would've believed you but, "Oh, he's biased, he's a psychologist."

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DR. MARKMAN: Thank you, Dennis.
(Applause.)
DR. MARKMAN: Our last speaker this morning is Dr. Robert Edwards from Harvard's Brigham and Women's University. For those of you who read Pain, you'll get to see the lucid writing of Rob all the time and it's really impressive. It's a pleasure to have him speak today. He's going to tell us what we missed so far with all this discussion.
(Laughter.)
Presentation – Robert Edwards
DR. EDWARDS: Hello, everyone. I think I have the, no doubt, deeply enviable task of trying to coherently synthesize and summarize everything that's been said and also to cover what else needs to be included when we're talking about phenotyping. That means we're really talking about the leftovers here. Now, people feel differently about leftovers.
Some people love them. France recently passed a law making it illegal to throw out

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leftovers under some circumstances. Some people are confused by leftovers and others are not so fond of them.
It may not be a big surprise that at a meeting on precision pain medicine, the leftovers are mostly psychological in nature. These are factors that tend to be dirty and multimodal -- and I don't mean that pejoratively -- and to be factors that respond to dirty and multimodal, pharmacologic and non-pharmacologic treatments.
So I'm going to try and do them some justice and summarize some of the psychosocial factors that we haven't covered in depth yet.
Before I do that, I want to talk through a couple of definitions. You can see an interesting one up there. So I'm not going to offer definitions for all of these terms that have been used at the meeting, but I want to list them on the screen because they've all been used throughout these talks.
I'm not sure if we all mean them in the same way or if they all mean the same thing to all of

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us. I suspect in the afternoon session and certainly in the paper, we're going to have to talk through and figure out what we think are the definitions of these terms and the differences among them in order to figure how we want to write about them.

I suspect we can agree on definitions of certain things like phenotype. They're worded vaguely and they have definitions in Wikipedia. And so we can just cite that as the preeminent source of information.

I doubt we won't have a lot of trouble agreeing on the importance of phenotyping for the sort of work that we all do. You can see some of the listed sources of importance up there.

Now, there's been a decent bit of work recently and, in fact many, many people in this room contributed to a manuscript that's now in press in Pain detailing patient phenotyping in clinical trials, essentially phase 2 and 3 clinical trials of chronic pain treatments.

In that manuscript, we tried to summarize a

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number of the important phenotypic domains and make recommendations for what measures, or methods, or assessment tools might be used to do this sort of phenotyping.

You can see up there some of the criteria that we used for selecting certain measures that we would recommend. I'm not going to spend a great deal of time in this talk trying to differentiate between, say, different neuropathic pain assessment instruments.

But just know that it's certainly something that will come up as we try to synthesize all of the information here and make recommendations for folks in academics and industry who are going to be looking to us to provide answers about what the best phenotypic approaches are.

In the document that was circulated, the guidance for industry document, they outlined a number of different enrichment strategies for clinical trials.

I'm going to wind up focusing mostly on what was their third enrichment strategy, predictive

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enrichment, and that involves what a lot of us think about mostly when we think about phenotyping, choosing patients that are most likely, or least likely, if that's how we are conceptualizing it, to respond to a drug or other treatment in question.

Now, we do a fair amount of prediction. We are, frankly, wrong quite a bit and we probably don't have all of the information that we need to predict accurately.

But we should know enough at this point to generate some specific and hopefully modestly accurate hypotheses about what sorts of phenotypes might be most predictive under which circumstances.

Now, I want to cover different types of prediction. I won't spend much time on this, because I think Nat did a really nice job outlining it and other speakers have alluded to is as well.

There are absolutely different types of predictive effects we might look at. In the in press review in Pain, we described these as general prediction.

These are predictive effects and studies in

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which there isn't a control group. So the phenotype of interest –- or, if there is a control group, the phenotype of interest predicts equally in the active and the placebo treatment groups. If there's no placebo group, then it just predicts in the active group, of course.

This is a sort of limited model of prediction but that is where we find the majority of the predictive studies.

Effect modifications style prediction has many, many fewer studies under that umbrella but they probably have the most interest to all of us and certainly have the most interest to trialists.

Treatment effect modification refers to cases in which a phenotypic characteristic is differentially associated with outcomes in different study arms. So a phenotype might predict the superiority of active treatment over placebo, let's say.

I bet we could also outline other forms of prediction. If we came up with a term like personalized prediction or personalized pain

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medicine prediction, that might involve predicting, for example, of all of the possible treatments or treatment combinations that you could administer to a patient, what will provide the most benefit to that individual with the least side effects and the least cost.

As far as I know, we don't have any studies that can really answer this question and it's not totally clear to me how we would or could design those studies. But I think that sort of concept of prediction is one that we'll be angling for in the long run.

Now, I want to acknowledge, as I talk about some of the phenotypic predictors that have emerged as important in the literature, the fact that a number of conceptually interesting and exciting things have been studied as phenotypic predictors and have not worked out.

Just for example, Steve Bruehl, down at Vanderbilt, is doing some really nice work measuring individual variability in resting, as well as pain-stimulated plasma beta-endorphin

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levels in healthy controls, as well as chronic pain patients, and looking at whether, for example, this variability in resting plasma beta-endorphin predicts opioid analgesic responses.

What you might not be able to see in the very small print up there in the table is that in most of the studies, it does not. The correlation between patient-to-patient variation in plasma beta-endorphin and morphine analgesic effects in this study, all of those correlations hover right around zero.

There are also a number of people looking at what we might call the umbrella term of brain endophenotypes. This is some recent data that generates some nice pretty pictures from an EEG study using some of the latest machine learning classification algorithms.

Sixty-two-channel EEG study, they used healthy subjects, brought them into the lab, determined whether they were morphine-responsive or not, and looked for EEG-related predictors of who responded to morphine and who did not, and there

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were none at all.

I'm going to wind up talking more about somewhat less sexy, but more predictive factors that are mostly in the psychosocial realm. As the biopsychosocial model of Pain, which I suspect we all subscribe to, tells us there's great patient-to-patient variability in pain report and pain symptoms, and this variability is influenced by a lot of forces, many of them psychosocial in nature.

I think a lot of the speakers, Dennis, Nat, Roy and others have nicely covered the concept of individual differences which, of course, we're all intimately familiar with going back to the time of William Osler, one of the founders of John Hopkins Hospital.

I am particularly interested in individual variability in psychosocial processes and psychiatric distress. This is something we see a great deal, as you all know, in chronic pain patients.

These psychosocial forces are important both

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as outcomes and as potential moderators or mediators of treatment outcome. There's a nice IMMPACT survey done by Dennis and a number of others some years ago surveying a large number of patients with pain, having them rate the importance of various outcome domains.

Two of the top three rated domains are psychosocial in nature and they're things like enjoyment in life and emotional well-being. These come out as some of the most important factors when you're talking to patients.

As part of the APPT initiative, the ACTTION and APS pain taxonomy initiative, a number of supporting articles are being published. These are articles that detail aspects of chronic pain that can support the newly proposed pain taxonomy, proposed by APPT.

We should have coming out before too long a review article on the role of psychosocial processes and the development and maintenance of chronic pain disorders.

I could easily spend a whole talk discussing

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the various psychosocial risk and protective factors. And we know, a lot about what psychosocial forces put people at greater or lesser risk for the development of chronic pain, or for greater or lesser disability in the context of chronic pain, et cetera, et cetera.

But that's not quite as relevant as I'd need it to be for our discussion of phenotyping here. Just know that there's a vast literature, probably most of you know this already, on the importance of psychosocial forces in shaping the trajectory of all sorts of chronic pain conditions, nociceptive, neuropathic, inflammatory, you name it.

Dennis talked quite a bit about lumping versus splitting, and a lot of the things that I'll talk about could be either lumped or split, depending on your particular proclivities.

Ajay Wasan has done a lot of neat work in this area. He is much more of a lumper. I tend to be a splitter. You can see there are some of the elements of negative emotion or negative affective processes that I'll be talking about as phenotypic

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predictors.

A couple of people now I think have mentioned the HADS, the Hospital Anxiety and Depression Scale, in their talks. This gets used fairly frequently.

It is a nice, brief, easy for patients to use, 14-item measure of symptoms of depression and anxiety. It's got wonderful psychometric properties and pretty easy to administer in any sort of randomized controlled trial setting in which you might be working.

This has been used a lot to phenotype psychosocial aspects of chronic pain patients. This is just some data from a hydromorphone study that Bob Jamison and I were able to get our hands on.

When you split patients in the trial as a function of their level of psychosocial distress on the measure like the HADS, you can divide them into low, and moderate, and high negative affect groups, which you can see there in that bar graph is the data from the Roland Morris Disability Scale.

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You can see that even after treatment, disability is highest in the high psychosocial distress group. This is a general prediction finding or at least that's how the findings were analyzed.

Although, if you looked specifically in the placebo data in this study, the high negative affect group actually had a greater analgesic benefit from placebo, which has shown up in a couple of other studies, as well. I'll show you some more detailed data from that.

That is fairly important, especially in the context of an opioid study, because as this recent meta-analysis notes, on average, opioid trials tend to have the largest placebo effects relative to other sorts of drug trials.

I'll give you a few details about a couple of recent studies that were done at Brigham and Women's by Ajay and others. One was an opioid study, one was and IV-opioid study.

In general, across these studies, when you phenotype patients' psychosocial characteristics,

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and these are studies of low back pain patients, the group that's high in negative effect tends to get quite a bit less opioid analgesia.

This is a fairly large and profound effect, 40-50 percent less analgesic response in the high negative affect group relative to low.

Indeed, if you do this in a double-blinded and placebo-controlled manner, as was done in the study, you can now see, on the right, if you look at the low negative effect group, they have the largest response to morphine, the HADS bars on the left, and the lowest response to placebo, the dotted bars on the right.

The high negative effect group obviously has a lower analgesic response to morphine. They get less benefit from the morphine, but they have a higher placebo response.

This is an effect modification sort of finding. The first study, the oral opioid study, was general prediction. This is an effect modification. If you take the low negative effect group, they have a much bigger difference between

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morphine and placebo than the high negative effect group, so an important sort of finding when considering what patients you might select for a future opioid trial.

We had actually done some work as part of Ajay's oral opioid study administering quantitative sensory testing measures. You heard a nice talk by Roland earlier about conditioned pain modulation and other pain modulatory processes.

We had the chance to take a look in this study at whether opioid's effects on QST or pain modulatory measures might vary as a function of patient's psychosocial phenotype.

What you can hopefully see in that graph there is at baseline, the low negative effect and high negative effect, the patients don't differ in CPM, or conditioned pain modulation, but by mid-treatment, the high negative effect patients have a reduced CPM effect.

I think several folks have mentioned there is some data on opioids impairing CPM and other endogenous pain modulatory processes in patients.

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We observed this selectively in the high negative effect group.

There are yet more effect modification findings to measures of negative effect or depression and anxiety. These are some data for that, which I won't go into great detail.

These are patients with chemotherapy-induced peripheral neuropathy who are randomized to either duloxetine or placebo.

What you might be able to see in the lowest rows of that table is that the response to duloxetine and placebo was partly related to patient's level of baseline emotional functioning.

There were more than twice as many pain responders in the high emotional functioning group in the duloxetine arm, but that was not true in the placebo arm.

This effect modification finding, if you want to get the largest difference between the duloxetine and placebo, you should take individuals with, in this study, high emotional functioning or you could think of it as low levels of depression and anxiety.

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Now, maybe most fascinatingly, there are a couple of recent studies on this sort of question in animals. I had no idea, but apparently you can induce a depressed phenotype in rats by giving them a bilateral olfactory bulbectomy.

When you do that, if you take rats who are then subjected to spinal nerve ligation and you compare the analgesic effect of amitriptyline with analgesic effect of a vehicle or saline, you only get an analgesic benefit of amitriptyline in the non-depressed rats who did not get the olfactory bulbectomy.

Those dark bars are the rats who did get the olfactory bulbectomy and in that group of rats, amitriptyline does not beat placebo in the way that it does in the non-depressed group.

This should come with dozens and dozens and dozens of caveats. But it's a fairly interesting conceptual parallel to some of the human findings.

Now, I get to talk about catastrophizing for a few minutes. Some of you have probably heard me

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ramble at length about pain-related catastrophizing before.

In catastrophizing, as I said, of negative cognitive and emotional and attitudinal processes related to pain and patients who catastrophize about pain, which we measure via self-report on questionnaires like the PCS, or the pain catastrophizing scale, those patients tend to ruminate about pain, they tend to magnify the threat value of pain, and they tend to feel helpless in the face of pain.

Now, I can let you know what the acronym IMMPACT actually means. So IMMPACT is an Insidious Mechanism for Massachusetts-based Psychologists to Advance Catastrophizing Theoretical Importance, IMMPACT.

(Laughter.)

DR. EDWARDS: We'll have to add that in for future meetings.

So we've done a fair amount of work on catastrophizing and there are fairly broad individual differences in any group that you would

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care to study. Even healthy adults or kids show individual variability and catastrophizing.

These are some data from patients seeking treatment at the Brigham and Women's Pain Management Center, patients with low back pain. You can see that in these nearly 300 individuals, there's a normal looking distribution. The mean score is about a 25, and there are some people who are down very close to zero and some who are very close to the top end of the scale. And you get this nice sort of variation in how much people say they catastrophize about pain.

There are, at this point, a bunch of general predictive studies in both nociceptive and neuropathic pain conditions.

This is some summary data from a few different trials, patients with diabetic painful neuropathy, PHN; or persistent neuropathic post-operative pain who are in trials for a variety of topical preparations.

When you split them by their baseline catastrophizing score -- and this is Mick Sullivan

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and crew dividing them into catastrophizers and the non-catastrophizers -- the non-catastrophizers are quite a bit more likely to get at least two points or more greater reduction on a 0-10 pain intensity scale in their neuropathic pain with treatment and quite a bit more likely to get an even larger reduction as well.

There are even now a couple of effect modification findings in catastrophizing -– I don't know how that interesting orange bar got there. But it probably prevents you from reading a bit of the description of the study.

So this is work by Bob Rakel and colleagues in the University of Iowa who are doing a TENS study in patients with severe knee osteoarthritis who had just gotten a joint replacement and were rehabbing after that.

What you can see there is that in this randomized controlled study, if you look at patients who got active TENS versus those who got placebo TENS, in the active TENS group, the low PCS patients do better that the high PCS patients.

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So catastrophizing level at baseline predicts response to this analgesic treatment but that is not true in the placebo arm. There are other effect modification findings, as well. I won't go into this in detail

But in this study of low back pain patients randomized to either placebo or an acetaminophen-tramadol combination, you get the same sort of effect modification result, where low catastrophizing is associated with good response to active treatment but not placebo.

So negative effect, catastrophizing, seems to at least have some phenotypic importance for predicting responses. There are a variety of other psychosocial processes, as well, which may be related to both these features.

Individuals who catastrophize quite a bit about pain, who are depressed and anxious tend not to sleep particularly well. And there is substantial overlap between sleep disruption and the experience of chronic pain.

There are some really neat animal studies

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looking at the effect of sleep deprivation on impairing opioid analgesia -- or maybe I should say anti-nociception in rats and a little bit of data in humans suggesting the same sorts of effects.

That is, when you help people who are not sleeping well at night and who are very sleepy, in this study, codeine does not beat placebo, but it does in the non-sleepy individuals. This is a laboratory study of heat pain responses rather than a chronic pain trial.

But you get some really interesting data from this summary of thousands of patients in a number of pregabalin trials. In this case, the researchers split people by their baseline level of sleep disturbance from mild to severe and looked at the relative pain improvement with pregabalin over placebo.

So this would be an effect modification sort of findings. Those with the most sleep disturbance got the most benefit from pregabalin over placebo.

Then that little figure on the bottom right when you did some fancy structural equation

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modeling sorts of statistics, they concluded that over 80 percent of the benefit of pregabalin, in terms of the improvement in pain, was due to improvements in sleep.

This seem widely implausible to me. That would be the vast majority of the benefit that people get from pregabalin, but it does at least highlight the potential importance of sleep and sleep disruption as a phenotype.

The last five to seven minutes or so, I want to cover not so much psychosocial factors but characteristics of patients' report of their pain and pain qualities as a potential important phenotypic predictor.

There's been some interesting work on individual patient variability in how variable their pain reports are. So you can do diary-style of the studies where you have people rate their pain on a daily basis and then measure how much it varies for an individual patient across days.

You can see there are a couple of sample participants, one with very low variability. So

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that person's got really stable pain ratings and the other with the same average pain level but quite a bit more variability.

I think this might have been the first study published on the topic. It was in patients with fibromyalgia as a randomized controlled trial of Savella.

What the Michigan group found in this study was that the more variable patient's pain was at baseline, the more they tended to respond to placebo.

Now, a quick plug for ACTTION here. This had been followed up by an ACTTION meta-analysis done by lots of people in this room. John Farrar is the lead author.

They have found that for randomized controlled trials of, I think, gabapentin and pregabalin in both diabetic painful neuropathy and PHN, you get exactly the same sorts of effects. That baseline variability in pain intensity ratings on diaries is associated with placebo effects in these studies.

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The more variable patients' pain ratings are day-to-day before you start treatment, the more they're likely to respond to placebo, which seems like a fairly important thing to know if you are designing a trial.

I have not seen any report in the trial's literature on other sources of daily variability, but I just took a look this morning at some of our data in knee OA patients, and you get just as much day-to-day variability in catastrophizing ratings as you do in pain ratings. Just for fun, I looked at what that daily variability and catastrophizing might be related to.

You can see there are moderate correlations between how variable patients' catastrophizing scores are day-to-day and their overall PCS level.

There are moderate inter-correlations between daily variability and catastrophizing and daily variability and pain. You can, I suspect, easily imagine that you could compute daily variability for dozens and dozens of other potentially important variables, which I don't

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think anyone has done yet but might neat to look at.

Outside of variability, it's probably important to consider a patient's pain characteristics or pain phenotypes. We have a number of measures that can do that quite well.

I think you've seen the PainDETECT already. And as Ralf and others have shown a very nicely, you can phenotype and subgroup patients using, for example, cluster analysis on some of these measures.

You get interesting, and neat, and fairly consistent clusters across pain conditions. So when you characterize people according to the degree of burning pain that they have and mechanical hyperalgesia, thermal hyperalgesia that they report on these instruments, you can subgroup or cluster patients into these roughly five different categories in most of the very large German studies.

You can also use measures of pain quality like the PQAS or the Pain Quality Assessment Scale

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which asks patients to rate the degree to which various adjectives apply to their pain, burning, tingling, cold, sharp, et cetera, et cetera.

There have been some effect modification-style analyses of these sorts of measures. This is a PQAS study in patients with a variety of neuropathic pain conditions.

They're randomized to pregabalin or placebo and what you can hopefully see in that slightly yellow highlighted column on the left is that there are some nice positive correlations between a number of PQAS items. So patients with more paroxysmal pain and intense electrical pain tended to respond more to pregabalin. But those PQAS items didn't predict the response to placebo.

If you categorized people in these ways, you could get better looking pregabalin effects over placebo in that subgroup of PQAS responders.

I think I actually will probably not spend any time on that study, which is a short-form MPQ study. The neuropathic pain symptom inventory is a measure that you've heard about before and I'm just

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going to hurry along in the interest of time here.

This is another measure on which patients can self-report the degree of neuropathicity, if that's the word, of their pain.

In this particular combo diabetic neuropathy study out of France, which had a really interesting and complex design, patients were randomized in an initial phase of treatment to either duloxetine or pregabalin and then randomized again to either high-dose mono therapy or combination therapy, which we don't have to worry about.

But in that initial period, if you look at the cluster of patients with the lowest level of neuropathic pain symptoms -- this is cluster 3, the greenish-looking lines and symbols -- duloxetine beats pregabalin significantly only in that cluster of patients with the lowest level of neuropathic symptoms.

In the Demant study, which we've heard mentioned a number of times -- I think possible every speaker has mentioned it -- you can also subgroup patients as a function not of the QST

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findings, but on the NPSI.

They find that the subgroup of patients reporting more paroxysmal and burning pain symptoms show better pain relief with oxcarbazepine over placebo.

You can all see the summary up there. I won't go into great detail, but this is my plug for phenotyping and assessing psychosocial processes as potentially important predictors and even effect modifiers in these sorts of studies.

Other measures like pain variability or patient's report of the quality or degree of neuropathic-ness of their pain symptoms might also be fairly important.

But a question that comes up, and these are my last couple of slides, exactly how phenotypically-selective do we want to be in these trials?

If we know there are a dozen or a couple of dozen factors that predict response, how small a slice of the population of patients that we might be studying are we willing to get?

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I just want to illustrate -- this is a really nice study of painful diabetic neuropathy, I think, done by Andrew Rice among others, the PiNS study, just a cross-sectional observational of phenotypic study.

They recruited over 200 patients with diabetes and possible, probable, clinical neuropathy, split them into groups who don't have any neuropathic pain, who have mild neuropathic pain, or who have moderate-to-severe neuropathic pain, and you can see them characterized there.

But when you run their actual breakdown, so of 209 initial folks, a little over half of neuropathic pain consistent with the literature, about a third have neuropathic pain of the intensity that would get you into a trial.

If you do some deeper sensory and self-report phenotyping and look for patients who both have moderate-to-severe neuropathic pain and have what we could have I guess casually called an irritable nociceptor subtype of pain, where that is present both on their report of hyperalgesia sorts

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of symptoms and on sensory exam, then you wind up with five subjects out of the initial 209 or a little over 2 percent who actually meet those phenotypic criteria.

That's not even looking at things like psychosocial functioning, sleep and a number of the other things that we've mentioned as potentially important.

So if we're putting up wanted posters in order to recruit individuals for our clinical studies, exactly how picky do we want to be?

Do we want to have a list of two dozen of these criteria, people have to have high intensity pain, low pain variability, low catastrophizing, but high sleep disturbance, low negative effect and some mechanical hyperalgesia, as well as specific qualities of their pain, et cetera, et cetera.

That sounds challenging to pull off and should make us wonder if we're going to be running our clinical studies on an ever smaller number of individual patient needles in the giant haystack of the population.

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There's probably an interesting debate about where the line is that we're going to want to draw and, presumably, we'll get to do a little bit of that when we work out a consensus and write the paper.

Thank you, guys, very much.

(Applause.)

DR. MARKMAN: Thank you, Rob. We're going to break here and have an hour lunch, and we'll be back at 1:00.

(Whereupon, at 11:58 a.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N

(1:26 p.m.)

Q & A and Panel Discussion

DR. MARKMAN: Good afternoon, everyone. I hope you had a good lunch. We're going to get started. The goal of the next 30 minutes or less is going to be clarifying questions for this morning's presentations. So we're just going to try and wrap it up.

Then the closers, if you will, Dr. Edwards and Dr. Dworkin, will come up here in the spirit of Mariano Rivera and another great Yankee, Sparky Lyle and --

MALE SPEAKER: Boo.

(Laughter.)

DR. MARKMAN: -- close it out. Any Boston fans, this might be your time to leave the underground, because we've got a history of doing this very, very well. Okay, great.

Does anyone have any questions regarding the four presentations this morning that we can have clarifying -- actually, I think it might make sense

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to have the speakers come up to the table actually, also, just so you can be mic'd up.

If I could ask Dr. Baron, Dr. Freeman, Dr. Turk, and Dr. Staud to join us, that'd be great. Please. Why don't we start with the questions as these gentlemen come forward? Yes? In the very back -- oh, is that Bob? Bob Kerns.

DR. KERNS: So I really am interested in hearing folks that are more on the basic preclinical science biological end of things reflect on the discussion about the importance of the psychosocial context and how that could be better integrated or where the opportunities for integration of at least the concept of a psychosocial context for your work.

DR. MARKMAN: There seems to be some uncertainty among the panelists regarding who should take this question.

(Laughter.)

DR. MARKMAN: Does anyone want to step up? I thought Serge gave a beautiful, eloquent answer to this question, but I defer to the gentlemen

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here.
DR. TURK: Direct it more specifically, Bob Kerns, to who you'd like, because if you say to the panel, we'll all sit there going at that.
DR. KERNS: Maybe to Ralf in terms of QST. I'm wondering in terms of profiling of QST, how much psychosocial variables, anxiety, in particular, maybe as a construct. Doesn't that affect results in that domain and do you take that possibility into account?
DR. BARON: I think nobody really has looked into these issues very closely. But we discussed this with others over lunchtime. I think all the evoked types of pain, in particular, those depending on central sensitization like dynamic allodynia or pinprick allodynia, might be dependent on psychosocial factors, as well, because this is influencing descending control mechanisms and so forth. It might very well be that there is an influence for these measures, obviously not for the negative phenomena and so forth, so they are stable.

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DR. MARKMAN: I think Dr. Carr and then Dr. Dworkin had a question.
DR. CARR: Dan Carr. First, a question, then an observation. The question is I'm thinking back to my endocrinology days when if one were to study something like athletic performance in women and their ability to reach a certain aerobic capacity, generally, these would be controlled for phase of the menstrual cycle.
I wonder -- I know there has been some pain literature, but I didn't hear much about that in the last day or two and wondered whether that might be a factor, also, in influencing individual testing responses.
DR. FREEMAN: I think these two questions are really good questions. I think when I spoke, I tried to make the point that what sensory phenotyping is doing is really just giving you an edge, increasing the statistical likelihood to some extent over what would be just a patient walking in without having sensory phenotyping.
I think both of these two questions answer

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some -- and that needs to be viewed within the context of the many other factors, age, gender, genotype, all of those other factors that go into pain processing and pain perception.
When we look then at the sensory phenotype, there are going to be many, many factors that go into the response, as well, including, as you say, the menstrual cycle, the psychometric issues that Dennis spoke about, and, also, circadian variability of pain processing, as well.
I think we can begin to take a more granular approach to sensory profiling, sensory phenotyping and this probably -- we are still at, I think, the very, very early stages in understanding these measures and what they work and how they work.
It would be wonderful if we could standardize them and do them at a particular time of day, a certain amount of time after a meal, with certain degree of hydration, with certain ambient temperature, and I could go on, and on, and on.
Many of those factors are not implemented. I think with time, they will be.

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DR. MARKMAN: Sounds like a factors-to-consider section for a manuscript perhaps.
Dr. Dworkin?
DR. DWORKIN: Yes. So I have a question for Nat, who I think should be up on the stage. Or are you playing hooky?
DR. KATZ: I'm wondering if somebody would outman it.
(Laughter.)
DR. DWORKIN: I won't.
DR. MARKMAN: It's a Red Sox boycott, I think.
DR. DWORKIN: I'll decline the opportunity to out Rob Edwards, who should actually also be up on the stage.
(Laughter.)
DR. DWORKIN: So Nat, if I understood your naproxen clinical trial correctly, the more abnormal the conditioned pain modulation, the sensory profiling -- should I start over or you -- so the more abnormal the sensory profile and

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the CPM, the greater the separation of naproxen versus placebo.
Couldn't that simply be result of the fact that the patients with the more abnormal profiling CPM had greater pain intensity and that what you found, unless you control for pain intensity, is that pain intensity is associated with signal detection?
DR. KATZ: I know that we talked about that internal and I think we looked at that and that didn't explain the findings. But I don't remember exactly. So I'll have to get back to you on that.
DR. DWORKIN: I think this is important, because the same question applies to Dennis' MPI profiling, to Ralf's profiling, and to Roy's profiling.
I think we need to demonstrate that profiling, phenotyping, whatever we call it, has an incremental benefit on predicting the analgesic signal over and above pain intensity, because if it doesn't, let's just have patients rate their pain on a 0-10 scale and we don't need to do all this

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fancy expensive stuff.
DR. MARKMAN: Dr. Woolf?
DR. CARR: It's Dan. I got to ask my question, but I didn't make the observation.
DR. MARKMAN: Please.
DR. CARR: The observation is that in discussing factors like we just are looking at many of the graphical representations of one or another finding, there are often swarms of points rather than a small bullet hole-size to point in aggregate.
It seems to me that the word "accurate pain medicine" might be a better word than the word "precise pain medicine," because precision, to me, implies the reduction of variance.
Yet, as we drill down to more and more granular knowledge, we don't diminish the variance. There is still a lot of variance. But the attraction of the approach lies, for example, in matching mechanism to clinical response, which would, to me, be more in tune with the word "accurate."

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DR. MARKMAN: Okay. That's helpful. I think it'll come back. Dr. Woolf, and then Dr. Gilron.
DR. WOOLF: I'd like to come back to the issue that was touched on Ralf and Roy, where the treatment changes the signature of the profile, because if it doesn't, then the whole basis for this discussion is rather moot. The mechanisms driving tactile allodynia or normal hyperalgesia, we target them with a treatment, that should change, that should disappear so that the profile is not a fixed fingerprint of the patient's pain, but should be dynamic reflecting the relative presence of different pain drivers which will respond to different treatments.
DR. BARON: Perhaps I could start. You say, well, your guess would be that if one particular medication will affect one mechanism, like central sensitization, then we should see something in the allodynia, in reduction of allodynia. But all the trials we are talking about, our endpoint is spontaneous pain.

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We look at baseline for the existence of allodynia. And if you have a predictor for this, it doesn't necessarily mean that also your allodynia is going down.
DR. WOOLF: What I was getting is that the patients on therapy, say pregabalin, for argument's sake, let's assume pregabalin has a specific effect on central sensitization, but --
DR. BARON: Then we should assume that allodynia has.
DR. WOOLF: You would assume that -- what I'm trying to say is the phenotype should be dynamic and reflect the activity of different treatments.
DR. BARON: We had this discussion earlier. But what we know is that opioids have an effect on the evoked types of pain in our QST profile. This we have shown, allodynia and hyperalgesia, for example.
All the negative phenomena are stable, obviously, because they are negative. They are not influenced by the therapy. Other therapies have a

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minor effect on the positive phenomena, as you observed, as well.

DR. WOOLF: Just to reconcile, because bringing Roy in this, that if, from your studies with Pfizer, there is the predictor of the presence of punctate hyperalgesia as a predictor of efficacy signal with pregabalin, then is the assumption that it's going to work, but without affecting the pinprick hyperalgesia?

DR. FREEMAN: I think I would answer it by saying the data are what the data are, and it didn't. We need to deal with that.

What you say is logical, that you would think that a drug that its efficacy is predicted by the presence of hyperalgesia and results in an improvement in a specific measure, as Rob said, not punctate hyperalgesia, but a specific measure of pain, patient self-report, is also going to improve punctate hyperalgesia. It didn't seem to be, at least for pregabalin.

Why that is, is obviously not clear. That wasn't addressed in any way prospectively in the

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study. I don't think that necessarily it makes the whole process moot. It makes the question interesting and perhaps more multifaceted than one would think at first glance.

DR. MARKMAN: Ian? I'm sorry. Turk?

DR. TURK: This isn't what I think you were asking, but I think I was showing some data that actually spoke to that. I did it quickly.

The rehabilitation program where people started out in one of the three profiles I had and then you gave a generic treatment, what you found out was that the 62 percent of the patients who started out looking as if they were in one profile, a less adaptive one, moved to the adaptive one.

The middle group, which was called interpersonally distressed, there was nothing in the treatment that dealt with interpersonal problems, and only 32 percent of them received the benefit.

It appeared to be the case that the treatment did have a more beneficial effect on a particular set of characteristics of the patient

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and it did not have as great an effect on those individuals who had another unique set of characteristics that wasn't covered by the treatment.

DR. MARKMAN: Dr. Gilron?

DR. BARON: I can add one more sentence, because this was a question before, whether in our database people were treated, and this might have an influence on this data.

Of course, they were treated. You can't collect thousands of patients, do all the things and wash out every treatment. Impossible. This is a KO criterion always. But they were under treatment.

DR. MARKMAN: Thank you.

DR. GILRON: Ian Gilron. Rob's comment about how thinly we want to slice the pie, it made me think about what precision means to different domains of what we're trying to accomplish here.

I think of precision pain care as clinicians who are frustrated because they don't know how to predict which patients do benefit. And they're

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treating their low back pain patients with pregabalin and don't understand why it doesn't work.

Of course, we know the pregabalin is labeled for post-traumatic neuralgia and diabetic neuropathy. And, of course, Bob and others in the room have authored some ideas about how to extrapolate efficacy to other areas.

The question is, does precision pain medicine mean something different than precision drug development? And so I am sensitive to the needs of industry.

But if we sort of use precision to get a highly focused, positive result and then get a drug on market, are we doing a service to precision care if the extrapolation is just going to become more widespread?

Are we going to be in the same boat, in fact, maybe even more, because we're going to have now drugs that are labeled for a specific indication that are being used more widely?

I just don't know how -- and then add the

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same thing for precision preclinical drug development, it might be a completely different picture. I don't know how to reconcile that.

DR. MARKMAN: Do any of you want to react to that?

(No response.)

DR. MARKMAN: No? Okay. Dr. Farrar, and then Dr. Rowbotham, Dr. Jensen.

DR. FARRAR: I'd like to make one comment and then make another statement about some work that's ongoing at the University of Pennsylvania.

The comment is that during one of the breaks, Serge and Roland and I had a conversation about the CPM and the fact that they ought to get invited to Bermuda, as well.

There was general agreement amongst the two of them, at least, that the criteria for defining CPM needed to be standardized and that apparently there was an attempt six or seven years ago, but there still remain many ways of doing it. And so I'll just leave that for what it is.

There is also some interesting data that

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they may want to present with regard to studies, Serge in particular, with some studies that he's done in terms of the continuity of that over time, as well as the variability within normal populations.

What I wanted to say about the University of Pennsylvania is that Garret FitzGerald has a center grant that really is looking at personalized medicine and its relationship to COX-1 and COX-2 therapeutics.

There have been a number of advances since the data that Nat has shown. None of them have been related to pain, unfortunately, because that portion of the grant was left out when the budget was reduced five years ago.

But just to make the point that there are now clearly phenotypes, genotypes really, of patients who either rapidly or slowly metabolize and convert the COX-1 and COX-2 into either active or non-active metabolites.

There are clearly -- we're beginning to look at whether people who metabolize nonsteroidals more

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quickly have as pronounced a response in a setting where -- we're looking at third molar extraction, for instance, and there may actually be ways of getting at some of that.

The advantage of that particular paradigm is that they have the ability to look at it in cells, in yeast, in zebra fish, in mice, and then in humans.

If you find something in humans, you can look down and see if it occurs in zebra fish. And if you find things in zebra fish that are interesting, you can look up to see if it occurs in humans.

That kind of structure, I think, actually provides a way at getting at some of this data that might be very useful and would have applicability to some of what we do here related to looking at animal studies, related to looking at some of the cell structures, cell cultures that Clifford is looking at to try and put it all together as a way of more rapidly advancing some of the precision medicine.

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I just wondered if any of the panelists knew of other instances where there's sort of the combination of both basic and clinical science to try and look at some of these issues.

DR. TURK: I'll respond to your first comment, your statement. Is this another thing for the list on Rob Edwards about desirable things, that is there was a meeting on CPM where they brought the experts together to try to come to a decision, but it wasn't held in Bermuda.

(Laughter.)

DR. TURK: Now, if in fact we have a meeting in Bermuda and demonstrate that the location of where the treatment was provided, actually, that would mean that location would become another important way to phenotype the studies in the patients in the population, right?

DR. FARRAR: I'm all for that. By the way, I have a way of measuring it, as well. I'd really like an invite.

DR. MARKMAN: Mike?

DR. MARCHAND: I want to react to that after

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that.
DR. MARKMAN: Okay.
DR. MARCHAND: It's for the Bermuda thing, yes.
DR. MARKMAN: Bermuda-related, several questions. We'll take them all now.
(Laughter.)
DR. MARCHAND: It's something else. I think it's quite important, because I know that CPM -- it's Serge, Serge Marchand. With the French accent, it's me. Every time there's a French accent, it's Serge Marchand.
What I would like to tell you is when we look at all the literature on CPM, I totally agree that there is like 25 ways of measuring it. But what is nice is most of the people find the same thing.
I mean, it's not perfect. There is some variability, but at least it seems that we can predict some treatment or whatever. It's probably just 20 percent of the variability, but at least it's there. I think it's important.

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Taking that, when I look at that in the lab and we can separate population very easily in different chronic pain conditions, and it's just one lab.
But when I talk with other people and we were together a few minutes, Andrew and I, and he's doing the same in the lab, we found, also, almost the same thing.
I think we need a subgroup of people, again, just to sit there and say, "You know, which ones have been used a little more and, also, can we use it in the clinic," because in my lab, it takes me 45 minutes or an hour to do it and you will never do that in the clinic. But I'm sure, I'm quite sure, I'm convinced, when you get older and gray hair and white hair, in fact, what you realize is you have some intuition on the research, and I'm quite sure we can do a short test for that, quite, quite sure. But I will need the help of people like you and I would like to thank you either away for being here, because it's people like you that will help us to do something like that.

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I want to react to [indiscernible] on the fact that if we're developing some phenotyping just to develop new drugs -- I mean, this is perfect and it's really nice to do, but the phenotyping, it's not for that, I think. We'd like to teach it to other clinicians to understand why they're prescribing the drug, because if we phenotype and we say, "Oh, this subpopulation is responding very well to this drug and let's develop the drug," and it's not going to the clinicians, there's no help at all, because they will prescribe the drug to everyone and will say, "My God, nobody is responding to that."
DR. MARKMAN: It's helpful. It's great.
DR. STAUD: Let me just respond to this one. I agree that different forms of CPM have similar results shown in multiple different occasions, but I think the importance is that depending on how CPM is structured, different mechanistic changes occur. This is, in my mind, the important part, that we are really dealing with the same analgesic response and not with [inaudible - off microphone].

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DR. BARON: I would just comment on your second point. I think we desperately need some back translation from our human world to the animal world again.
I strongly believe that the heterogeneity we see in the patients also exists in animals. But so far, animals that do not show pain behavior were thrown away. You know this. They were not tested.
I think Frank Porreca was the first who just went into this and looked for neuropathy, animals with pain and without pain and looking in brain stem things.
Andrew, you touched upon this issue, as well, that we can do sensory testing with thermal stimuli and cold stimuli. And so in animals, as well, I think we really should do this and we should take this into the manuscript, back translation of these ideas more broad.
DR. ROWBOTHAM: This is Mike Rowbotham and I've got a couple of comments and one question. In terms of outcome measures, as Ralf was saying, things that are dynamic, like dynamic allodynia or

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even area of pain, an area of allodynia have been used in clinical trials before and are dynamic.

There's a possibility, I think, that some of the thermal sensory abnormalities can be reversed, as well, by treatment, although that, I would agree, is a tougher target.

I just wanted to mention something that I heard directly from somebody in EMEA some years ago in terms of electing patients, subgroups for pivotal trials and how they would or would not be to a label.

This was around using topical capsaicin to either -- like what Campbell did in the clonidine study. Because it's a nonstandard test, in other words, there's not a reference capsaicin preparation and all the other things that go around that, you can't really use that to select that subgroup for an indication. It's got to be something that would be accessible to a clinician in practice.

That, I think, needs to be kept in mind in terms of how much profiling you do. If you get to

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the point where there isn't a local reference center or there isn't published standards or other things, you can't really use it to develop your population.

My question is about the interaction between things like catastrophizing sensory testing and Ralf mentioned that at the beginning of his remarks.

But I'd like to hear more about it, whether or not there's an interaction that is adding to the noise that's being seen when you're trying to look just at the sensory phenotype and you're getting quite a bit of spread in the results of treatment, because you're not also looking at things like catastrophizing that might be important either confounders or co-variables.

DR. MARKMAN: Ralf, do you want to answer that?

DR. BARON: We discussed this. I think it's very important and perhaps we should include these psychosocial measures into our cluster analysis together with the sensory phenotype which you

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could.

We did this in fibromyalgia patients once, where we included PainDETECT data and the psychosocial data and did everything with a cluster analysis. You get a really different structure and I think this would capture this influence of both.

DR. MARKMAN: Dr. Edwards?

DR. EDWARDS: Just to expand on that, that's a really good question and I think I have two answers for it.

The first, I think, thing to consider is that most of these, we can call them risk factors or phenotypic constructs or whatever it is we're talking about, most of them are not perfectly independent from one another.

Measures of catastrophizing and measures of anxiety are quite highly correlated. Measures of catastrophizing and measures of sleep disruption are moderately correlated.

In our hands, at least, catastrophizing is associated with the degree of temporal summation that pain patients exhibit, both neuropathic pain

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patients and fibromyalgia patients.

A lot of these correlations are in the 0.3-0.4 range, but they're not perfectly independent. I think that does raise some interesting statistical challenges when we're trying to figure out which phenotypes predict best.

Then just to follow-up on that, it might very well be -- and I'm sure this is the case with genetics. I bet Luda could give a much better answer than I could. But it might very well be that some interesting interactions give us the best phenotypic predictive power.

It might not be just to the case that patients with irritable nociceptors or sensory subtypes or punctate mechanical hyperalgesia respond best to drug X, but it's patients with that sensory phenotype, plus at least moderate sleep disruption, plus low catastrophizing, plus good compliance with treatment.

You could keep adding pluses to that, I suspect, endlessly and it may be that studying interactions of those clusters of interrelated

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phenotypes winds up giving us our best predictive ability. But we're obviously going to need absolutely enormous studies to tease that out, I think.

DR. TURK: Can I interrupt?

DR. MARKMAN: Yes.

DR. TURK: As I looked at all the psychosocial predictors, they really have one thing in common. They all sort of split people or trichotomize them into levels of emotional distress, whether you want to call it catastrophizing or anxiety or depression.

I would wonder if you did a higher order of factor, if you get all those measures together in the same way they did in personality literature where they came out with the Big Five or whatever that they talk about, would you, in fact, find -- if we have a meeting in Bermuda where we could get people around with those different measures and come to agreement on what will be our negative emotional distress measure that everybody would use, we could then resolve having too many of

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these psychosocial measures that heavily overlap with each other.

DR. EDWARDS: That is spoken like a true lumper.

(Laughter.)

DR. EDWARDS: I am more toward the other end of the spectrum, although I will say right now on record, whatever it takes to get to a meeting in Bermuda, just let me know.

(Laughter.)

DR. MARKMAN: Sounds like we need a timeshare.

(Laughter.)

DR. MARKMAN: Dr. Jensen?

DR. EDWARDS: To follow-up on that real quickly, there are a number of predictive studies -- none of them are quite as large or high quality as you'd want -- that do show that pain-specific measures of emotional distress like catastrophizing or fear of pain or that sort of thing can be quite predictive or pain-related outcomes from changes in pain intensity with

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treatment to pain-related disability, et cetera, over and above the effects of more general distress-related measures, like the HADS.

You can put those things into a regression and they both independently predict some important variants in the outcome.

DR. TURK: If you put them in a factor analysis, all of those measures into a factor analysis, would you end up with some higher level factor, because you can't ask all these questions. I mean, the patient burden would be -- I don't know.

Would there be an advantage at least to having some common, relatively brief measure of emotional distress and to be very specific on the level of care, but would that help? Because my fear is -- when we wrote in one of the papers that I think you were on, we were looking at all these different factors that are important for people to consider in the AB taxonomy, and I sat there saying no one will do this, because it's requiring too much [inaudible - off microphone]. So we've

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got to simplify it. And that would be one way to -- you could use a PROMIS item bank, if you want to go that direction.

DR. EDWARDS: I think NIH would appreciate that suggestion.

DR. BARON: One word to this correlation you mentioned. In our prediction model, we did a factor analysis. I put this in. If there was a correlation, only the strongest survived to reduce the fact.

DR. MARKMAN: Dr. Jensen, and Dr. Silberberg, and Dr. Colloca. And I think that's going to be all the time that we have.

DR. JENSEN: I have a question here. Just a brief comment first. We have been doing quite a lot of effort here at this meeting to try to examine profiling, sensory profiling, genetic profiling, psychosocial profiling, et cetera.

We may come up with something which is interesting. But I think we are neglecting or forgetting something, and that is the outcome, which is, of course, the pain and the pain

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intensity.
Now, I think in general, in the pain community, we are doing astonishingly bad when we are trying to measure the outcome. We're just asking on a simple scale from 0-10, how much pain do you have.
If we're not going to dissect this further, I don't think this sensory profiling is getting us anywhere, because pain is such that -- it's, as we know, of course, subjective phenomena which is completely different from what people in the cancer world are doing. They're looking at are you surviving or you're not surviving, are you dead or are you not dead, is the tumor gone or not.
But when it comes to pain, we don't have any clue about what is behind a reduction of the pain. Is it because of the psychosocial factors that are reduced or is it because you have reduced the allodynia or something else?
We need to do better in terms of outcome and that has to be linked to the whole process of profiling.

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DR. MARKMAN: Would any of you like to make a comment?
DR. WOOLF: Can I just interject something, just to add to that? When we see this in the context of drug development, I think we should be thinking about drugs that are symptom-suppressors and drugs that are potentially curative.
DR. JENSEN: I think it's pathetic that we if we look into the human world, we're just looking on this pain intensity. But the basic scientists are using all sorts of measures. They're looking on functional behavior, they're looking on responses to Von Frey hairs, to thermal stimuli, genetic outcomes, et cetera. We're just looking on pain intensity.
DR. MARKMAN: Dr. Silberberg?
DR. SILBERBERG: I have to apologize, again, because I'm looking at this as someone from the outside and trying to wrap my brain around all the questions and the answers I've heard.
I want to go back actually to the very first question, to Clifford's question, which is you come

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up with all these tests and if we just think about the physical tests, not the psychophysical tests, and you try to stratify the patients to say who's going to benefit from a particular treatment or not, and then you treat them. If I understood Clifford's question correctly, the question was once they're treated and if they got better, if you go back and do that test, do you see a change.
Roy, I understood, you said that you don't see a change. And, Ralf, I didn't understand the response.
(Laughter.)
DR. SILBERBERG: But I think that's extremely important for the next step, because, A, you could say if it didn't improve, is that a right parameter to use; and, even if it is a right parameter, what is it telling us if you go back to the basic research? What is it telling us the fact that it didn't improve, but yet it's a predictive factor?
To try to improve on, going down the road, to improve on the prediction, if you can say, okay,

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I see this correlation, but it's not changing after the treatment, it means that it's not really part of the mechanism, it's some kind of side effect and to understand that.
I think that kind of also talks about this business all we're doing or you're doing -- I'm certainly not doing that -- measuring pain at the end, asking them, that might help to find or identify what should be done to better define getting better or not getting better.
DR. FREEMAN: A couple of things. First of all, to answer for Ralf.
(Laughter.)
DR. FREEMAN: I don't know if you know the Dutch footballer Johan Cruyff who died this year, but once he was asked in an interview how he did something absolutely remarkable.
He answered and then the reporter said to him, "You know, I don't understand." He said, "If I wanted you to understand, I would've answered differently."
(Laughter.)

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DR. SILBERBERG: I figured as much.
DR. FREEMAN: To address your question, I'm not sure. I understand what you're saying, that if it's going to change, then it should be on the pathophysiological or pathological continuum.
But I would say not necessarily. For example, I'll just give one -- just say -- and we'll pick on punctate hyperalgesia, because Clifford mentioned it. It may be that that is a phenomenon that takes longer to change, that it may take more than 12 weeks before central sensitization or whatever is driving punctate hyperalgesia changes.
It could well be part of the process, part of the continuum, but that -- and nobody, I think, in this room would argue with what Troels said about how hard, rudimentary the measures that we use as our primary efficacy endpoint in pain trials are.
Clearly, we need to think of better ways of doing it, and we need to incorporate other aspects, and we need to ask the questions differently and

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all of those things.
There are a gazillion ways that we showed and could change it, but this is the way it is and this is what we all were attempting to predict at this point in time and merely because the predictor did not change, it doesn't mean that it is not necessarily relevant or it doesn't work.
The first thing is it doesn't mean that it's a bad predictor and it doesn't necessarily mean that it's not on the pathophysiological continuum. I tried not to be on Cruyff, but maybe I was.
DR. BARON: Perhaps I should mention something, as well. I agree that with the central sensitization, allodynia and pinprick, we would assume that there is an effect.
But we look at profiles. Just imagine that a loss of the warm fiber generates the pain and is a predictor for your drug. If you treat the patients with baseline loss of warm fiber, you won't change anything in the warm threshold, because this is a loss.
But it's a predictor and you look at

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spontaneous pain at the endpoint and this is reduced. A little bit clearer perhaps? So it's not necessarily that the predictor will change as an outcome parameter.
DR. MARKMAN: I think Dr. Colloca has a question, as well.
DR. COLLOCA: Luana Colloca. Just a comment. We spoke about placebo analgesia as a model to understand endogenous pain modulation.
There are some studies currently in patients, patients with low back pain, patients with IBS, and we are learning more about this mechanism as a sort of inner-mechanism or protective mechanism to help patients to cope with their pain or also to respond to different treatments.
What I would like to say is that we don't need the placebo to study placebo effects. Indeed the [indiscernible] paradigm and some other mechanisms show that patient expectancy matters a lot.
If they expect to respond to a remifentanil,

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the front area in the brain shows an activation. If they are receiving remifentanil and we say, now, we stop remifentanil, the same areas stop to work.
We need to be careful when we look at outcome and consider the possibility to measure expectancy in patients. This doesn't require FMRI, PET or very expensive and time-consuming methods.
But at least the study that we ran in the lab, where we look at different brain imaging, [inaudible - off microphone] covariants, an interaction study, where, for example, it has been shown that endogenous opioids are released and this release in the brain occurs as a measure of neuropathy, plus specific genetic polymorphism and variance for OPRM1 helped to identify the better phenotype for placebo analgesia.
This is complex. But still asking merely how much do you expect to improve can predict this path of mechanism in our brain. But why don't we include, also, a very simple, not time-consuming and extremely cheap measure of expectancy in your profiling and phenotyping, QST, CMT, other

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measurements [inaudible - off microphone]?
DR. MARKMAN: That's a great point. I hate to cut this short. This is an incredibly stimulating discussion. But I think in the interest of time and the larger process, this is going to be our breaking point. I'd like to thank the panel, as well.
I think Dr. Dworkin and Dr. Edwards are now going to come and tie this all together and put a bow on it. Thank you, everyone.
DR. TURK: If you're interested in this discussion, the next meeting in Bermuda will continue it.
MALE SPEAKER: Absolutely.
(Laughter.)
DR. ROWBOTHAM: I was going to say, at the end of that other point, to put it in as few words as possible, you can have variables that you don't expect to change as factors, but what we're looking for is surrogate outcome measures that are more objective and are going to change, that are more objective than the 0-10 scale.

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DR. DWORKIN: Exactly. They are two different groups of measures. In fact, Kushang and I were just whispering that an epidemiology distinction is made between modifiable and non-modifiable risk factors, and Kushang pointed out the genetics are a terrific example of non-modifiable risk factors.
But BMI and HbA1c would be examples of modifiable risk factors. And so yes, that will be in the manuscript somewhere.
This is the closing session of the meeting. We have a hard stop at 4:00 because of plane reservations and people's schedules and taxi cabs.
In the almost-two hours remaining -- and we don't have to use up the full two hours, but we've got two hours -- there's really one objective.
We all have to make sure that Rob Edwards leaves here happy. If we can make Rob happy in 15 minutes, everybody gets to go home early or make an earlier flight.
The kind of operational definition of Rob Edwards' happiness is, is that he has a pretty

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clear idea in his head about the manuscript that he's going to draft that you will all be invited to be authors on.
At the point at which Rob kind of thinks it's come, this has all come together and that he sees a manuscript to draft, that as Dennis said yesterday morning, you will all have many, many opportunities to comment on, more than you want, because it's at least two or three circulations before we submit.
There are typically two rounds of reviews and several iterations to address reviewers' comments. So you're going to see Rob's manuscript over and over again.
What we want to do in the next two hours is make sure we're all on, more or less, the same page that Rob can draft a manuscript and to begin that sequence of multiple revisions.
Any questions about that? As I said, you're all invited to be authors. If you don't like the way the manuscript looks, you don't have to be an author.

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All right. So Rob and I took some time over the lunch break to try and at least come up with some scaffolding of what a manuscript from this IMMPACT-XIX meeting could look like.
We ended up with three broad sections. A first section that would be a kind of literature review, highly selective, not systematic of promising models for accelerating the development of precision pain medicine and that these promising models would span the spectrum of preclinical, translational, clinical.
I can say more about this, but let me just start off with the three broad sections. So a broad section at the beginning of the paper about promising models, exemplars.
The second section where we make general recommendations for what needs to be done to accelerate the development of precision pain medicine. Clearly, we have a consensus already on one of those recommendations, which is a series of many meetings held in Bermuda.
I don't know whether Frank Keefe will

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publish that in Pain, but we'll do our best. So a section of general recommendations that will be fleshed out in text and summarized in a table.

Then we imagined a third section, if we can do this and come to some agreement, of pretty specific recommendations, for example, clinical trials or studies that we think should be done if the money were to become available.

It wouldn't be as detailed as an RFA, but we could have a bunch of bullets of studies, that if funding was available, we think should be started next month.

That was what we came up with as a kind of broad scaffolding, the promising models for the development of precision pain medicine, general recommendations, very specific recommendations.

Did you raise your hand?

DR. PATEL: No, I was scratching my head.

(Laughter.)

DR. DWORKIN: Does that seem reasonable? Any alternatives? Because, of course, this is what the next two hours is to be.

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Clifford?

DR. WOOLF: I think it'll be critical to define what the goal is in terms of what we see precision pain medicine as being and what is actually achievable in a reasonable timeline, because I think we'd all agree we're a long way from it.

And the question is, what is the path that would bring us closer, and what are the elements that are achievable quite soon and the others that we'll be exploring for some time?

DR. DWORKIN: I think that's great. When we get to talking about general recommendations and specific recommendations, I think it would make sense to focus on recommendations that could be implemented in the next five years. But there are obviously some longer-term recommendations.

Rob and I also discussed that we need definitions and say exactly what we mean by precision pain medicine. And we'll start off asking Dr. Riley, who isn't here today, what the official NIH definitions are, et cetera.

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The way I see this paper -- I think the way we thought about this meeting is, what kinds of things should be done in the next 5-10 years that would bring to patients more targeted therapies, therapies where they're either likely to be more robust in their response. Maybe not from this meeting, the other possibility is less likely to have side effects. That's kind of the --

Shai?

DR. SILBERBERG: I'm going to say one thing and then not say one more word.

(Laughter.)

DR. SILBERBERG: Listening here for a day and a half as an outsider, my only comment is I wouldn't call it "precision medicine," because I think it's so far off to come to precision medicine.

I heard lots of terms which make, to me, a lot more sense, like the last one, which was phenotypic predictive power, to have more accurate prediction, improving clinical practice.

There are lots of terms but

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"precision" -- it wasn't defined here but in my personal opinion, it's talking about you take a patient, you say I know that this patient should get this or shouldn't get that treatment. That is, I think, so far off that maybe it's doing a disservice to call it that way.

DR. DWORKIN: To me, this is very important. I think precision -- I mean, we need to be on the same page about this before proceeding. To me, precision pain medicine would be, let's say, the Danish Demant study of oxcarbazepine replicates with beside QST, whoever's beside QST is used.

Then we can determine a 10-minute procedure of beside QST that this patient is relatively likely to respond to oxcarbazepine and this patient is less likely to respond. Is that not precision pain medicine?

DR. SILBERBERG: I think it's a matter of degree. So if you have 60 percent/40 percent difference, one has 60 percent probability that they will, the other one has only 40, so you say, I'm not going to favor that one, that, to me, is

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not precision medicine, because still 4 out of 10 would benefit from this or 4 out of 10 won't benefit from it. It depends, but --

DR. DWORKIN: But isn't precision medicine that you know what to use first line? I'm not saying you don't use --

DR. SILBERBERG: I think that's good practice. As a novice person, I think that's what you guys are doing all the time. A patient comes in, you evaluate them, you decide on the first line of treatment.

But you don't know that it's going to work. You kind of -- based on all kinds of measures.

DR. DWORKIN: What would you call what we've been talking about?

DR. SILBERBERG: I would say better practice, improved -- "precision" means, in my opinion, that you've got a very high probability that you are right. That's what precision means.

DR. DWORKIN: Bob Kerns?

DR. KERNS: I couldn't agree more. I don't think we ever heard the phrase specificity and

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sensitivity in the conversation in a day and a half.

As somebody that had a father who had cancer, when they're talking about choice of drugs, it was really much more approximating what I've come to this meeting understanding the concept of precision medicine and anything that we're talking about here.

DR. DWORKIN: Mike?

DR. ROWBOTHAM: I think there's a [inaudible - off microphone] biomarker-driven more along the lines of the cancer field, where with this biomarker, that means you definitely get that treatment and then none of the other ones.

Then there's precision pain medicine which is [inaudible - off microphone] to that. I think we're talking about here more using profiling and personalizing medicine.

When you look at a whole host of factors that allow you to give treatment recommendations that don't exclude the other treatment, they just help you prioritize which ones of the available

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ones the patients are most likely to respond to.

DR. DWORKIN: Shai, actually, I used to think of it as personalized pain medicine. Does that term make you happier?

DR. SILBERBERG: Yes. Personalized. First of all, I think that's kind of what you do anyway. It's just a matter if you have more tools or less tools to make a better decision, and that's kind of the way I took what's going on in this day and a half, is coming up with better tools to provide better personalized medicine.

DR. DWORKIN: We were using President Obama's term, but he's on the way out and by the time this paper gets published, there's going to be someone else. So we could use "personalized pain medicine."

Roy?

DR. FREEMAN: The way I think of all of this as really increasing the probability, increasing the likelihood that an intervention is going to be effective.

Now, at what point that increased

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probability becomes so strong that we will satisfy Shai that this precise is, I think, a matter of opinion.

I think somebody else may find -- I see Luana looking at me. Somebody from Italy may find that, you know, the train arrives 40 minutes late, that's pretty precise.

(Laughter.)

DR. TURK: After the humor dies down -- and I'm not being humorous. So we're not looking for perfect pain medicine. That's an impossible task to be looking for.

Can we improve upon what we have and is that precision, or precise, or whatever you want to call it?

DR. DWORKIN: Lots of people have comments on this, but I don't know that we want to spend from now until 4:00 deciding on it.

How many people agree with Shai that "precision" is too precise a term for where we are for the next 5-10 years?

(Show of hands.)

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DR. ANDREWS: You should use a phrase, something like "defined pain medicine," because, for example, with what, say, Alban's presentation, where he was understanding the idea of BCUs, biomarker paired with the analysis, raised BH4 levels and a neuropathic patient would respond to an SPRI inhibitor.

DR. DWORKIN: Nick, I think if we come up with a new term, we're going to confuse everybody. I'd like to see if we could stick with something that people are somewhat familiar with.

How many people are unhappy --

DR. FREEMAN: I was lost in my -- I got a little lost in on trains. Can I finish the thought?

DR. DWORKIN: I'd rather. And then Luana gets to revise.

(Laughter.)

DR. FREEMAN: I think that we should think of precision medicine as a goal to strive for and that's how I would present this. Whether how close we are and whether we are there, I think, is --

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DR. DWORKIN: Half the room is agreeing with Shai. How many people are unhappy with changing it to "personalized pain medicine"?

(Show of Hands.)

DR. DWORKIN: Only a couple.

MALE SPEAKER: Unhappy with it.

DR. DWORKIN: I know. Unhappy with "personalize pain medicine."

MALE SPEAKER: Can we separate the issues here? Because there's an existing NIH way of thinking about things and if we come up a totally different way and don't use their way, are we, in fact, going to be missing the way it's being talked at, at a national level?

DR. COLLOCA: I think it is a matter of contextualizing, as long as we refer to something that has been proposed at lunch, like President Obama.

We are finding this attempt to use phenotypes to target and tailoring the treatment to each single pain patient. That is the goal, tailoring treatment.

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DR. JENSEN: Bob, could I?

DR. DWORKIN: Sure, Troels.

DR. JENSEN: Just a small suggestion or proposal, because, like 20 years ago, we had a paper by Clifford, saying towards a mechanism-based classification. So maybe we could use the word "towards" a precision type of medicine.

DR. DWORKIN: We could certainly do that. There was something about accelerating --

DR. MARCHAND: It's accelerating the development.

DR. DWORKIN: Right.

DR. MARCHAND: For me, I mean, I understand what you mean, but we're just heading there. And maybe we will never be there, but at least, we're heading there.

FEMALE SPEAKER: Attempting.

DR. MARCHAND: I think it's okay like that.

DR. DWORKIN: I think we have a sense of the room, which is a somewhat greater comfort with "personalized" than "precision." I could imagine we'll -- the draft paper might have something like

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"accelerating the development of personalized," also known as precision pain medicine.

That way, we'll address Dennis' concern that nobody will get an NIH grant if we just use "personalized pain medicine." I think there's a way to have both.

But Bob Kerns is still unhappy.

DR. KERNS: Is it important to -- as soon as you start talking "personalized," contrast that with another term that people use a lot, which is "patient-centered." I know that's an entirely different kind of context and framing, but does that become important to clarify?

DR. DWORKIN: It's a different source of funding. I think that could be something reasonable in the text, yes. All right. Maybe we'll emphasize "personalized," but we'll make it clear that we're in the same ballpark as "precision."

Ian?

DR. GILRON: I'm just wondering if any of this would be easier if in the title we were to

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separate treatment development and clinical care, because psychological therapy, is that medicine? I don't know if it is. That's one issue.

Then the other issue is precision methods in preclinical development can be -- absolutely would address Shai's concerns. It'd be very precise in terms of developing treatment.

But then if we're talking about implementation in patient care, we could say personalized or tailored patient care.

DR. DWORKIN: I'll tell you what I think about that. I think this paper is not about clinical care in the community. It's about therapeutics development.

Actually, I really like your point that instead of talking about this is as precision or personalized pain medicine, the title should be changed to pain treatment or pain management so that we can talk about things like catastrophizing and cognitive behavior therapy and hypnosis, for all I know.

So, yes, let's lose "medicine," emphasize

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"personalized." So some of us can get funding, put "precision" in. I think Bob's point about patient-centered is excellent, how what we're doing is not really the same as what PCORI is focused on right now.

Can we now move to the byline of the article since we've spent a half hour on the title?

Mike?

DR. ROWBOTHAM: I was just going to say the goal is still -- I agree with Troels. We're still trying to move towards precision medicine.

Consensus Discussion

DR. DWORKIN: So now that we have, more or less, a title, any comments on this kind of structure of three sections, selective review of promising things, general recommendations, specific recommendations? Does that sound reasonable scaffolding?

Bob?

DR. KERNS: I do think it is important to kind of [inaudible - off microphone]. You said five and then you said 5-10. Especially for that

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third section, I think --

DR. DWORKIN: When we get to --

DR. KERNS: -- it's next steps really.

DR. DWORKIN: Right. When we get to sections 2 and 3 and actually start coming up with lists of recommendations, we'll see what it looks like.

When Rob and I were doing this over lunch, I think we were kind of implicitly thinking 5-10 years, but getting to Bermuda as quickly as possible.

Any other comments about this structure? Does that seem like a reasonable structure, three broad sections? Okay.

Dan? John?

DR. CARR: I like the structure. But are we not actually directing the effort toward something like advancing process of development of pain?

We're talking about the process. We're not talking about individual things. Advancing the process, words "personalized" or "precision" pain medicine, because I think the effort overall is

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talking about the process, not specific things.

DR. DWORKIN: Why don't you hold that and let's see what lists of recommendations we have and what the best way of characterizing our general and our specific recommendations would be?

Okay. So for the first section, and here, it's just like Rob and I having a couple of thoughts over lunch. This is really just to get the discussion going.

When we thought about kind of promising models, exemplars of precision, -- of kind of what's going on in our field that's sort of a foundation for thinking about the next 5-10 years of advances -- Luda, I haven't said anything yet, but go on.

DR. DIATCHENKO: No, no. I'm sorry. I thought you were asking a question.

DR. DWORKIN: No, I wasn't asking a question. So what we thought in terms of a preclinical/translational arena of what we heard the last two days, clearly, anti-NGF antibodies are on the horizon and have an interesting and

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worthwhile to look at briefly preclinical/translational history.

I was thinking of -- Nat gave a presentation last year where he talked about the intense effort that went into the preclinical development of anti-NGF antibodies. Setting aside issues of safety and tolerability, that's a success story.

Then a second example, of course, is Nav 1.7 and inherited erythromelalgia and genetic loss of function, gain of function situations. The two exemplars, if you will, that we came up with were anti-NGF and kind of sodium channels and what we've learned from rare genetic conditions.

If that sounds reasonable to you, we would hope -- we would all very much hope that Nick, and Luda, and Alban, and Clifford, and Andrew -- Andrew still here? Yes -- would help Rob in drafting -- and Nat certainly would help Rob in drafting together a kind of preclinical/translational two or three models and exemplars.

We didn't include in that very first bucket

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BH4, only because there isn't yet kind of a translational component. You don't have any human data.

While the preclinical part is very compelling with kind of sodium channels and anti-NGF antibodies, the story is a little bit better as a model, because you've got that translation into the clinic.

But you all who know the preclinical and translational world, let us know if there are other examples in addition to those two.

DR. DIATCHENKO: I made my career on CMT. CMT, we just did a full review on all genetic data, just released in Neuroscience. So CMT continues to be the most cited gene in the human pain genetic.

CMT has all the components. It has association in an animal model. Actually, I mean unlike GCHI, it does have a clinical trial. It has been done with propranolol, a control for CMT genotype. So it actually went through a whole cycle.

A lot of discussion here, it's neuropathic

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pain, which CMT is not contributing to. But in the musculoskeletal CMTs, it's a very strong evidence for.

DR. DWORKIN: I can't imagine a reason to object to adding that CMT and your propranolol trial to this now three examples of promising avenues of development for personalized pain medicine. We have three examples of kind of in the preclinical/translational arena.

Does that sound reasonable to people? These are just examples. So if a reviewer at Pain, where we will submit this, says, "You haven't done a systematic review." We say, "Yes, we haven't done a systematic review. We're not even sure what a systematic review would be of preclinical research that's relevant to precision pain medicine."

We will be really unabashed about saying these are just examples of what we think is promising in terms of preclinical research directed towards precision/personalized medicine.

Yes?

DR. DIATCHENKO: We did a full review and

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the CMT is the most cited gene in musculoskeletal and Nav 1.7 is the most cited in neuropathic pain. I mean, that's it. We can focus on them, right? We have a formal reason to focus on these two.

DR. DWORKIN: Perfect. You will send us that review, right? Excellent.

DR. DIATCHENKO: I can help write this.

DR. DWORKIN: This is great. This is the point of the day where everyone is so tired, everyone starts to get agreeable.

(Laughter.)

MALE SPEAKER: That's a trick you use.

DR. DWORKIN: In the same first section of the article, we obviously want to give some clinical examples, kind of promising avenues of clinical development.

Some of these seem kind of really noncontroversial, because it's what we've been talking about for the last two days. One is obviously the distinction between irritable and non-irritable nociceptor phenotypes, profiles, whatever we call it, because the best study we have

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so far in this domain of personalized pain medicine is the Demant study of oxcarbazepine. That would be one example to describe.

Andrew?

DR. RICE: The difficulties of doing preclinical systematic reviews, I take. We do them, so I can tell you how difficult they are because of the volume.

But I think there's a strong chance of confirmation bias here that we're looking towards the one study, the two studies that really confirm our hypothesis.

Actually, the literature isn't that large. I think a systematic review of that area would be more valuable and will enhance the article.

DR. DWORKIN: Say more. What do you have in mind by a systematic review, of what?

DR. RICE: We say how we've searched and we say --

DR. DWORKIN: No, no, no. I know that. But what are you searching for?

DR. RICE: Clinical trials that have set out

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to look at whether you can relate to response. If we have done the systematic reviews, we don't know, there may be some, in some obscure part of the literature, it doesn't.

DR. DWORKIN: We've had over 50 pain specialists in this room for two days. I think if there is a clinical trial published somewhere that pre-specified a kind of stratification hypothesis, like the two Danish studies of lidocaine and of oxcarbazepine and nobody in this room knows about it, I'm comfortable ignoring it.

I don't know that we need to spend resources and time doing a systematic review. That's my personal feeling and I've actually argued with Cochrane people about this.

I'm not so interested in the study that was published in the Outer Mongolian journal of pain therapeutics if none of us have heard about it. I know that's kind of an outrageous thing to say but I think with the people in this room --

DR. FREEMAN: Can I just make a quick comment? I agree with you and I don't think a

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systematic review is necessary.

But I could not help but notice, with respect to the two Danish studies, that both address a specific hypothesis with a specific class of drug. I would think that the one that was a positive study was quoted probably 10 times more frequently at this meeting than the one that was a negative study, negative in support of the hypothesis.

I think we just need to be careful, not so much about publication bias, but about result bias in doing this non-systematic review.

DR. DWORKIN: I seemed to recall there was an editorial published along with the lidocaine trial that argued -- was it you, Ralf -- that while technically, it was negative study, boy, if you look at the data, it's what the FDA might even consider very supportive.

DR. FREEMAN: No arguments. But I think the point still stands.

DR. DWORKIN: But I think we can trust Rob to point out that there was one positive study and

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one negative study but that the negative study could be viewed as supportive.

Shai?

DR. SILBERBERG: Bob, as an honorary Mongolian --

(Laughter.)

DR. SILBERBERG: -- I want to explain what I think Andrew was saying. For the specific examples that you gave, that you're considering talking about, the anti-NGF, the Nav 1.7 and so on, to have a comprehensive evaluation of the literature, a systematic review, to make sure that you've looked all the data out there, not only cherry-picking the ones that fit kind of the model would, I think, make the paper a lot stronger.

we covered all the literature on this specific topic and it all suggests this or there's strong evidence for this or it's not that strong.

DR. DWORKIN: I don't want to beat a dead horse. If you all think we need to do systematic reviews of anti-NGF antibody preclinical research, of sodium channel preclinical research, of COMT

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preclinical research and then a clinical research on even the things on my piece of paper that I haven't gotten to, I suppose we could devote six months of resources to doing a series of eight systematic reviews.

I guess I personally don't see the need for systematic reviews when we are saying upfront that we're just illustrating a process. We're not saying we've done a comprehensive review of the literature. We're not making treatment recommendations. We're illustrating something.

Andrew, you started this so what do you think?

DR. RICE: As usual, Shai has put it much more eloquently than I can. I think exactly as you put it.

DR. DWORKIN: You both think to illustrate something, to say, This is a really nice example of X, that we can't say that until we've done a systematic review?

DR. RICE: There might be really good examples of why showing the opposite. We don't

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know until the literature says empathically by cherry-picking the one or two papers that support the hypothesis.

DR. DWORKIN: But we're not going to conclude that because of some studies that are disappointing, like the topical lidocaine Danish study, that we're going to abandon the development or the hope of precision pain medicine.

You all realize the enormous resources to do a series of half a dozen or more systematic reviews that we wouldn't really intend to publish, but are just so that we could put a sentence in that we did a systematic review.

(Crosstalk.)

DR. FREEMAN: Can I just comment quickly? This is going to save hundreds of hours if -- I totally agree with your point over here. You are using selected and I think it's quite reasonable to say these are cherry-picked pieces from the literature to buttress an argument.

It doesn't mean that there is not a counterargument but you are cherry-picking in order

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to support an argument to take things in a certain direction.

I think a systematic review is a different story and there you would want to give a balanced -- but I think as long as you say explicitly these articles are taken from the literature to support our position, I think that's fine.

DR. DWORKIN: I guess, Andrew, to me, you're saying you can do a systematic review and come up with the other conclusion.

But I can't imagine that there would be anything in the literature that would lead to a conclusion that we recommend efforts to develop a personalized pain medicine should be abandoned.

I personally can't imagine that Rob is going to write an article where that's the conclusion, let's abandon talking about irritable nociceptor phenotypes or sodium channels being relevant to some patients rather than others.

If we can't imagine that outcome -- and as Roy said, we're just illustrating some things, why

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do we need to check on what was published in Outer Mongolia? I still don't get it.

DR. RICE: I'll concede. But I think Roy's point is explicitly pointing out that we haven't done that and we cherry-picked, it should be in the manuscript.

DR. DWORKIN: We are now routinely getting the comment when we submit IMMPACT manuscripts to Pain, "You haven't done a systematic review." And we always say, "Yes."

If we haven't already got the sense in the article, we had a sense saying, "We have not done a systematic review." However, is everyone happy enough with that that we're not going to six or eight systematic reviews?

(No audible response.)

DR. DWORKIN: Okay, great. Irritable versus non-irritable nociceptor, the positive and the negative, but perhaps supportive study. Another example obviously is kind of the role of abnormal CPM, DNIC as a potential avenue for accelerating the development of precision pain medicine.

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We haven't talked about central sensitization, but maybe there's a story to be told about central sensitization and NMDA receptor blockers.

Then I think most of us found Dennis' presentation, combined with Rob's presentation this morning very compelling that we don't want to leave out -- along with Ralf's data, don't want to leave out talking about and giving examples of a personalized pain treatment, not medicine, involving psychosocial profiling and presumably psychosocial treatments.

That would be a bucket of three or four clinical examples of what we've been talking about. Irritable versus non-irritable, conditioned pain modulation, central sensitization perhaps -- and Alban, we'd need some help from you about this, because you're the expert -- and then also psychosocial.

Do those seem reasonable? Did we leave anything out?

Ajay?

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DR. WASAN: Two quick comments. One is I think we should have at least a sentence or two about why we're not discussing pharmacogenomics, because that'll be -- it's off and on people's concerns. That's the one.

DR. DWORKIN: Absolutely. Let the record say that, because we do need to say that and that goes into sentences we have early on in the article about what we consider beyond the scope of the present effort.

DR. WASAN: Yes. And the second comment is that on the psychosocial section, you could pull in some of the discussion we've had about placebo, because if you do precision medicine for placebo and you're identifying those likely to respond to placebo, you've inherently identified a group who is better at pain modulation.

That gets to the psychosocial profile and psychosocial treatments, in mind, body and treatments, and pain self-management treatments. That's something to think about. You could tie some of the placebo piece into that and it's

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another aspect of precision pain medicine.

DR. DWORKIN: If you and Luana are willing to help us, I think I kind of -- I guess it's a fifth bucket in this section and we're really only talking about a paragraph or two at most, would be something like profiling to identify robust placebo responders. That would be a very cool, I think, thing to add to the paper.

DR. WASAN: My own little editorial for five seconds is that any study that has a placebo arm and is a precision medicine study that has a placebo arm and you do the same kind of analysis in a placebo arm, you actually doubled your search.

You've inherently potentially doubled the impact by applying the same techniques to the placebo arm in any study you do. That would be another comment I would put into that section.

DR. DWORKIN: Maybe Ralf knows or somebody else. Has anyone ever attempted to use either QST or CPM to identify a robust placebo responder? In other words, what is the sensory profile of a patient who gets a 30 percent or greater pain

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reduction with placebo?

DR. MARCHAND: I would be happy to hear what Luana has to say about that. But we manipulate the CPM with placebo manipulation and it's working very well, just like other people have manipulated the effect of morphine, for example.

DR. DWORKIN: But I think I'm talking about something different, which is kind of sensory profile, identify a healthy placebo responder.

DR. BARON: To my knowledge, not with QST or with CPM, but if it comes to Roy's data with the NPSI, we looked at this in the placebo arm and there are differences in NPSI profiles predicting a large placebo -- unpublished, but you can do it.

DR. DWORKIN: Nat?

DR. KATZ: This is unpublished, too, but we've done -- in our explorations of this whole accurate pain reporting paradigm, we've done now two randomized controlled trials, as well as an intervention study where it turns out that in this thermal -- not just thermal stimulation paradigm where we're measuring how accurately people report

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their pain, it turns out that the people who have a high variability in reporting experimental pain, they also have much larger placebo responses than people who have low variability, as well as a larger separation between the drug and placebo.

We just finished this interventional study, where we did a randomized controlled trial of training people to report their pain more accurately versus not training them and everybody got pregabalin or placebo.

These are patients with painful diabetic neuropathy. It turned out that the people who are trained to report their pain more accurately had a much lower placebo response and a larger separation.

This is all going to start rolling out into the literature, but it does seem like there's a very close connection between variability and experimental pain and the propensity to respond to placebo.

DR. DWORKIN: This is wonderful. Thank you, Ajay. We will have a couple of paragraphs on sort

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of profiling, placebo response and placebo responders with help from Luana and Nat.

Ursula?

DR. WESSELMANN: Yes. But Nat just related to the difficulty of some pain patients to accurately sense an external stimulus or an external sensation. That might apply actually to a lot of tests that we give, not only to the response to a given drug or a given interaction.

DR. DWORKIN: Some of these factors we've talked about at previous IMMPACT meetings and in previous publications. Anything else as possible clinical models of promising avenues for the development of personalized pain treatment?

Luda?

DR. DIATCHENKO: I thought that maybe in the first section, when we talk about what is known today, especially because it's personalized medicine, biological markers are -- it's a big part. We use psychological and phenotypic markers, but biological markers are important.

Maybe it should be two, three paragraphs

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talking about what has been done so far with the molecular markers. Maybe you see this in a different part of the manuscript or maybe you see it outside. But I would think this is something which would be to say there is not much that has been done.

As I said, we did some systematic review very recently on what has been done at all on genetic of chronic pain condition. And so one surprising thing we found is, okay, so by diseases, who did most of the studies?

Well, migraine by far, followed by actually musculoskeletal. From those, surprisingly, TMD is like number one. Neuropathic pain is like almost the last in all the studies, which has surprised me hugely because there is so much basic research in animal study done on the neuropathic pain, but somehow not genetic.

Again, I would suggest to put it in -- we can write feasible, about more -- other molecular markers. But in terms of genetic markers, my message will be we didn't do it enough yet. We did

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so much so far and there is something which we need to continue to develop.

DR. DWORKIN: We actually have to have what you just described because the previous -- well, two of the most recent IMMPACT meetings, and one article is in press and one article is being revised for resubmission, were on biomarkers and on phenotyping.

So there's going to have to be some discussion of how the recommendations we've made for biomarkers -- and Shannon has spearheaded that article -- and how the recommendations we've made for phenotyping kind of dovetail or not with what we're now saying about precision medicine and also as you point out, what we haven't included, what's been beyond the scope of all three of those efforts.

John?

DR. MARKMAN: I know there was a point made earlier that I missed, part of about rehabilitation type testing and outcomes. I'm very interested in symptom-specific functional testing in low back

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pain syndromes.
For example, matching treatments to patients for problems such all right neurogenic claudication and spinal stenosis for either drug treatment or surgical treatment.
To me, if we could think about the ways that symptom-specific activity limitations, specifically pain symptom could be a way to think about optimizing treatment matching as well for precision. I'd be happy to write that sentence or that series --
DR. DWORKIN: Yes, that could be in the psychosocial bucket if we define psychosocial as including physical functioning, et cetera. Absolutely.
DR. MARKMAN: I appreciate it.
DR. DWORKIN: Andrew?
DR. RICE: Can I just make one very niche point that you may or may not think merits just a single sentence. It relates to Luda's point about genotyping.
The human genotype in a small niche area is

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not the only genotype that's interesting for outcomes and that's in the context of neuropathic pain and infectious diseases, which is my area of interest.
Particularly for HIV neuropathy, the virus is routinely genotyped and it's a fantastic example of precision medicine actually because the prescribing of antiretrovirals is dependent on that these days.
The viral proteins that may cause the neuropathy are dictated by the genotype of the virus. That information is routinely recorded in all HIV patients' files, the genotype of the virus.
I think you probably know also that Judy Breuer is very interested in the genotype of Varicella-zoster viruses and whether they might cause neuropathic pain. But the first piece of information for HIV patients, viral genotype is already available in all their case notes.
DR. DWORKIN: We clearly have to say something briefly about these questions, because we want to be specific and clear about what we're not

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including. So yes, we should add that. So you stay on top of that. If it isn't in the first draft, make sure it gets added.
Okay. Let's move on to -- now, it gets to be more fun. These would be recommendations we would make and some of these recommendations are kind of -- at least what Rob and I came up with as possibilities are pretty strong.
Maybe on the first one, everybody agrees on. The first one on the list, and there's a lot of discussion about this, is we kind of I think strongly recommend that efforts should be devoted to developing and validating bedside approaches -- bedside meaning something that can be applied in the clinic in phase 3 trials and in clinical practice.
Bedside approaches to phenotyping, sensory profiling, developing measures that can be done in the bedside and this is true of QST, of CPM. And we talked about earlier today, translating the hour to hour-and-a-half DFNS protocol into something that ideally your primary care doctor could do in

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five minutes.
We feel that that really is a kind of top priority to develop such clinically feasible or feasible in the clinic measures of sensory profiling and that -- this gets a little bit kind of provocative -- and that we think that consensus measures should be developed, that we think that if what our goal is to accelerate that the purpose of acceleration is not served by having three different bedside QSTs and six different bedside CPMs.
We won't talk about Bermuda in the article but the offer does stand that it seems like this group consensus that getting consensus measures of bedside QST, consensus measures of CPM is really a priority. Otherwise, precision medicine is not going to advance. That would be a first very strong recommendation.
Lee, I think we also put in that this should be done according to the drug development tool guidelines, if that --
MALE SPEAKER: But this raises the question

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that takes me back what you started out talking about, the purpose of the work.

Besides highlighting all the stuff that's going on, are we talking about a tool, such as the QST that you'd put together by consensus, that would be used for drug development and drug approval or are you talking about a clinically applicable bedside test for the primary care practitioner to use to perhaps choose different therapies under different circumstances?

If you are talking about that, the latter, you don't need to go through the process of doing a DDT program but you cannot use it in the context of getting drugs approved.

Under those circumstances, I do think you need to have some clarity. We have this problem in lupus. We have these ridiculous outcome measures in lupus that nobody can understand in the context of the clinic so nobody uses them. And they don't work in clinical trial design to give us new drugs as opposed to a lot of other things that we use in rheumatology.

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In the context of this, since we're doing it from scratch now, using what people have created as implementation issues, it should have a clarity about what you want to use it for.

Anything you develop for a drug development tool can be used in the clinic if it's easily acceptable. The alternative is not true. The former is going to take resources, a lot of resources.

The latter may not be, just opinion. So I think we have to get clarity about what we want. I would opt for a DDT tool to give us both opportunities sooner for newer drugs than later.

DR. DWORKIN: I think we have to address that, because I think if we're talking about phase 3 trials, I'm not going to be doing a phase 3 trial anytime soon nor is Rob.

Then it really is DDT and it has to be that our bedside CPM is something that can be used in a phase 3 trial and end up as part of the drug approval.

Mike?

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DR. ROWBOTHAM: I would say that going along with some of these things that are being said, especially since we are talking about moving towards precision pain medicine, we really should include a recommendation that blood sample be obtained and biobanked in such a way that you could look at expression profiling more than just regular gene sequencing. You may want to include something that's relatively easy to obtain in a complicated process and analyze [inaudible - off microphone].

DR. DWORKIN: Ian?

DR. GILRON: Getting back to QST, is there a need to say that we have to do more validation in terms of stability over time or susceptibility to ongoing treatments?

DR. DWORKIN: If consensus was achieved on a bedside QST measure, clearly part of the validation of that approach would involve exactly those things.

It's not going to get anywhere with drug development tool qualification unless you've got

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reliability and boatloads of validity. That would be a critical part of developing, validating, qualifying bedside QST.

Now, what starts in Bermuda doesn't stay in Bermuda. It extends for years afterwards.

Kristin?

DR. SCHREIBER: Kristin Schreiber from Brigham and Women's. Because I want to go to Bermuda, too, I wanted to also just bring up one thing, maybe a little too specific but hasn't been touched on.

In terms of QST, so for certain conditions, it makes sense to do testing at the site of most pain which is what I think has been done in a lot of these studies.

But other types of pain and even pain prediction, like for example, chronic post-surgical pain which hasn't happened yet, the testing is done in an area that's not currently painful.

It would just be nice to address how do those two things relate, the QST that's done at the site of injury and sort of the QST that's done as

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an assay of someone's nervous system processing.
DR. MARCHAND: Can I comment on that? I think it's really important but it's important also in patients. I think even if you want -- every time you do -- maybe it should be in the report.
If you do a test in a patient, you need a side where you have no pain I mean just to be sure that the measuring you're doing -- if you have normal data and everything, then it will apply for both cases.
DR. DWORKIN: Is that Gary? I can't see back there.
DR. WALCO: It is. Gary Walco, Seattle. Being the token pediatric person at this meeting and given that I need to leave in a couple of minutes to catch a flight, the only thing I would love to include somewhere in this document is that we really need to have a developmental lifespan perspective to see how whatever we do may apply to the younger people and the older people and not just assume that it's all static.
DR. DIATCHENKO: Longer, I would say,

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because otherwise other people will be upset.
DR. DWORKIN: Sorry, Serge.
But you're absolutely right. These considerations have to be part -- and Kristin's point have to be part of the development of the bedside QST because you've got patients where you could do a contralateral side --
DR. WALCO: Absolutely. Absolutely.
DR. DWORKIN: -- other patients where you can't.
DR. WALCO: Exactly.
DR. DWORKIN: Then your point about are we only testing the affected area or do we want to know if there's widespread augmentation or whatever we call it. It's not going to be a two-hour meeting in Bermuda.
Yes, Ralf?
DR. BARON: Perhaps we should consider to include one sentence about questionnaires because we -- I have seen some signals with the LANSS with Nat's study and we with PainDETECT.
Perhaps many of you know that we developed

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or we are in the process of developing a new questionnaire which is called PainPREDICT exactly for this purpose together Pfizer.
This is much more extensive than PainDETECT and the others and is capturing nociceptive, as well as neuropathic kind of symptoms, what we think is symptoms. This has been validated due to the standards you would like to see but it's not published yet. That's the only problem. Perhaps you can tell something about this.
DR. GOLI: Thank you for that information. This is Veeru from Pfizer. I just wanted to add there's a validation study done on that tool that took us a couple of years to complete. We are actually in the process of having a publication plan that has just been finalized so we are hoping to, with Ralf's help, have that data available soon.
DR. DWORKIN: So this would be used for profiling.
DR. BARON: Yes. It's profiling based on patient-reported outcomes just from patients. But

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we tried to capture some evoked types of things so if you are in contact with heat, what do you feel, without touching the patients, just a questionnaire.
DR. DWORKIN: Roy?
DR. FREEMAN: This does remind me of an issue which I think is, in a way, quite critical particularly once we are beginning to think of instruments that might be used communally.
That is public domain versus non-public domain. I think some comment should be made in this sphere. I realize that this is a sensitive issue but I think it's one that's worthy of -- at least worthy of discussion. The Pfizer involvement did remind me of this.
I also want to say there are other islands. Bermuda is not the only other island.
(Laughter.)
DR. DWORKIN: Okay. It sounds like there's agreement on the need to develop consensus profiling methods.
Second, this seems like a low-hanging fruit

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to Rob and me as a recommendation: to devote efforts to conducting post-hoc analyses of existing completed clinical trials, to interrogate existing data to see if there's any kind of predictors of treatment effect modification in all the anti-NGF trials which have probably now cost over $1 billion if you look across the three or four companies that developed anti-NGF antibodies.

In NSAID trials, think about all of the rofecoxib, etoricoxib, celecoxib trials that were done in the late '90s and early 2000s and can we go back into those data and look and see in a kind of mining approach that Ralf talked about this morning about, are there profiles of clinical and demographic baseline characteristics that identify kind of robust responders and distinguish them from nonresponders?

That seems like a really easy recommendation for us to make that to the greatest extent possible, interrogate existing databases. Does anyone want to add to that, disagree with it? It seems painfully obvious and reasonable.

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MALE SPEAKER: I want to point out that if you begin to do that, there are actually a series of studies that were done by officially Searle, then Pharmacia, then Pfizer that looked at the -- they called the APS outcome of acute pain which is that pain in the first seven days versus -- because most of these were longer-term trials.

But there is a whole bunch of data that sits there as it relates to the first seven days of responsiveness. And that could also be interrogated to determine differences in that context.

DR. DWORKIN: This is sort of like Gary's -- Gary's argument was we shouldn't forget kids. Your point is let's not forget acute pain.

We've really focused on chronic pain for the last day-and-a-half but I don't think anything we've said is not also potentially applicable to acute pain. Absolutely.

Troels?

DR. JENSEN: I'm sorry just to take up a

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point that we discussed earlier and that was the issue about systematic review. I know you hate it.

(Laughter.)

DR. JENSEN: But sorry about it. I don't think you need to necessarily do a systematic review of all sorts of things of phenotyping and et cetera. But in terms of a pharmacological treatment, I think it might be necessary.

The reason for that is I'm not sure if we are having all the studies. For example, in post-surgical pain, I think there might be studies -- I can't give you the studies here but I think there might be studies where people have looked into predictors for finding a response to a treatment. Maybe one of Henrik Kehlet's studies could be an issue.

I think it would be -- as I said before, I think this paper would be much stronger -- you don't have to do systematic reviews of all other things because the reason why we're having this is that was the studies of irritable nociceptors and we just present that.

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Then make the argument that you'd have to do systematic reviews of the other things later on. But I think there might studies here if we are neglecting.

DR. DWORKIN: If we're going to add acute pain, obviously acute post-operative pain is a reasonable thing --

DR. JENSEN: No, I'm not talking about acute. I'm talking about people with long chronic-standing type of pain. Some of the post-hernia studies, there was a post-hernia study, for example, where they did also topical application of lidocaine.

I think they tried to identify patients before and after so --

MALE SPEAKER: [Inaudible - off microphone].

DR. EDWARDS: I think there are multiple aspects studies --

DR. JENSEN: Also, one on QST on hernia. There is an issue there, I think.

DR. EDWARDS: Sorry, Troels. I completely agree. Just wanted to clarify one thing, did you

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mean a systematic review of studies that predict individual variability in acute and chronic post-operative pain or studies of, let's call them, peri-surgical anesthetic interventions that might be reduce the incidence of chronic post-operative pain or do you mean in an established group of people with persistent pain after surgery?

DR. JENSEN: I mean patients that had already some chronic types of pain and where people were identified before an intervention was done.

DR. EDWARDS: Okay.

DR. JENSEN: A little bit similar to what we did in our oxcarbazepine study.

DR. EDWARDS: Got you, yes, I think that would be wise to include.

DR. JENSEN: I don't think it will take a lot of effort to do something like that.

DR. DWORKIN: We can certainly ask Henrik, if we haven't found something, does he know of anything that we should look at or to look for.

Okay. So to move on to something a little bit more controversial as a recommendation, as a

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general recommendation.

Something like resources permitting, we believe the proof of concept trials should include assessments of patient factors that are hypothesized to modify the treatment effect of whatever is being studied in the phase 2 trial.

So a pretty strong recommendation that if you have a treatment and you're doing a proof of concept phase 2 trial of it, we think the investigator should think about, are there any patient factors that he or she would hypothesize modify the treatment effect? And if that investigator can come up with a hypothesis, include the measure in your phase 2 trial.

It's a strong recommendation, but we start off with resources permitting and so if you ain't got the resources to do it, you don't have to do it.

But if you're a large pharma company and you've got some treatment in phase 2, spend a little bit of time thinking about whether there's a sensory profile, or catastrophizing as a

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psychosocial characteristic, or whatever that might modify the treatment effect and put it in your phase 2 trial.

Nat?

DR. BARON: Put it in, in terms of stratification or post-hoc?

DR. DWORKIN: Well, put it in to at least assess it and then whether you stratify or post-hoc is really up to the investigator.

Nat?

DR. KATZ: I personally agree with that but I have a supplemental question which is, it seems like what we're talking about now are what I might call generic approaches, like do this in every study, and don't think about it too much and use the off-the-shelf thing, and whether it really marries up to the disease you're studying or the drug that you're testing.

That's not what we're talking about now. I wonder if we could go beyond that and maybe provide a little bit more direction in the paper about how investigators or companies sponsoring studies could

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think in more detail about the actual disease that they're studying.

Maybe there are some biomarkers or some ways of fine-tuning diagnostic categories that might give more of a sense of like what disease factors they're studying and do that in concert with their drugs.

I'm thinking about Simon's presentation, for example, how they went through this very beautiful elaboration of the biology of their disease. And I thought about how that married up to the class of drug that they were studying. And then that led them to consider certain ways of testing patients and considerations of certain biomarkers.

I know that the Biogen did a similar exercise in another recent program and other companies are a little more aggressive about looking for sort of biomarkers.

I showed the biomarkers of OA for safety but one could also imagine using biomarkers of not only OA but other disorders for efficacy. It's been done in RA where inflammatory subtypes have been

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looked at.
I don't think we should just leave this to our paper, but I think we need to go beyond that.
DR. DWORKIN: If I'm understanding you correctly, it's a great paragraph or two where we kind of provide a little bit of guidance about what it really means to think about the mechanism of your drug or other kind of treatment, the indication that you want to study it in and how to develop hypotheses about treatment effect modification, and then go from those hypotheses to actually doing some kind of profiling, phenotyping. That's a great discussion, a couple of paragraphs.
Nick?
DR. ANDREWS: Is there any sort of reason to at least put a little bit of lip service to the FAAH inhibitor that Pfizer talked through which actually flatlined? There was a beautiful example of target engagement and increase in the biomarker, which was the endocannabinoids.
It sort of goes against what we've -- it's the negative reason -- I don't know. Is it

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something worth considering?
MALE SPEAKER: Wasn't the biomarker a sort of -- it wasn't an outcome biomarker. It was whether they was target engagement with the drugs. It's not strictly relevant here, is it?
MALE SPEAKER: [Inaudible - off microphone].
MALE SPEAKER: It is?
MALE SPEAKER: [Inaudible - off microphone].
MALE SPEAKER: No, but it's not a biomarker that -- it was looking at variation between individual patients.
DR. DWORKIN: Let's investigate this offline, because I remember having some concerns about that trial that made me feel it wasn't definitively negative in a way that I would've wanted it to be definitively negative before abandoning the whole program.
Simon?
DR. TATE: I just want to comment about incorporation of phenotyping into phase 2 studies, which I agree with the recommendation, by the way, and we are going to start doing this.

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But my point relates to standardization in a multisite study, because we actually incorporated the step protocol into our radiculopathy study and it wasn't that easy in terms of making sure that even within a country that you have standardization of the protocol across all the different sites.
Actually, what we ended up doing in Denmark in that study was having study nurses travel between sites to carry out the procedure.
So I wonder if we can actually put some couple of sentences in towards how this is going to be carried out in a multisite phase 2 study which can be up to 40, 50, 60 sites in 10 to 15 countries. That is a realistic concern.
DR. DWORKIN: That's closer to phase 3. I think we were thinking phase 2, but --
DR. TATE: In these rare pain conditions, then you have to go out to quite a few sites.
DR. DWORKIN: I think we all completely agree that we need -- we have to put front and center feasibility. I don't think there's anyone in the room who doesn't think that that's been like

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the --
DR. TATE: I don't think it's difficult per se. I just think it's just to recognize that we have to pay attention to that standardization.
DR. DWORKIN: Yes. Roy and I had a personal experience with this that was compelling.
DR. FREEMAN: The videos that I showed were part of that process which --
MALE SPEAKER: A quick question. The last recommendation, did you mean something different than the other recommendations in the phenotyping papers, because very similar recommendations are in the phenotyping papers that we put out. Is there something different or am I missing something?
DR. DWORKIN: I think the phenotyping paper was about specific measures. This is a strong recommendation to come up with hypotheses and implement phenotyping in a phase 2 trial.
MALE SPEAKER: Okay.
DR. DWORKIN: I don't know that that was in the phenotyping paper.
DR. EDWARDS: Yes, the most recent

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phenotyping paper, the one that's in press in Pain did focus pretty heavily on recommendations for specific measures of phenotypes of interest that were identified.

For example, we recommended the HADS if people were wanting to measure general emotional distress. And I think we recommended the DFNS protocol when possible as a sensory profiling phenotype, et cetera, et cetera.

DR. DWORKIN: We're going to get pushback on a strong recommendation to implement profiling/phenotyping in all phase 2 trials. But let's try and see what we get.

Another recommendation that just seems kind of straightforward, we didn't really talk about adaptive clinical trial designs but certainly, there are types of adaptation that could be implemented in phase 2 that would limit the number of subjects, give some early readout on whether the phenotyping is making a difference.

I think this is really a two- or three-, at most four-sentence recommendation. And we get some

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input from biostatisticians to consider the use of adaptive Bayesian, interim, however we talk about it, analyses as a way of kind of reducing the number of subjects that stratifying, of course, increases.

I think several years from now, we'll have an IMMPACT meeting focusing on those kinds of designs we haven't yet.

Kristin?

DR. SCHRIEBER: Would that include enrichment for a certain population? I mean obviously not all --

DR. DWORKIN: We'll get to that at least by -- in terms of how I think of enrichment. And I think the FDA has addressed that a little differently.

That was a recommendation for phase 2. For phase 3, how about this? It doesn't seem so controversial. When the evidence base is sufficient -- it's not clear that there are many examples of it being sufficient.

But when the evidence base is sufficient in

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a phase 3 trial, stratify randomization or at least conduct assessments that allow you after the fact to stratify the analysis to determine whether some patient factor has a modifying effect on treatment outcome.

The key phrase there is, in terms of phase 3, is when the evidence base is sufficient. And, boy, Rob and I couldn't come up with very many examples at the present time where there's a sufficient evidence base that you would actually implement stratification either in terms of randomization or analysis in a phase 3 trial.

Lee?

DR. SIMON: It's really important to recognize that you're saying two different things. One is post-hoc analyses looking in screening for things that might mean that or are you specifically talking about --

DR. DWORKIN: Prospective.

DR. SIMON: -- a priori defined events.

DR. DWORKIN: A priori.

DR. SIMON: But then you have to then do

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either balanced randomization predicated on that or stratification predicated on that.

Because you can just imagine what will happen. People get scared of the stratification because of the 40-percent increase numbers that are necessary and then they won't balance randomize. And then it's uninterpretable.

You have to insist that if we're going to do this kind of profiling, they must actually at least do balanced randomization for that. It's the insisting part that puts this as an obligation.

DR. DWORKIN: At least to the extent I understand these issues, that gets us into kind of statistical questions about kind of the prevalence in your --

DR. SIMON: But you're talking phase 3. If you want it to be interpretable --

DR. DWORKIN: Absolutely.

DR. SIMON: People will not assume that. If you're talking about profiling, they won't assume that they have to do something unless you tell them.

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DR. DWORKIN: No. We will have to -- we will definitely put that in. And this is not a recommendation that's relevant for the next five years. This, I think, is in the bucket of 5-10, at best, years.
DR. SIMON: At least.
DR. DWORKIN: Right. We're really not talking about anyone doing that kind of phase 3 trial now, with only one possible exception that we could think of that we'll get to in a minute.
Ian?
DR. GILRON: I just wanted to follow up with that, at least that maybe there are a few sentences to follow that to say what if 10 percent of the population have the phenotype that responds and then what's the regulatory response to that.
DR. DWORKIN: That's exactly Lee's question, right, how you're going to design the trial. And it goes back to the FDA guidance we circulated.
The FDA, not unreasonably, wants to know if you're going to say the treatment works better in this group, does that mean it doesn't work at all

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in this group, or the treatment effect is half the size of this group and you can only find that out if you have both groups of subjects. That raises power issues.
We really appreciate that Lee has agreed to spearhead the drafting of the phase 3 paragraph.
(Laughter.)
DR. SIMON: As long as you don't want to do a post-hoc.
DR. DWORKIN: I think that was an earlier recommendation that when you've got -- when you've got rofecoxib data lying around and you have nothing to do, do a post-hoc analysis to see if anything predicts rofecoxib response.
Mike?
DR. ROWBOTHAM: I think there's two things that are being discussed right now. One is differentiating drug versus placebo in an adequately powered trial.
But then the other part, though, and especially in patients who are relatively treatment-naïve, is some kind of either sequential

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treatment or multiple -- within the same overall trial, looking at multiple treatments that you could say patients with his profile should be treated with this first line rather than that, among available drugs.
DR. DWORKIN: Yes. Those studies have been done in psychiatry and they're --
DR. ROWBOTHAM: They're there.
DR. DWORKIN: -- fabulously expensive and fabulously interesting. I've given up hope that anybody is going to pay for it in pain. But it would make sense to put in something about that.
Similarly, the Kwan and Brodie epilepsy study that I think you showed --
DR. ROWBOTHAM: I was just going to make a pitch for including something about pragmatic trials, because that's where you do it, because they're all approved treatments and it's just seeing who responds best within a healthcare system.
DR. DWORKIN: There are shaking heads. We all agree these studies should be done, but at

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least I personally am just like totally despairing that anyone is going to do what NIMH did for antipsychotics and antidepressants. Those are so interesting.
This was Ian's point earlier and I think it's a very reasonable general recommendation that doesn't seem controversial. One should consider the potential implications of the personalized phenotyping/profiling on what you expect treatment effectiveness in the community to be.
If it's only 5 percent of patients with diabetic neuropathy that respond to lacosamide and 95 percent don't and you show that in a compelling way, you really need to discuss -- if I understood you correctly, Ian -- the fact that most of the patients with DPN in clinical practice are not going to respond to this drug.
The treating clinician needs to know that and that the investigator needs to help that clinician out by addressing it in a publication.
DR. GILRON: I agree. To add to that, we're talking 5, 10, 20 years down the line. Some of

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this work with validated measures could help us with currently available treatments as well. And we could actually get precision or personalized care improve with what we have now.

DR. DWORKIN: This is the kind of generalizability, kind of external validity relevance to clinical practice paragraph that is critical.

We want to add about the importance of back translation. Ralf mentioned that earlier so that's a general recommendation. Mike's point just now about biobanking, and that's obviously kind of important in phase 2 and phase 3, to the extent the patient gives permission, let's collect those samples. That was our list of general recommendations. It's something like eight or nine at this point.

Nat?

DR. KATZ: Question. It seems like our phenotyping comment, goals so far have been directed towards efficacy. And I just wonder if we should consider safety in some way as well.

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DR. DWORKIN: That's a great question. We could consider it briefly in this paper, because we haven't spent any time talking about it or we could put it on the docket for a future IMMPACT meeting or maybe we just do both, consider it briefly in this paper and say it'll be considered much more depth at a future IMMPACT meeting.

DR. WASAN: One caveat I would like to raise.

DR. DWORKIN: There's too many people talking at once. Ajay first and then --

DR. WASAN: One caveat, given all the issues, particularly with opioids and the opioid epidemic we have, where actually safety may actually be a primary outcome that is akin to efficacy, meaning at that bar, just reducing the abuse liability.

I think it would be worthwhile in terms of some of the issues that Ian raised with getting to how we can recommend better research to be done now with what we know to actually mention safety that it could actually be a primary outcome. And so all

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the same considerations would apply.

DR. DWORKIN: There's agreement that we'll mention, not very extensively, kind of personalized precision approaches to safety outcomes in this paper and that we will put on the list for a future IMMPACT meeting accelerating the development of a precision approach to safety outcomes in pain clinical trials.

Nat?

DR. KATZ: To expand very slightly on that, I mean, ultimately, we're interested in the risk-benefit balance with the drug and so the safety and the efficacy, I think it's worth just framing it in a kind of long-term risk-benefit goal context.

DR. DWORKIN: I deeply appreciate you mentioning that, because it gives me an opportunity to say that Kushang is working on an earlier IMMPACT paper on exactly that topic.

Is Kushang here? He's hiding.

(Laughter.)

DR. DWORKIN: We are eagerly looking forward

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to Kushang's IMMPACT paper on approaches to evaluating the risk-benefit profile of treatments.

Any other general recommendations to add to this list, this table?

Lee?

DR. SIMON: I have one question to ask you about what you just said. In the context of understanding risk and harm or harm and benefit, are you actually including patients helping to write that since they're the ones that actually help us understand issues associated with the potential harm versus the potential benefit?

DR. DWORKIN: I don't remember whether Tina and Penney were at the meeting that Kushang is writing up. But I think it's a great point and we should have patients involved in helping Kushang draft this manuscript.

DR. DIATCHENKO: It will please PCORI, too.

DR. DWORKIN: Yes, Nat?

DR. KATZ: I'm a roll, so I'm going to keep going. We haven't talked about pharmacokinetic phenotypes, whether a patient should be classified

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based on whether they actually have some pharmacokinetic subtype that impacts their exposure to the drug.

It's kind of shocking how rarely we address that in our clinical trials. We try to make sense out of the data and don't even worry whether the people actually had adequate exposure to the drug in the first place.

I wonder since it is directly relevant to a discussion of phenotyping and the context of drug development, whether we're planning on addressing that in any way.

DR. DWORKIN: Mike?

DR. ROWBOTHAM: To expand on what Nat is saying, what you want to assure is that you've got targeting of data that based on the pharmacokinetics [inaudible - off microphone].

DR. KATZ: That's one important implication. Another one is, yes, the ultimate goal is target engagement, but what if 80 percent in group 1 are rapid metabolizers and 20 percent in group 2 are slow, there's some sort of -- there's some

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fundamental clinical trial scientific integrity issues that really can't be understood unless you know whether your patients are being exposed to your drug or not.

You could just look at PK, but at least to think about whether there might be any major phenotypes that could impact -- metabolic phenotypes that could impact your results. It seems like it's worth at least checking out.

MALE SPEAKER: I completely agree. I could make the same -- do want to genotype the people in that regard or phenotype? Phenotyping is probably easier to be honest.

DR. KATZ: I don't have an opinion about that question.

DR. DWORKIN: But that's going to depend on the drug and any kind of resources but I think we need to -- the same way we're going to put in something about genotyping and how an in-depth discussion is beyond the scope of this paper, we need to do the same thing with pharmacokinetics because we wouldn't be able to deal with it in

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depth. But it's obviously critical.

Mike?

DR. ROWBOTHAM: I just want to get back to the point you just were raising about the NIMH studies where you're looking at multiple treatments and sequence.

If we're talking about fairly complicated profiling like for example including QST and psychological variables or catastrophizing, which really study a lot of subjects -- and we're not doing a systematic review.

There's one paper, I think, that we should cite in there about it's not truly an N of 1 study but it's Michael Byas-Smith's paper from 1995 with Mitchell Max where they took patients who appeared to respond to transdermal clonidine even though the overall trial was negative and then ran them through a period of crossovers.

You could use that as a fairly efficient technique to try and verify that you're seeing something real in patients who may comprise a small proportion of your overall trial group. But it has

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a particularly interesting correlation between their drug response and something worth profiling.

DR. DWORKIN: We haven't gotten --

DR. ROWBOTHAM: I'll send you the reference.

DR. DWORKIN: Yes, I know. I have it. I know the study well.

We're going to get to clinical trial designs, I think, in a bit. Anything else that's kind of generic, general recommendations for this middle third of the paper?

Shai?

DR. SILBERBERG: For my understanding, we heard the recommendation [inaudible - off microphone] was measures that you've included in phase 2 --

DR. DWORKIN: Yes.

DR. SILBERBERG: -- that might affect the outcome. Is that like the list of common data elements that expand [inaudible - off microphone] for all sorts of pain?

DR. DWORKIN: No. As I understand the recommendation is we're just telling the

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investigator who's designing a phase 2 trial -- and this goes back to what Nat was saying.

Think about your drug's mechanism of action, think about the kind of pathophysiologic mechanisms of the patients in whom you want to test it and come up with some hypotheses about which patients you would predict are more likely to be robust responders and put measures of that in your trial.

We're not saying anything specific. That's why we talked about it's a very general recommendation that we think investigators should do their very best to come up with hypotheses of treatment effect modifiers.

But we're not fleshing it out at all. We're leaving it up to the investigator because, of course, it depends on the pain condition; it depends on the drug.

DR. SILBERBERG: [Inaudible - off microphone]. All diseases that you might want to include like in a table saying, regardless of what area of pain we're looking at, these thing you should look at.

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DR. DWORKIN: Yes. Rob had a slide of many, many potential characteristics that could go into a lengthy profile, and that would be a reasonable -- I think it would be a reasonable table to have in the article, which would be as comprehensive a list as we can come up with of potential patient factors. So age, sex, weight, height and extending for another 30 or 40 bullets.

DR. MARCHAND: You can say that you know that it's not everything, but it's mainly what we see --

DR. DWORKIN: But we can try to make it pretty comprehensive like what are all the potential things that one could consider. Great idea.

Nat?

DR. MARCHAND: At the risk of leaving it -- you know, think about it. People will say, yes, I thought about it and I didn't find anything that --

DR. DWORKIN: It's really a checklist. It's a checklist to help the investigator make sure

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they've considered all the possible things to include in the profile, what a wonderful idea.

Nat?

DR. KATZ: Yes, another question. We do know something about meaningful phenotypes of certain common painful disorders that are commonly the subject of clinical trials.

For example, there's a small literature on phenotyping in osteoarthritis, which, by the way, Lars has another great paper on that that I just emailed to you.

We know something about phenotyping and back pain. There's some biomarkers that have been studied in back pain, for example, something about phenotyping a postherpetic neuralgia that's been discussed today, et cetera, et cetera.

In this paper, are we going to have any kind of disease-specific sections where we describe what's known about the phenotypes in specific disorders that are commonly studied in clinical trials?

DR. DWORKIN: We could. This is a nice

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segue into the third part of the part of the paper, where the two of us came up with some examples of specific recommendations that were really talked about earlier today and yesterday.

But it's different than what you're suggesting. I don't know whether one or the other or both. We were thinking would it make sense to have a list of specific recommendations that would be kind of if all of a sudden The Gates Foundation took a serious interest in pain, what clinical trials and other studies do we recommend be undertaken?

We kind of said in such a list of what we think should be done, if there was money available, a study of CPM in patients with OA in a separate study and some neuropathic pain condition and duloxetine.

A placebo-controlled trial of CPM and as a treatment effect modifier for duloxetine. It could be a tricyclic just as easily in patients with OA and in patients with some neuropathic pain condition.

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Now, that's very different than what you were suggesting. You're suggesting a section of an article where we actually talk about why one might think CPM would be interesting to look at in OA?

DR. KATZ: Maybe, but I was actually thinking of something much less ambitious than that, which is simply postherpetic neuralgia. You're considering doing a study on postherpetic neuralgia. Here's what the literature has to say about phenotyping patients with PHN.

I mean, go back to Mike's paper and Ralf's work, et cetera, you're considering doing a study in fibromyalgia. Here's what you know about phenotypes in fibromyalgia, epidermal nerve fiber biopsies, whatever. You're considering doing a study -- in other words, summarize the literature on what's known about phenotypes and disorders of interest to the people reading the paper.

DR. DWORKIN: I just want to say for the record, because Andrew is staring at me, what you just said requires a systematic review.

(Laughter.)

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DR. DWORKIN: This is an example of where Bob does agree with Andrew. Up until this moment, we totally disagreed but now, we're in agreement. It looks like Ralf's on board, also.

Nat came up with an example of where we do need systematic reviews. Now, the issue is there's a whole boatload of acute and chronic pain conditions.

This, Nat's suggestion, if we pursue it expands the paper, because we have much more to discuss and we do have to do some systematic reviews before we say to a PHN investigator these are the phenotypes that you should consider.

John?

DR. FARRAR: I think it's a separate paper. I think we risk diluting the effectiveness of this paper if we include all of that. And if we're going to be thorough about it, one could argue that for the major pain syndromes, you might actually want separate short papers of the systematic review.

I mean, it depends on how complete you want

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to be. I would strongly argue that it's a separate paper.

DR. DWORKIN: All right. How about this? ACTTION has resources. If any of you like Nat's idea and have a fellow, a resident, a graduate student, a junior faculty member or yourself want to do a series of systematic reviews and kind of do the paper that Nat and John just described, we would be happy to support it.

DR. MARCHAND: Are we talking about a systematic review, for example, for CPM and another one for something else or altogether?

DR. DWORKIN: We'd have to think about that, Serge. Nat was talking about it in terms of pain condition.

DR. MARCHAND: Okay.

DR. DWORKIN: Are there studies of CPM and PHN? I don't think so, but there could be.

(Crosstalk.)

DR. DWORKIN: They might be from Outer Mongolia, so we'd have to think about -- you'd probably want to do both at the same time in a

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systematic review, look at conditions, look at CPM, QST, catastrophizing, et cetera.

So this involves a bunch of good questions and if anyone of you is interested or know someone who's interested, we need to do this offline and think of it as a kind of ACTTION project or a series of projects.

DR. EDWARDS: Just one very quick addition to that, I love that idea. I think it's really neat. Nat, as I'm sure you already know, the universe of phenotyping papers for a given condition is much larger than what we've been talking about at this meeting, which is phenotypes that predict treatment response.

If you wanted to do, say, a systematic review of phenotyping in fibromyalgia, you would come up with huge numbers of papers that would identify characteristics on which fibromyalgia patients differ for which you could form subgroups.

But there might not be any data or very little data anyway on whether those phenotypic profiles predicted treatment response. You'd find

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papers on fibromyalgia phenotypes associated with greater or less physical disability or a cognitive dysfunction or that sort of thing.

So we just want to specify, I think, in advance, how broad we wanted to be in our systematic review of the "phenotyping" literature for a given condition.

MALE SPEAKER: I would suggest you don't base it on the condition, but on the method.

DR. EDWARDS: Okay. That would --

MALE SPEAKER: The one on CPM, for example.

DR. EDWARDS: Yes.

DR. DWORKIN: We don't have to think about this further, because we don't know whether anyone is going to volunteer to do it. But if someone volunteers to do it or volunteers a fellow or a spouse to do it --

(Laughter.)

DR. MARCHAND: She's on the phone right now. She would like to talk with you.

MALE SPEAKER: You mean ex-spouse.

(Laughter.)

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DR. DWORKIN: Shai, I think there are some ex-spouses in the room kind of floating.

(Laughter.)

DR. DWORKIN: We will convene a little working group to kind of flesh out these details of whether the systematic review is by condition, by profiling. But first, we need a volunteer.

What do you all think -- because we're certainly coming to the end of the list of what Rob and I came up with -- about recommending some specific trials, like CPM as a treatment effect modifier in a trial of duloxetine, in OA, maybe axial low back pain, maybe neuropathic pain.

Another example, kind of replicating the oxcarbazepine trial with pregabalin, like do irritable nociceptors modify the treatment effect of pregabalin? It's a different mechanism of action than oxcarbazepine. It would be kind of interesting if you got the same pretty figure for pregabalin.

Another example, capsaicin, the capsaicin response test that was used in the trial of topical

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clonidine. Let's look at that as a potential treatment effect modifier for oxcarbazepine, for topical lidocaine.

We can continue this but would it make sense in this article -- because we can fill it out offline -- to list 6-10 phase 2 clinical trials that we think Bill and Melinda should fund when they decide they've done enough with malaria or is that going too far out on a limb?

DR. MARCHAND: I think going with a recommendation is okay. I mean, especially, the example you're giving are making so much sense. I mean, we want that. For sure, people will come with other ideas after that.

But the idea is just to go and say, what will help in the short term, as you said, and in the next five years?

DR. DWORKIN: Shai?

DR. SILBERBERG: As an NIH person, I would recommend not do it, because inevitably bias creeps into the [inaudible - off microphone], the people on the paper, the groups that are here, the

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[inaudible - off microphone].

I think that could detract from the paper as opposed to being kind of a more consensus paper for the whole community not to make recommendations about specific things, but, in general, what needs to be done.

DR. DWORKIN: John?

DR. FARRAR: As a slight modification to that, I agree that if we recommend specific diseases and specific drugs that there's going to be a perception of bias.

But I liked your concept of basically looking at things that have been done in specific disease -- and we could express it as on taking successful efforts to look at this in specific diseases with specific drugs and expanding that to look at other diseases and other drugs.

So that in a more general way, I think you could express a need to move forward with some very low-hanging fruit without necessarily identifying the drug and the disease entity.

We could quote that there's the

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oxcarbazepine study and that this study ought to be reproduced with different drugs and different diseases. You just say that.

DR. DWORKIN: That's easy enough to do.

John?

DR. MARKMAN: I thought when you asked the question yesterday, Bob, it kind of crystallized the discussion and sharpened it a bit when you posed these hypothetical trials of duloxetine [inaudible - off microphone].

I think to address Shai's concern, it might be useful though, I think, for the reader to have a table, which talked about sort of what bucket these models fell into and an example of an illustrative study and what it would look like.

I think it's a way to sort of define the issue of all of these special interests, but also to give an example, to crystallize the readers, in their mind, what is an illustrative example of a trial where we do a pharmacologic challenge or a psychophysical challenge? So they have something specific to latch on to and maybe list four or five

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different types of these.

DR. DWORKIN: If there's some value, one way of addressing Shai's concern, which I personally hadn't thought of and I think is really very important for ACTTION to be concerned about, is instead of saying duloxetine or oxcarbazepine, say kind of either SNRIs or tricyclics as treatment, with CPM as treatment effect modifiers, so the broad class of dual reuptake of inhibition, or sodium channel blockers instead of saying oxcarbazepine, or topical anesthetics instead of saying topical lidocaine.

Maybe there's a way to address your concern, but also what John is saying. We'll try and do -- and it'll be very brief, because this does sound controversial -- this kind of midrange recommendation, not highly specific, but more specific than the general recommendations we just listed and see what you all think.

Luana?

DR. COLLOCA: Probably instead of suggesting in detail kind of study, it makes sense

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to identify gaps and try to reconcile the first part where you propose promising models with the second part of the recommendation.

Based on the first two paragraphs, the 31 can reconcile and in a sort of concise way suggest a concept or a methodological issue that needed to be disentangled, because today, we don't know how we can accelerate this development of personalized pain management, pain medicine.

I would suggest studies, but concept, area, gaps where we need to do more. And for Robert, who introduced the idea of interaction and explore together instead of continue to have this dualism psychology versus neurobiology.

It's time to frame everything in terms of psychoneurobiology, because there is this distinction. We distinguish because we are physicians, psychologists, but patient come to the lab or to the clinics, it's their pain, their effective component, their genes.

It's a time where we should sit together and try to work together to reconcile this domain

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that we separate, but in our patients are not separate.

DR. DWORKIN: We only have about less or more than 10 minutes. First, I'm going to call on Troels, and then I'll tell you what we'll do with the remaining nine minutes.

DR. JENSEN: I just want to ask, is there going to be a section or a paragraph about outcome parameters?

The reason I ask is, for example, if you go -- I'm taking up the point, which has been many times by Henrik Kehlet, if you're looking into post-surgical pain, you have to have outcome parameters, which is related to the particular condition you are talking about.

If it's a patient who has a mastectomy, you don't want to ask about, for example, walking. You want to ask something about which has to do with breathing, et cetera.

If you're having a patient with hernia, you want to ask whether you have pain, for example, during sexual activity, et cetera. If you're

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having a patient with a knee, you want to ask something about walking.
This is important. It's also important, for example, for postherpetic neuralgia, where is your postherpetic neuralgia, et cetera.
DR. DWORKIN: Yes. We need to include that when you're doing phenotyping, you need to consider what the measure that's assessing efficacy. Absolutely, Troels.
DR. EDWARDS: I think we also need to include -- Andrew's about to talk and I just cut him off.
But I was going to mention that he did a really nice job in his presentation identifying some of the limitations of what are used as outcome measures in the preclinical literature. I think we should certainly address that in the manuscript as well.
DR. DWORKIN: Andrew?
DR. RICE: Thank you, Robert. It was just to support Troels' point, but I think it goes a bit further with the comment I made yesterday. I think

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in fact, Troels, I think, was one of the first people who suggested it.
Within the German databases, we now have actually quite a lot of information about specific conditions for sensory profiling. And some of them are very, very homogenous.
So it might be worth raising the concept of condition or hypothesis-specific sensory profiling. There's no point in doing certain profiling measures in some conditions where it's not relevant.
DR. DWORKIN: Luda?
DR. DIATCHENKO: If we're talking about something which -- if we would have money, so there is a very good point Michael brought that we should recommend collect biological samples. But what for are we going to recommend?
If I may, what I would suggest is -- and I don't know if we can do this within practice -- actually, if we can collect all samples on treatment of neuropathic pain and do javas [ph] on them and make publicly available, then everyone

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will benefit from this.
It's not that much money. I mean really you can do javas for $50 right now. We're really talking about $100,000, which is small in comparison with clinical trial itself, right?
What we heard from NIH, from the yesterday person --
MALE SPEAKER: Will.
DR. DIATCHENKO: Will, right. So he said, well, we will collect samples, and then you guys can look at this. And then you can contact them and can phenotype them. I mean, this all will happen in 10 years like the earliest.
On the other hand, if we will all collect all samples and we'll do javas, then everyone can come back to your own cohort and see the specifics, which you did for this cohort, but in the realm of genome-wide significance.
This is what I would envision as will be kind of best to do. I don't know the structure which allows to do this, but maybe in practice, the structure.

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DR. DWORKIN: My only concern about that is to kind of really talk about that and provide the rationalization in, say, something about mechanisms is more than a -- I worry -- is more than a few sentences. We need to really see if it's something that can be incorporated in a paper.
DR. DIATCHENKO: Five sentences. I can do it in five sentences.
(Laughter.)
DR. DWORKIN: Rob, I know -- I'm confident I can speak for Rob in saying he would love to have you send him the five sentences.
Shai?
DR. SILBERBERG: One has to consider here you need to consent the patients to give the samples which adds complexity, because it depends on what the form says, how it's written, et cetera.
Then you've got to biobank them. And where are you going to biobank them? And you have to have them well phenotyped, which all takes time. So it's not as -- from an NIH --
DR. DWORKIN: Slight modification, Luda is

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going to draft five sentences. Before you send them to Rob, send them to Shai. If Shai approves them, Shai can send them to Rob. Okay? So we got a plan.

So we've only got 5 or 10 minutes left. So you've all had your say. What I would like to do is to see if Rob has any questions. Because remember -- remember the objective. I've done all the talking. You guys have done all the talking.

The objective of the last two hours was to make Rob happy. And if he's not happy, we're all staying here. So, Rob, are you happy? Do you have any questions?

DR. EDWARDS: So just as a general comment and for future reference, tropical drinks with little umbrellas in them on the beaches of Bermuda tend to make me happy.

(Laughter.)

DR. EDWARDS: This has been a delightful meeting. You guys have been great. I have many pages of notes. I think if I were to go through my notes right now and estimate length of this

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manuscript, it would be probably longer than is feasible to write. So some sections we'll wind up having to condense a little bit, I'm sure.

But we don't need to do any work on that now, I don't think. That'll happen organically as this gets produced.

I don't think I have any questions, but I will extend a hearty thank you in advance to Luda, and Clifford, and to all of the other people whose help I will draft in writing various sections of the manuscript. I suspect this will be a good read for a lot of people and hopefully quite useful for the field.

DR. DWORKIN: Thank you all very, very much for your participation. And you will be hearing from us. Have safe flights home.

If Valorie and Andrea are back there, thank you, Valorie and Andrea, for another flawless meeting.

(Applause.)

(Whereupon, at 3:50 p.m., the meeting was adjourned.)

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