

ACTION - IMPACT-XIX
Accelerating the Development of Precision Pain Medicine

June 4, 2016

A Matter of Record
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11		11	Robert Dworkin, PhD
12	Saturday, June 4, 2016	12	Dennis Turk, PhD
13	8:06 a.m. to 3:50 p.m.	13	
14		14	
15		15	
16		16	
17	Westin City Center	17	
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1	C O N T E N T S	1	P R O C E E D I N G S
2	AGENDA ITEM	2	(8:06 a.m.)
3	COX Inhibitors and NGF Antibodies as	3	DR. TURK: Good morning. Good morning.
4	Targets for Precision Pain Medicine	4	Please take your seats. We want to get started.
5	Nathaniel Katz, MD	5	We're hoping to get out of here by midnight and
6	Descending Inhibition as a Target for	6	we've got to get started now.
7	Precision Pain Medicine	7	Hope you all had a pleasant evening. From
8	Roland Staud, MD	8	the conversations that I sort of milled around and
9	Signs, Symptoms, and Comprehensive QST:	9	listened to, it sounds like we stimulated a lot of
10	A Perspective from the German Research	10	discussion, which is perfect, exactly what we want
11	Network on Neuropathic Pain	11	these meetings to do.
12	Ralf Baron, MD	12	It's not so much just what goes on in the
13	Signs, Symptoms, and Bedside QST: a2-. and	13	formal presentations, but really what goes on over
14	Other Targets	14	the coffee exchanges, at dinner, and collaborations
15	Roy Freeman, MD	15	of things that people work on. We, Bob Dworkin and
16	Non-Pharmacologic Treatments in Precision	16	I and the organizers are delighted to see that
17	Pain Medicine: Rationale for	17	you're doing that.
18	Splitting (Stratifying) vs. Lumping	18	A couple of housekeeping details just before
19	Dennis Turk, PhD	19	we get started. As a reminder, this is being
20	What Else Needs to be Included When	20	recorded and transcribed. So when you ask a
21	Phenotyping is Considered?	21	question, when that comes about, please say your
22	Robert Edwards, PhD	22	name, even though you may have said it several

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1 times already. It helps the transcriptionist so
2 that she's able to do that.
3 The other housekeeping details are on there.
4 There is a sign-up sheet on the desk back where
5 Valorie and Andrea are for taxis.
6 So if you are looking at taxi times, sign
7 up. There will be plenty of taxis. It just gives
8 them some advanced warning so they can make sure
9 that they have things out there.
10 Check-out time is at noon. There's a break
11 at 10:30, 10:40 or something like that. So either
12 you can decide that you want to check out then or
13 you can wait until noon if you want to. We can put
14 stuff in the back of the room or you can go to the
15 bell check-out.
16 If you have a cell phone, please, as you did
17 nicely yesterday, make sure that they're not going
18 to be going off during the meeting itself.
19 Remember the microphones, you speak into
20 them. I noticed yesterday when some people want to
21 talk to somebody on the side, they turn like this
22 and we lose you from the microphone. So even

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1 though you're talking to Mike Rowbotham, you've got
2 to talk directly in front of or move your
3 microphone if you will.
4 Any concerns, questions, or logistical
5 details that I can handle, I'm happy to try to
6 answer them. But Valorie and Andrea can do most of
7 that.
8 As far as your stipends and things that
9 kind, they take care of all that. So if you have
10 any questions about that, anything about flight
11 problems, anything like that, definitely check with
12 them, room problems or what have you.
13 Any concerns, questions, things that people
14 want to know? There will be a break and then there
15 will be a lunch period that will be in the same
16 facility where we were at yesterday.
17 Anything else people want to know, want to
18 worry about?
19 (No response.)
20 DR. TURK: Okay. Then let me introduce John
21 Markman, who is going to be the introducer for the
22 morning sessions. John, when you have an

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1 opportunity.
2 Dr. Markman is from the University of
3 Rochester. Many of you heard him yesterday. And
4 hopefully all of you were here for the
5 congratulations to Mike Rowbotham for the Mitchell
6 Max Award. We were delighted to do that and thank
7 John for arranging that.
8 DR. MARKMAN: Good morning, everyone. It's
9 a true privilege to introduce our next speaker in a
10 quartet of distinguished speakers, Dr. Katz.
11 Nat Katz and I have a personal relationship.
12 He was my first teacher of pain medicine when I was
13 a resident. So it's a true privilege to introduce
14 him.
15 He is professor at Tufts University and,
16 also, I think, one of the most distinguished
17 thinkers about clinical trial design. And he's
18 going to be speaking to us about COX-2 inhibitors
19 and NGF antibodies as sort of illustrations of the
20 potential for precision pain medicine.
21 Presentation – Nathaniel Katz
22 DR. KATZ: Thanks, John. Hi, everyone.

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1 I was asked to take on this topic of
2 presenting to you what's known about phenotyping in
3 patients for the prediction of the outcome of
4 treatment with nonsteroidal anti-inflammatory
5 drugs, cyclooxygenase inhibitors, and NGF
6 antibodies.
7 I could probably just wrap up my whole talk
8 right now, because the bottom line is that nothing
9 is known about that.
10 I have not been able to find any published
11 clinical trials where there was some attempt to
12 phenotype patients at baseline based on the sorts
13 of phenotyping that we've been talking about at
14 this meeting, and look to see whether that mediates
15 the efficacy or actually the safety of either
16 cyclooxygenase inhibitors or NGF antibodies.
17 So that's my presentation. Thank you very
18 much. We can chitchat for 20 minutes.
19 (Laughter.)
20 DR. KATZ: Of course, not only do you have
21 to fill up the time, but you actually have to go
22 over your time, don't you? So I had to find

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

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

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

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

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

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

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

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

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

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

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1 biomarker or whatever.

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

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

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

16 (Laughter.)

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

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

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

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

22 These are just some of the factors. Of

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

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

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

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1 analgesics.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 Yet, inter-individual differences, as far as
2 I know, have not been looked at as mediators of
3 outcome. And if someone else knows more about it
4 than I do, which would not surprise me, I hope that
5 in the discussion you educate all of us on that.
6 What's the bottom line here? The bottom
7 line here is that there are important
8 inter-individual differences on factors that might
9 impact the pharmacological outcome of these drugs,
10 but it just has not been looked at.
11 Another thing that these same authors in
12 this same paper looked at was genotypes for
13 metabolic subtypes. Different people have
14 different genes in terms of the metabolism of
15 cyclooxygenase inhibitors and, also, different
16 genes for isoforms of the cyclooxygenase enzymes
17 themselves.
18 Without going into the details, since I
19 don't really fully understand it anyway, I will
20 just say that they matter, these genes. So if
21 you're in a genetic subtype that has a different
22 COX-1 isoform, you will show a different degree of

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1 Cox 1 inhibition and since that seems to be the
2 main thing that produces salient side effects of
3 NSAIDs, that could be important. And that held
4 true for both celecoxib and rofecoxib. Of course,
5 the people who metabolize it more poorly have
6 higher plasma concentrations which is not a
7 surprise.
8 So inter-individual differences based on
9 SNPs for different genes that relate to both the
10 pharmacokinetics and the pharmacodynamics of NSAIDs
11 do seem like they have the potential to matter.
12 But they've just not been looked at in clinical
13 outcome studies, to my knowledge.
14 That's kind of all that I was able to glean
15 from the literature on inter-individual differences
16 and how they relate to cyclooxygenase inhibitors.
17 Now, the next question that I'll attempt to
18 deal with is we've been talking a lot in the last
19 day or so about these sensory profiles and do they
20 matter in terms of the outcome of analgesic
21 treatments, particularly the efficacy outcome.
22 As I said in my introduction, there's no

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1 published study looking at whether sensory profiles
2 predict the outcome of NSAID therapy, but there is
3 an unpublished study that I actually did that we've
4 been sort of perpetually packaging up for
5 publication, and I'll just show you a little bit of
6 data from that.
7 This was a randomized, double-blind,
8 placebo-controlled, crossover study funded by
9 Astellas.
10 It was a methodological study just to look
11 at performance of different endpoints, et cetera,
12 et cetera. One of the things that we looked at
13 was -- we had already previously developed what we
14 call a bedside sensory testing kit to see if we
15 could evaluate sensory profiles in patients with
16 different disorders, and we developed it actually
17 for use in patients with osteoarthritis of the
18 knee. We had a little publication about a year ago
19 that described just the development of this little
20 kit.
21 I think about it as kind of a dumbed-down
22 version of the German Neuropathic Pain Network for

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1 people in multisensory trials who are only going to
2 spend 10 minutes in doing this, what can you do to
3 generate reliable data.
4 We showed that we could generate reliable
5 data using this bedside approach. Then in this
6 study, we wanted to see did the classifications
7 that this simple bedside sensory testing approach
8 generated predict the efficacy of naproxen in the
9 treatment of osteoarthritis of the knee. That's
10 what the study was.
11 This was just a picture of the stuff that's
12 in the box, so when you get it. The main things
13 that we focus on are we used a pressure algometer
14 to measure pressure pain thresholds in the
15 arthritic knee.
16 Then we also used pressure algometry in the
17 knee to do a DNIC test or a CPM test, whatever word
18 you like, and we used that with ischemic
19 pressure in the -- ischemic pain in the forearm was
20 the conditioning stimulus.
21 We tested for cold allodynia over the knee,
22 which didn't really yield anything. We tested for

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1 using Von Frey filaments for light touch threshold
2 at the knee, which also didn't really yield
3 anything. And those are the basic components of
4 what's in this kit.
5 Here are the results. What we did is we
6 divided patients into three categories based on the
7 results of this test. The first test was did they
8 have what we considered primary hyperalgesia, which
9 was based on pressure algometry in their arthritic
10 knee.
11 Then we looked at what we called secondary
12 hyperalgesia, which was pressure algometry at the
13 elbow, non-affected area. Then the third thing we
14 looked at was DNIC, whether it was what we
15 considered to be intact or dysfunctional based on a
16 pre-specified cutoff that we introduced.
17 So if you have three tests and you have two
18 different outcomes for each test, that gives you
19 eight mathematical permutations of all those three
20 tests. So this is just the eight possibilities.
21 I'll just draw your attention -- for a small
22 study, we had 51 patients. To have eight subgroups

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1 in a small study means that you're not going to be
2 able to analyze a lot of your subgroups. That's
3 just math.
4 What we did was we focused on three groups.
5 This top row is the people who everything was
6 normal or at least what we considered to be normal.
7 And that actually was the largest subgroup, 19 out
8 of 51, almost half.
9 Then these people down here, everything was
10 abnormal. That's the other extreme. There were
11 only seven so it's a small group. And the rest of
12 these people had a mishmash where some things were
13 normal and some were abnormal, and we ended up just
14 combining them.
15 Now, we have three subgroups and the
16 question is did that have any impact on the outcome
17 of NSAID treatment. So we looked at this in four
18 different ways.
19 I know this is a complicated table, but I'll
20 just try to draw you to the highlights. The first
21 approach was to look at all of the different tests
22 that we did, and that was basically this here

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1 collapsed into two groups.
2 If you look at the patients -- and the
3 endpoint that we looked at was a standardized
4 effect size of therapy and the endpoint was the
5 WOMAC Pain Subscale, the standard endpoint in
6 osteoarthritis clinical trials.
7 Standardized effect size, the difference
8 between drug outcome and placebo outcome divided by
9 the pooled standard deviation. So the normal
10 meaning of standardized effect size.
11 You can see that the people that were all
12 normal, their standardized effect size was 0.44,
13 which is kind of what you'd normally expect from
14 naproxen in a study for osteoarthritis in the knee.
15 The people who were all abnormal had almost
16 double the standardized effect size, which was the
17 opposite of what I predicted now probably four
18 years ago when we started designing this study.
19 The second way that we approached it was
20 just looking at the DNIC test, which is these
21 groups here, and forgetting about this hyperalgesia
22 measure. Again, we looked at normal versus

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1 abnormal.
2 You can see here that in the normal, there
3 was standardized effect size of 0.33, not so
4 terrible, about double in the patients with
5 abnormal sensory, all abnormal sensory function.
6 If you look at it just based on the
7 hyperalgesia, which was the other component, again,
8 the same pattern where the people who were all
9 normal -- that was these people here, standardized
10 effect size of 0.42; people all abnormal, again,
11 these are only 11 patients per group, double the
12 effect size, 0.80.
13 Finally, we also used the LANSS
14 Questionnaire which is just a paper-and-pencil
15 questionnaire. Many of you are probably familiar
16 with it. It's one of these questionnaires that
17 purports to divide patients into neuropathic versus
18 non-neuropathic pain.
19 The neuropathic group are the people whose
20 pain score is above 12. That actually turned out
21 to be the best differentiator of all, which is kind
22 of embarrassing, because I really wanted the kit to

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1 work better than the paper-and-pencil
2 questionnaire. Otherwise, why would you bother
3 doing the bedside sensory testing kit?
4 Actually, you had almost four times the
5 standardized effect size in the people who are
6 so-called neuropathic versus non-neuropathic.
7 Of course, I'm immediately rushing to remind
8 everyone about the limitations of this study. It's
9 small, it's unpublished, there's small cell sizes.
10 I don't think any of these differences were
11 statistically significant. I neglected to put them
12 on the slide, because these are very tiny cell
13 sizes.
14 But it suggests a pattern, no matter how you
15 look at the data, that the patients with
16 dysfunctional sensory profiling, if you will, no
17 matter how you look at it, those patients had
18 appreciably larger effect sizes of naproxen versus
19 placebo, the opposite of what I was expecting for
20 this so-called peripherally-acting drug.
21 As far as I know, this is the only study
22 looking at sensory profiling to see if it predicts,

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1 in a randomized, placebo-controlled context, a
2 difference between outcome of a cyclooxygenase
3 inhibitor for any chronic pain syndrome.
4 Now, what I've learned over the years is
5 that whenever I think I've got something
6 innovative, the first thing I should do is look in
7 the literature and I'll find that Lars Arendt-
8 Nielsen has already published something on it right
9 before I did.
10 (Laughter.)
11 DR. KATZ: I thought that this was the case,
12 because just yesterday when I was just trying to
13 update myself before today, I found that Lars had
14 published a paper about a year ago looking at
15 etoricoxib, which is a selective COX-2 inhibitor
16 that's on the market in, I think, every country of
17 the world besides the United States, for a variety
18 of very interesting reasons.
19 He did the ideal type of study that I
20 outlined at the very beginning, that conceptual
21 paradigm where you phenotype everybody at baseline
22 using all the millions of things that only he seems

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1 to be able to pull off and then did a clinical
2 study, a clinical trial, where the patients got one
3 month of etoricoxib and one month of placebo on a
4 crossover paradigm with, again, as I mentioned, a
5 lot of different approaches to phenotyping the
6 patients.
7 I thought that I was going to be
8 scoffed [indiscernible] when I saw this paper,
9 because I thought that he was actually going to
10 publish -- I thought he would do the obvious thing,
11 which is say, "Okay, here is the difference between
12 etoricoxib and placebo in phenotype A versus
13 phenotype B." But for some reason, unless I
14 misread it, his paper doesn't actually have that.
15 He just presents the open label results of
16 etoricoxib, which is exactly what I said earlier,
17 is the wrong way of looking at this kind of data.
18 And so why he didn't present the etoricoxib versus
19 placebo difference and whether the phenotypes
20 mediated that difference, I have no idea.
21 I actually plan on sending him a note and
22 asking him if I misinterpreted his paper or maybe

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1 he, for some reason, chose not to present it. And
2 maybe he'll come out with some follow-up paper that
3 presents what we really want to see.
4 This paper looks very exciting. It looks
5 like he has the data, but it actually does not
6 address the question at hand, because of the way
7 he, I think, presented the data.
8 That's what is known. That's the world's
9 literature on phenotyping to predict effect
10 mediation for cyclooxygenase inhibitors for the
11 treatment of pain.
12 I see I'm already over time, so I think what
13 I'll do is just carry on to say a word or two about
14 antibodies to nerve growth factor.
15 You're all familiar with the
16 pathophysiology, so I won't go over that. We all
17 know that these drugs work for pain. They're not
18 approved yet in any jurisdiction for a variety of
19 interesting reasons.
20 There are uncommon, but very severe safety
21 problems associated with this class of drugs, the
22 main one being what's so-called the rapidly

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

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

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

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1 don't really understand it.
2 But the bottom line is that they are looking
3 at ways to model sensitivity and specificity of
4 different predictive algorithms resulting from
5 combining these biomarkers in as intelligent a way
6 they can think of to try to do this prediction.
7 It seems like some of the performance of
8 some of these algorithms actually looks pretty
9 good, although we're talking about, obviously, a
10 very small numbers of cases, 30 cases of this and
11 50 cases of that.
12 That's all I want to show just to give you a
13 sense that this work is going on and that's really
14 all I have to say about it for today.
15 This is actually my final slide. My
16 conclusions from exploring this literature, as well
17 as the very small amount of work that I've done in
18 this area, is that there are
19 actually -- considering that nonsteroidal
20 anti-inflammatory drugs have been used since the
21 time of Christ in the form of willow bark extract
22 for pain relief, we know virtually nothing about

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1 who's going to benefit and who's not going to
2 benefit, which is kind of shocking, I think.
3 It's now 2016. So after 2000 years of using
4 these drugs, in the last four or five years, we're
5 starting to see some emergence of a literature on
6 whether we can predict what your outcome is going
7 to be, whether it's from a safety or an efficacy
8 endpoint, using both soluble biomarkers, sensory
9 profiles, et cetera.
10 With the anti-NGFs, it's actually very
11 important for us to do that and even that work is
12 really still in its infancy. So that's what I was
13 able to find out, and I do think it's an area where
14 further research would be beneficial.
15 Thanks for your attention.
16 (Applause.)
17 DR. MARKMAN: In the interest of time, I
18 think we're going to hold off on questions. Our
19 next speaker is Dr. Staud, from the Center for
20 Musculoskeletal Research at the University of
21 Florida. He's a professor with the international
22 leadership on thinking about fibromyalgia and

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1 central sensitization.
2 Today, he's going to talk about the
3 potential to affect descending inhibition and how
4 it might inform our future research in precision
5 pain medicine.
6 Presentation – Roland Staud
7 DR. STAUD: As we heard from the previous
8 speaker, the identification of phenotypes in
9 precision medicine will be or is a very important
10 part.
11 What I'm going to do in my talk here is to
12 give you some information regarding the current
13 state of the knowledge that's available in
14 identifying phenotypes and, also, how it can be
15 used for precision medicine.
16 What we know and what I'm going to talk
17 about is that endogenous pain modulation, which is
18 the focus of this talk, is highly variable in
19 healthy individuals, as well as in patients.
20 This
21 is, to some degree, determined by genetic and
22 environmental factors.
The pain inhibitory function, generally, in

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1 many publications, has been found to be inefficient
2 in chronic pain disorders. The question here is
3 now if this function can be used for characterizing
4 individuals that may respond either to particular
5 drug classes or to particular individual treatment
6 response.
7 Again, to the question about phenotypes,
8 phenotypes is an approach that has been begun, but
9 is definitely not complete. And much of these
10 phenotypes are just hypothetical phenotypes, as for
11 example, mentioned here in this particular slide.
12 When it comes to pain modulatory phenotypes,
13 to separate groups of individuals into either so-
14 called normal phenotypes compared to the pain
15 facilitatory phenotype, as well as, here, to the
16 pain inhibitory phenotype and saying that or
17 hypothesizing that the pain facilitatory phenotype
18 is these individuals at higher risk for pain
19 disorders, whereas individuals with a predominantly
20 pain inhibitory phenotype are protected for pain
21 disorders, as well as pain.
22 Now, if we use pain modulatory function for

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1 the characterization of phenotypes, this has
2 precedence here. For example, this is Irene
3 Tracey's approach to identify endophenotypes just
4 based on neuroimaging here.
5 From her work, her suggestion is that when
6 functional brain imaging, as well as structural
7 brain imaging is used, phenotypes can be described
8 according to activation of certain areas either in
9 the pain inhibitory system or activation of limbic
10 system, as well as the nociceptor system, and that
11 even changes in brain morphology can be used to
12 identify subtypes in pain.
13 What I have done, and I have really no proof
14 for a clear definition for this phenotype, is in
15 terms of pain modulatory endophenotypes, as a
16 suggestion here, the different possibilities that
17 are available here. So in terms of pain modulatory
18 function here, it is do you use temporal summation
19 as the pain facilitatory phenotype, as well as the
20 response to chronic pain stimuli.
21 Then the analgesic phenotypes here, in
22 particular, the response to context-related or the

<p style="text-align: right;">Page 41</p> <p>1 occurrence of context-related analgesia, response 2 to spatial summation, offset analgesia, conditioned 3 pain modulation, and then the stress response in 4 general. 5 What I'm going to focus mostly is on the 6 top-down approach from mostly central factors to 7 more peripheral factors in pain modulation. 8 So the pain pathways are relatively well 9 established. Pain is signaled to the spinal cord 10 and the central nervous system and results in a 11 response that is, to some degree, well delineated, 12 often with activation of, here, the periaqueductal 13 gray, the RBM. 14 This has a direct effect on dorsal horn 15 neurons, usually in the presynaptic and 16 postsynaptic fashion. And many of the mediators 17 are known, particularly opioids, norepinephrine 18 and, to some degree, serotonin. 19 Now, the effectors that change endogenous 20 pain modulations are here, which are really due to 21 mood-related factors, as well as to factors that 22 are related to cognition and, in particular, the</p>	<p style="text-align: right;">Page 43</p> <p>1 poorly described, generally speaking, in clinical 2 trials. So the combination of all these factors 3 entails the control that is used and it includes 4 the placebo effect. 5 We know a lot about the activation of 6 certain brain areas associated with placebo 7 effects. We know that it's an active process that 8 leads to activation particularly of prefrontal 9 areas, the cingulate cortex, as well as the insula, 10 as well as some of the basal ganglia. 11 But particularly, as important, the 12 projections of these particular pathways then to 13 clearly well-known areas of pain modulation, like 14 the periaqueductal gray, as well as the RBM, then 15 here, again, from these areas, either directly or 16 indirectly going to the dorsal horn, where they 17 influence activation of the dorsal horn neurons. 18 The brain imaging, which is part of what I 19 frequently do, is able more recently to show more 20 difficult-to-approach details of the central 21 nervous system, like the brain stem, as shown here. 22 This is the brain stem and you can see, in</p>
<p style="text-align: right;">Page 42</p> <p>1 factors that relate to placebo analgesia. 2 What I wanted to point out here is that 3 endogenous pain modulation seems to happen at every 4 level of the central nervous system, from the 5 brain, brain stem, the spinal dorsal horn, 6 autonomic nervous system, and further down. 7 These systems seem to interact, at least to 8 some degree, but they also have intrinsic pain 9 modulatory function. 10 I wanted to demonstrate the pain modular 11 function essentially from the brain in a caudal 12 fashion and to start with placebo analgesia, which 13 is one of the most important pain modulatory 14 functions that is available. Placebo is a generic 15 term which is really used essentially as a control 16 for a usually active treatment condition. 17 Placebo entails the placebo effect, which is 18 here shown on the right side, which is an effect 19 that is due to expectations and learning, due to 20 influence from multiple factors here. 21 But what, in clinical trials, is often 22 important are these factors here that are very</p>	<p style="text-align: right;">Page 44</p> <p>1 terms of placebo analgesia, that during analgesic 2 response is that activation of the PAG, the RBM are 3 visible or detectable on brain imaging. 4 More recently, we have started to do imaging 5 of the spinal cord. This is not our work, but we 6 are also able to identify activations within the 7 spinal cord. 8 Here, this study by Eippert, has 9 shown -- this is the spinal cord here and the 10 activation, you see this little dot here. That's 11 how small the activations in spinal cord imaging 12 are. 13 Over on this side shows the difference in 14 activation. So here, in the control, there is a 15 large amount of activation. In the placebo 16 condition, shown here, there is essentially no 17 activation. And this is just the contrast, so 18 showing the area in the appropriate location that 19 is affected by a placebo mechanism. 20 The molecular mediators of placebo analgesia 21 are known, to a large degree. Many of them are 22 opioidergic and involve these particular areas</p>

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1 here. And then I want to just place your attention
2 to the dopaminergic pathway. There are also
3 pathways that are involved with cannabinoids.
4 The particular interest that we may have in
5 terms of early trials, as well as in terms of
6 interventions, is that placebo effects can be
7 effectively modulated.
8 I showed you here this meta-analysis of, I
9 think it's at least 30 studies, which show the
10 effect sizes, here on the right side, of different
11 interventions.
12 Here, for example, verbal suggestions that
13 increase the placebo effect, we can see that they
14 have moderate-to-strong effect sizes; and, then
15 here, changes in conditioning, which also has
16 moderate effect sizes; and, then here, changes of
17 placebo analgesia due to looking at images.
18 Overall, the overall effect size is moderate
19 and some of the effect sizes are relatively strong.
20 So you can imagine that this is important for
21 clinical trials, but it's also important for
22 clinical care that placebo effects can be effective

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1 or could be effectively included into a treatment
2 armamentarium.
3 I was thinking here in terms of the placebo
4 effect in precision medicine. The important factor
5 is that placebo effects are really highly reliable
6 when they are executed in a similar environment and
7 in a similar context. You can really repeat this
8 really well.
9 The second part, which is well known here,
10 is that when placebo interventions are repeated,
11 they usually seem to increase the placebo efficacy.
12 It is possible that with the identification of
13 placebo responders, that this can inform trial
14 design and benefit treatment of individuals.
15 Going further down in the central nervous
16 system, I will focus now in temporal and spatial
17 filtering of pain as a potential indicator for
18 precision pain medicine.
19 Temporal and spatial filtering of pain
20 relates really to offset analgesia and conditioned
21 pain modulation. These factors are usually brain
22 stem and spinal cord-related but they have, also,

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1 influences from brain areas.
2 The mechanisms of some of them are well
3 known; others not so much. For example, offset
4 analgesia, which is a method of increasing pain
5 sensation through a -- increasing and then a
6 constant stimulus, which is followed by a small
7 increase in the intensity of the stimulus.
8 Here, in this particular situation, it's
9 heat. And then after about five seconds, the
10 temperature or the stimulus intensity drops back to
11 baseline.
12 As you can see, under these circumstances,
13 the initial increase is relatively small, but the
14 subsequent change results in a strong decline of
15 pain reporting, and this is called the offset
16 analgesia effect.
17 The brain activity to offset analgesia is
18 shown here, and this is the brain activity of
19 offset analgesia on this side. I will talk about
20 the brain activity of CPM later on.
21 Again, as you can identify that brain areas
22 become activated due to offset analgesia, but,

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1 also, it involves brain areas that become
2 deactivated, here in blue.
3 Red areas are activated. Blue areas become
4 deactivated. And it is not quite understood what
5 the particular meaning of these particular
6 deactivations is, if it's a direct effect or an
7 indirect effect.
8 I just want to point out some of the areas
9 here which seem to be important, as the interior
10 insula.
11 The pharmacologic characterization of offset
12 analgesia has been attempted here, for example, to
13 look, with opioids, if it can modulate offset
14 analgesia.
15 This is a relatively small study, where the
16 individuals are shown here and the mean changes are
17 depicted at the bottom here. And you can see
18 there's a very small and non-significant change of
19 offset analgesia detected after individuals
20 received hydromorphone.
21 To look at offset analgesia in the context
22 of NMDA receptor antagonists, like here, ketamine,

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

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

13 (Laughter.)

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

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

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

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

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

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

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

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1 investigators.

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

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

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

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

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1 testing.

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

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

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

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1 The relevance of these test sets may be for
2 chronic pain disorders, and there are multiple
3 chronic pain disorders where CPM is either minimal
4 or absent, most predominantly in disorders like
5 fibromyalgia, irritable bowel syndrome, and so on,
6 but, also, in disorders like osteoarthritis, for
7 example.
8 Here in this meta-analysis of CPM trials,
9 where the effectiveness of CPM was detected, you
10 can see there are over 30 studies published where
11 the effect sizes range from mild to moderate to, in
12 several cases, very, very strong effect sizes.
13 This is for TMD, IBS, and migraine. And
14 here is one effect where the test identified
15 impaired, overly effective CPM in patients with
16 stroke.
17 Again, the pharmacological evaluation of CPM
18 here in terms of can it be improved with certain
19 pharmaceutical agents as oxycodone, this is the
20 effect on pain over time.
21 We have 180 minutes and just as a control
22 here, temporal summation was used, whereas

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1 oxycodone had no significant effect on CPM, it was
2 effective on temporal summation, which has been
3 previously reported.
4 Similar findings have been obtained with
5 hydromorphone. Again, this is a relatively small
6 study and, again, only non-significant changes of
7 CPM were detected.
8 The opposite, the inhibition of opioidergic
9 pathways has been attempted by multiple
10 investigators. The majority of these
11 investigations showed no effect of naloxone, an
12 opioid receptor antagonist, on CPM.
13 Interestingly, I wanted to show this to you,
14 this one publication with tapentadol, which looked
15 at CPM in patients with diabetic neuropathy. This
16 was a placebo-controlled trial.
17 Here, an effect on patients, CPM with
18 tapentadol, was obtained. This is a significant
19 improvement of CPM. At the same time, the pain of
20 these patients improved.
21 Similar effects have been done here with
22 apomorphine, which is a dopamine agonist, again, to

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1 seem to have improved CPM.
2 As for all types of research reliabilities
3 of critical importance and the evidence of
4 reliability studies is mixed. There are several
5 studies that showed excellent reliability of CPM
6 testing, whereas a similar number of studies showed
7 poor reliability.
8 This may be due to multiple factors,
9 including the different forms of how these tests
10 are executed by different investigators. As I will
11 point out afterwards, standardization, it is of
12 critical importance that we finally agree what the
13 appropriate form of CPM testing is.
14 I just wanted to show you an interesting
15 study that looked at the reliability of CPM in
16 terms of sex differences. As I'm showing here, I'm
17 showing here that the reliability of men, for some
18 unknown reason, was much, much lower compared to
19 women. There was no real explanation available
20 about this.
21 The use of CPM so far as a predictor,
22 as Dave Yarnitsky has shown, that it predicts

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1 chronic post-operative pain. In one of his
2 studies, it has been identified as a predictor for
3 opioid-induced hyperalgesia.
4 And the last and probably controversial line
5 of evidence, the analgesic response to serotonin
6 norepinephrine reuptake inhibitors -- and I want to
7 briefly discuss this, because it seems to be an
8 interestingly important topic, but it needs some
9 further clarification.
10 So I just want to show you the way it was
11 done. This was 30 patients with diabetic
12 neuropathy. They received an open label
13 intervention, first 1 week of placebo, followed by
14 30 milligrams of duloxetine, followed by 4 weeks of
15 duloxetine.
16 CPM was tested before any of the treatments
17 occurred and then right at the end, during the last
18 week.
19 Now, it had an effect on diabetic
20 neuropathy. The pain was significantly reduced.
21 But interestingly, the efficacy of pain reduction
22 was different or seemed to follow a regression line

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1 here that individuals with efficient CPM, which is
2 shown here -- this is the reduction of pain with a
3 conditioning stimulus -- that the efficiency
4 negatively predicted the effect of the drug on
5 neuropathic pain.
6 So the more efficient the CPM was, the less
7 effectiveness of the drug was obtained. And the
8 less efficient it was, the more effectiveness. And
9 the important part of this trial was that these
10 findings were reversed at the end of the trial, at
11 this end of these 6 weeks, so that individuals who
12 had inefficient CPM now had efficient CPM.
13 Here, it's the same thing shown here, that
14 CPM before and after the treatment has
15 significantly changed, and indicating that
16 potentially the intervention, the identification of
17 individuals with less efficient CPM are a
18 predominant target for these particular
19 interventions.
20 Let me conclude with pointing out that
21 descending pain modulation is a critical part of
22 acute and chronic pain relief and that decreased

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1 endogenous pain inhibition seems to be a
2 characteristic of many chronic pain conditions.
3 It appears that CPM can be used to determine
4 endogenous pain inhibition in groups and possibly
5 even in single individuals.
6 The usefulness of CPM for offset analgesia
7 in precision medicine will, however, require some
8 more standardization of CPM and offset analgesia
9 and, in particular, that prospectively controlled
10 trials will be necessary before either CPM or
11 offset analgesia can be used as a predictor for
12 treatment response.
13 Thank you.
14 (Applause.)
15 DR. MARKMAN: Do you want to take questions?
16 DR. STAUD: Yes.
17 DR. MARKMAN: John?
18 DR. FARRAR: It's a fascinating area and
19 certainly, we've known for years, just in clinical
20 practice, that some patients sail through a serious
21 surgical procedure, have relatively little pain
22 afterwards, and do very well. Others have very

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1 significant problems.
2 I wondered, there have been some attempts to
3 try and offset or to change basically the patient's
4 expectation for pain after surgery with a variety
5 of mechanisms, and I wondered whether you knew of
6 any attempts to try and look at that in the
7 clinical setting.
8 The prime example is where you test a
9 patient with a heat probe. You then give them a
10 drug. You test them with the heat probe again, but
11 in half the patients, you use a lower heat so it
12 "enhances," in quotation marks, the effect. And
13 then you do the testing again later that's been
14 done -- Irene and some others have done this with
15 FMRI.
16 I just wondered whether you know of anything
17 where that's been looked at in the clinical
18 setting.
19 DR. STAUD: No, so far. I thought this is a
20 very important part of evaluating the particular
21 effect. So far, no attempt seems to have been
22 made, at least to my knowledge.

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1 MALE SPEAKER: Yes, quick question. Thank
2 you very much. Very interesting information. The
3 CPM, is that a trait or a state in an individual
4 patient?
5 (Laughter.)
6 DR. STAUD: Yes. This is like a question
7 that has been interesting for many of us so far.
8 But the long-term evaluation or the long-term
9 characterization of this particular effect has not
10 been done yet.
11 Clearly, there seems to be potentially some
12 relationship to age, that as we know, that CPM
13 seems to decrease with aging. There may be some or
14 there is potentially some trait effect, but we can
15 only speculate at this time.
16 DR. MARKMAN: One more question. DR.
17 MARCHAND: I wanted, yes, to react to the -- yes,
18 absolutely. We just finished the one study, I have
19 the data here, I can show you if you want, where we
20 tested it in young adults.
21 We tested the CPM now and after that, a day
22 after, a week after and one month. Even at one

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1 month, it's really stable, I mean it's really,
2 really stable.
3 But I agree with you. I will say it's a
4 trait and a state. It depends. You have both,
5 because if you compare a young and older adult, for
6 example, you will see a difference, also.
7 Then age is clearly playing a role and sex
8 in playing a role. Also, gender is playing a role.
9 And there are other factors, for sure. But I think
10 that at least if you compare it -- because if it
11 was moving around all the time, it will be of no
12 use at all, because if you measure it to see what's
13 happening with a drug, for example, and you know
14 that it's not stable over time -- but it seems to
15 be quite stable, as a matter of fact.
16 DR. STAUD: Yes. I think one of the
17 important work that needs to be done is with the
18 context-dependence. For example, it is well known
19 for placebo analgesia if similar changes also
20 influence significantly CPM, and this awaits to be
21 completed, this work.
22 DR. MARKMAN: As we're all, I think,

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1 probably mourning for Muhammad Ali this morning,
2 with these talks, I think you're giving a sense of
3 all the work to do. He said, "It's not the
4 mountains ahead to climb that wear you out. It's
5 actually the pebble in your shoe."
6 We're going to now switch gears to a
7 different approach and a different mountain that's
8 being climbed, which is through QST, with
9 Dr. Baron.
10 Dr. Baron is, I think arguably, the world's
11 leader in using QST to characterize patients with
12 different pain conditions and try and think about a
13 treatment response. He is professor of neurology
14 at the University of Kiel. It's a pleasure to
15 introduce him.
16 Presentation – Ralf Baron
17 DR. BARON: Thank you, John. Well, my task
18 today is to talk about QST, as you have heard. I
19 put always these pictures at the beginning of my
20 talk, and some of you might know them, just to show
21 you that many individuals are heterogeneous in
22 their appearance, and I think this holds true for

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1 patients, as well. And I will talk to this a
2 little bit.
3 This is the group or some of the group, I
4 think, in Kiel, in Germany. They are doing all the
5 work, as you know. You also know that neuropathic
6 pain -- and we would like to concentrate on
7 neuropathic pain today -- has many, many different
8 etiologies, and I put together some of them. But
9 just for this purpose of the talk, just imagine one
10 patient with -- or two patients with painful
11 polyneuropathy.
12 You see two patients and they come to your
13 office and you ask them, "Please describe to me
14 your sensory perceptions, what you feel." And
15 again, it's the very similar etiology behind this.
16 This is polyneuropathy.
17 One patient says, "Well, I'm suffering from
18 thermal hypersensitivity," and pinprick you can
19 measure and mechanical allodynia. And the other,
20 patient's profile is characterized by burning pain,
21 prickling, and shooting sensations and, in
22 particular, numbness, and there are no evoked pains

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1 whatsoever.
2 This was the observation we had many, many
3 years back. And we thought that if patients are so
4 heterogeneous, there might be different underlying
5 mechanisms and we might be able to identify this
6 with the QST setting.
7 This leads me to the agenda for today. I'm
8 calling this personalized treatment, but whatever,
9 precision is fine with me.
10 I would like to show that classification of
11 patients is possible based on these distinct
12 sensory profiles, perhaps speculate a little bit
13 with you about mechanisms -- because Clifford is
14 here, I think we have to do this -- some words
15 about genes.
16 We had some data on genes and I showed you
17 this some years ago already; therefore, very
18 briefly. And then the most important thing, can we
19 use these profiling options and techniques to
20 predict the treatment response.
21 I would like to give you three examples.
22 One is on capsaicin, topical capsaicin treatment;

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1 very briefly, the oxcarbazepine study Troels
2 already mentioned; and, then, something about
3 tapentadol.
4 The tapentadol is, in particular, in the
5 light of the talk of Nat because -- well, you will
6 see why in a minute.
7 We think that the answer to all the problems
8 we have with the many negative trials and so forth
9 might be this concept, the mechanism-based
10 classification or treatment approach.
11 This is my slide. You have seen many, many
12 others from Troels and Clifford, but this is mine.
13 We know that there are individual
14 pathophysiological mechanisms operating in our
15 patients.
16 This is the idea we have; that is, linked to
17 genes, perhaps to etiology, and to the environment.
18 And the treatment response is also linked to the
19 mechanisms.
20 We have the problem that we are not able to
21 look directly into the mechanisms in our patients,
22 but this is much easier in people who are working

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1 in the animal world, but we can't. So we need to
2 use surrogates to look, to have some ideas about
3 the operating mechanisms. We think that the
4 sensory profiling approach might be such a
5 surrogate where we can identify some mechanisms and
6 then identify in treatment responders.
7 In the first part of my talk, I would like
8 to briefly share with you some data about QST,
9 about the sensory testing protocol we have.
10 You all know, and we have mentioned this
11 several times during this meeting, this is the DFNS
12 QST protocol which we established in Germany 10
13 years ago now. We have many, many stimuli, 13
14 parameters all together, which we apply, mechanical
15 parameter, like pinprick, Von Frey hairs,
16 vibration. This is for positive signs like
17 allodynia. We also use algometer and, obviously,
18 the heat, the thermode [ph].
19 We have a variety of stimuli assessing
20 temperature and mechanical sensation and assessing
21 small fibers as well as large fiber functions.
22 This is, I think, the important thing with the

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1 protocol.
2 Just to mention this briefly, the algometer
3 is the only stimulus which is assessing deep
4 somatic innovation, like muscle innovation. All
5 the other stimuli are applied to the cutaneous
6 tissues, to the skin. So we mainly have an idea
7 about the innovation properties of the skin. This
8 is the logo of the German network.
9 What we can do with all these data -- and
10 this is now so-called sensory profile of one
11 particular patient and you see here at the bottom
12 are the 13 parameters, for example, cold detection,
13 warm detection, and so forth. So here are the
14 mechanical stimuli.
15 This is DMA. It's a little bit differently
16 coded. Therefore, we have an extra part here.
17 This is paradoxical heat sensation, so we talked
18 about these phenomena already.
19 What you can see if you put data of one
20 patient, like in this example, into the Z room, you
21 can see on one glance if a certain parameter is
22 normal because you have zero line and if you, if

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1 your value hit the zero line, then you have normal
2 data compared to our normative database.
3 If you are in the upper part of the figure
4 and, again, on function part, you have a
5 hyperphenomena, a phenomenon like hyperalgesia,
6 allodynia, and so forth, and if you are here in the
7 lower part, you have phenomena to this particular
8 stimulus in the hypo area, so hypoalgesia,
9 hypoesthesia, and so forth.
10 We think that this might indicate a
11 degeneration of fibers and this is in hyperactivity
12 state, be it in the periphery or in the central
13 nervous system.
14 This, again, is one patient and we did this
15 now in many, many, many patients in our networks.
16 We not only have data within the German network,
17 but also within different European networks.
18 This is the so-called Neuro Pain Network.
19 This was sponsored by Pfizer, with many, many
20 centers across Europe. And this is the IMI
21 European, as you have already heard, with many,
22 many, many centers all over Europe.

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1 What we did in the last years is that we
2 concentrated on neuropathic pain patients with
3 peripheral origin, so peripheral neuropathic pain,
4 and we excluded all the central patients we also
5 have in the data on pain.
6 This is a little bit different from the
7 approach we used some years ago and what you have
8 seen in earlier talks from me. Here, we
9 concentrate on peripheral neuropathic pain, because
10 we thought that the mechanisms in central and
11 peripheral neuropathic pain differ.
12 We excluded CFS from our database, because
13 we, again, thought that CFS might differ in terms
14 of underlying mechanisms. And we excluded
15 trigeminal neuralgia, again, for the same reason.
16 We included in this particular analysis all
17 the polyneuropathy patients, different etiologies,
18 zoster, postherpetic neuralgia, and radiculopathy
19 patients.
20 So if you just concentrate in these
21 entities, we can come up with more than
22 1,100 patients now which are in our database. This

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1 is a very clean database.
2 The QST is standardized in all centers. All
3 centers have to do training sessions. So they are
4 trained. We have very strict quality assurance in
5 place.
6 They send data to the central database and
7 this is checked and so forth for plausibility and
8 so forth. So it's a relatively clear database with
9 these patients.
10 If you look in this a little bit more in
11 detail, and I show you many, many different
12 patients now which we analyze in this video, you
13 can see that patients really are not the same. So
14 they are heterogeneous. They have different
15 sensory perceptions. And if you look at all the
16 different 1000 patients, you can get this. I think
17 I can convince you that some are here in the
18 negative range, but some are in the positive range
19 and so forth.
20 This is a variety of different perceptions
21 and problems and perhaps underlying mechanisms.
22 To get some order in this seemingly

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1 heterogeneous picture, we used a statistical trick
2 to do a subgroup analysis, a pattern analysis, and
3 we also used hierarchical cluster analysis.
4 If we do this, apply this in this particular
5 group of peripheral neuropathic pain patients, we
6 could come up with three very stable different
7 subgroup clusters, and these are the different
8 clusters.
9 I'll show you the mean of these groups now
10 in this particular graph. We call them -- the
11 first one, the blue one is the group sensory loss,
12 which we call sensory loss.
13 You see the blue profile, nearly all of the
14 values are located in the negative area of the Z
15 profile. So everything is indicating loss of
16 function, degeneration.
17 The red one is thermal hyperalgesia. It's
18 one-third of the patients in this group. This
19 group, which you can see here, is mainly
20 characterized by thermal hyperalgesia for cold, as
21 well as heat. So the main hyper phenomenon is
22 thermal hyperalgesia.

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1 The green one is very interesting. It's
2 characterized by loss in the small fiber range. So
3 this is warm/cold in combination with mechanical
4 hyperalgesia for pinprick and severe allodynia, as
5 well. And because this is dominated by those
6 mechanical hyperalgesia problems, we call this
7 mechanical hyperalgesia, and a quarter of the
8 patients form this category.
9 If you look at these three different
10 profiles, this is very, very similar to the
11 original three profiles Mike identified in
12 postherpetic neuralgia patients when we published
13 this paper back in 1998. So this was really
14 confirming for us that there might be some truth in
15 these statistical approaches.
16 If you look at the values which best
17 discriminate between all these three groups,
18 because I think this is very important if it comes
19 to use in clinical routine, this is warm detection
20 threshold in mechanical pain sensitivity, which is
21 the pinprick stimulus. I will show you in this 3D
22 plot how the data really look like.

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1 The green one -- again, the color coding is
2 the same -- is the mechanical hyperalgesia group;
3 the red one, the thermal hyperalgesia group; and,
4 the last group is in blue.
5 Obviously, you can see, if you see here, the
6 values just for the two different parameters, one,
7 detection threshold; and, the pinprick threshold.
8 Pinprick is over here on the left side and this is
9 the warm.
10 You can see, obviously, that there's an
11 overlap in these three groups. But still, if you
12 look at the centroids -- these are the
13 centroids -- there's a clear discrimination between
14 both of them.
15 I think if we just use the two parameters,
16 we can, with a certain probability, allocate
17 particular individual patients to one of these
18 three subgroups, which I think is very important
19 for the future if it comes to clinical trials.
20 We did a replication. So this is the
21 original cohort and you see here, again, the three
22 different subgroups and the profiles. We did a

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1 replication in the second cohort.
2 These are the patients who were included
3 into the trials, Troels' trials, which he was
4 discussing yesterday, this Demant trial with the
5 lidocaine patch and the oxcarbazepine.
6 These patients were not in the original
7 group and, therefore, we had access to this
8 replication cohort. And you see a very, very
9 similar structure as it comes to the profiles.
10 How is the distribution within etiologies
11 with these three different subgroups? You can
12 find, identify each of the subgroups in each of the
13 etiologies, but there are certain frequencies and
14 particular frequencies.
15 Perhaps this is important, again, for trial
16 design. If you have a drug, for example, which is
17 particularly active in hyperalgesia phenomena, you
18 should look into these graphs, which classical
19 clinical model you can choose for your trial.
20 These are all the patients, the polyneuropathy
21 patients.
22 Clearly, the most important profile here is

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1 the loss profile. And as Troels already mentioned,
2 allodynia, mechanical allodynia, which is hidden
3 here in the green one a is very rare phenomena in
4 polyneuropathy.
5 This is radiculopathy, peripheral nerve
6 injury, much more hyperphenomena in the thermal
7 range, as well as in the mechanical range. For
8 postherpetic neuralgia, this is striking. This is
9 the most important, and the most frequent clusters
10 or subgroups are these hyperphenomena. I think
11 it's very interesting to look at these different
12 distributions.
13 Some speculation about mechanisms now, so
14 this link. Can we really look into mechanisms?
15 And I think if we start with a sensory loss
16 subgroup, I think this is pretty straightforward,
17 we think that in these patients -- and you see the
18 graph here -- the peripheral nerve fibers, the A
19 fibers, the C fibers here, the spinal cord, these
20 patients are characterized by a degeneration of all
21 fiber classes, because we have losses in the small
22 fiber range, as well as in the large fiber range;

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1 so degeneration here and here.
2 The pain might be produced perhaps in the
3 spinal cord, in the spinal ganglion, those root
4 ganglion, so ectopic problems in the dorsal root
5 ganglion. Marshall Devor's work, I think, points
6 to this direction.
7 Also, if there is a deafferentation in the
8 spinal cord, the pain might be produced as a
9 deafferentation pain spinally.
10 Another example, thermal hyperalgesia group,
11 again, characterized by heat and cold hyperalgesia
12 mainly, so what could be the underlying mechanism
13 in this subgroup. We think this is then due to
14 upregulation expression of some channels and
15 receptors. And we talked about TRP V1, perhaps
16 others, sodium channel expression.
17 And we can explain the thermal hyperalgesia
18 phenomenon which we call peripheral sensitization
19 and the spontaneous pain is produced by spontaneous
20 activity in the surviving hyperactive fibers in
21 this subgroup.
22 So perhaps I can convince you that there

<p style="text-align: right;">Page 77</p> <p>1 might be a link between the mechanisms in our 2 specific profiles, and we call this peripheral 3 sensitization. 4 Just one brief word to this link. Can genes 5 influence the individual mechanisms and the 6 phenotype? We collected DNA of many of the 7 patients in our network and did a very classical 8 association study where we looked for association 9 between the QST parameter and profile, in 10 particular, polymorphisms which we choose before. 11 I know this is old-fashioned and this is not 12 replicated, but after all the correction 13 procedures, and I think this is pretty 14 straightforward, we could find one polymorphism. 15 This is the A1 and the TRP A1 gene, which acts as a 16 protection gene against cold hyperalgesia. 17 If you have this polymorphism -- and this is 18 located here in the TRP A1 -- and you will get 19 postherpetic neuralgia or diabetic polyneuropathy, 20 you are protected against cold hyperalgesia. 21 Perhaps you can get heat hyperalgesia or other 22 spontaneous pain, but statistically, you are a</p>	<p style="text-align: right;">Page 79</p> <p>1 identify significant differences in the baseline 2 profile for cold pain threshold and for the 3 mechanical pain sensitivities or the pinprick 4 threshold. 5 That was really irritating for us, because 6 we thought -- our hypothesis was that this might be 7 something -- has something to do with heat, because 8 it's capsaicin, but it was cold. 9 There's a co-localization of TRP A1 and V1 10 in many, many nociceptor fibers. Perhaps there is 11 some underlying sense, I don't know. 12 If you combine both of these parameters, the 13 cold pain threshold and the mechanical pain 14 threshold, and you define a threshold, you can 15 predict the response based on the data here 16 retrospective with relatively good specificity and 17 sensitivity values. So perhaps a hint that we can 18 use these profiling to identify responders to 19 capsaicin. 20 The second example is Troels' and this 21 really is the first profile stratified trial. And 22 I really would like to stress this. We know we</p>
<p style="text-align: right;">Page 78</p> <p>1 little bit protected against cold. 2 The same holds true for heat hyperalgesia. 3 Again, a protection SNP in the TRP V1 channel gene 4 here, in this area it's located. Again, it's weak 5 data, but just to show you for the whole story. 6 This is the main and most important idea. 7 Can we use the profiling techniques to predict 8 treatment response and to identify responders? 9 The first example is on topical capsaicin 10 8 percent. This is a small study. What we did in 11 this study is we treated 20 patients with capsaicin 12 topically. 13 We did the profiling before we initiated the 14 treatment. So at the beginning of the trial, the 15 profiling was done and then we did a post-hoc 16 analysis, retrospective analysis, looking for 17 responders and non-responders to this treatment. 18 This is the responder profile on the left 19 side. On the right side is the non-responder 20 profile, which we could identify. By chance, it 21 was 10 and 10, which was nice. 22 If you look and compare both, we could</p>	<p style="text-align: right;">Page 80</p> <p>1 came from the scenario that many, many sodium 2 channels failed in phase 3. 3 You mentioned this yesterday. Novartis 4 didn't get approved and so forth. So the question 5 is, does it work in subgroups, and this is the 6 title. And I really like the title, because 7 there's everything in there, it's randomized, it's 8 double-blind, it's placebo-controlled, and 9 phenotype stratified, so the best that you can do 10 at this point of time. 11 This is the data, how I show it. It's 12 exactly the same data. If you now allocate the 13 original profiles which Troels found in his trial 14 for responders and non-responders -- so the 15 stratification due to your things -- if you 16 allocate this and compare this with our 17 profiles -- so this is the 31, these are the 18 profile, the mean average profile of the 31 19 patients you put into your group -- irritable 20 nociceptor, correct? And the underlying shade is 21 the profile of our statistical result of the 22 thermal hyperalgesia subgroup. And perhaps I can</p>

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1 convince you that it's very similar, except one
2 here, but this is due to Danes, I think. So this
3 is a difference in Danes.
4 On the other hand, they allocated 52 percent
5 into the other group, non-irritable nociceptor
6 group. And I underlay here the sensory loss
7 profile of our cluster analysis and this, again,
8 neatly fits. And again, there's a small peak,
9 which is not correct, at the pain pressure
10 threshold.
11 I hope I can convince you that there are
12 some similarities of these two groups, the
13 irritables in the Demant oxcarbazepine study and
14 our groups, which we could identify.
15 Interestingly, we put into the European
16 Medicine Agency CHMP qualification advice and asked
17 them whether they are willing to use our QST
18 certification testing for trials in the future.
19 We got a positive reply and this is the
20 exact wording from the reply, that they think that
21 our sensory profiling and subgrouping strategy is
22 an adequate stratification tool for -- and

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1 particularly for phase 2 trials.
2 But -- and there's a "but" --this is phase
3 2 and I think we can implement all these techniques
4 and things into phase 2, but we need something like
5 a bedside testing, and we will hear more in a
6 minute about beside testing.
7 We are doing some bedside testing things, as
8 well. We tried to establish a bedside test which
9 mimics as closely as possible the QST battery,
10 because we have all the data from the QST battery.
11 If you see this part here, these are small
12 metal pieces and these are exactly the same size as
13 the thermode of the Medoc machine, and we can cool
14 and warm them. I don't want to go into detail, I
15 can't, I think. But this is an ongoing project,
16 and we will really look for and validate this
17 bedside test exactly against QST. Perhaps we would
18 like to see what this will do.
19 Can I have five more minutes? This is the
20 second example. I just wanted to share the data,
21 because they are brand new and they are under
22 revision now in the European Journal of Pain.

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1 We calculated a prediction model, a real
2 huge prediction model in pain research. From my
3 mind, I think this is the first really prediction
4 model in pain research. We know all these
5 prediction models from oncology and we heard a lot
6 about oncology, but this is the first in pain.
7 This is in the cohort. These are data of a
8 clinical trial with tapentadol in patients with
9 back pain radiculopathy; so a huge group of
10 patients, back pain radiculopathy.
11 I have to admit, these are data from an open
12 label trial, no placebo arm. And I know what Nat
13 is now saying and looking, "This is all rubbish."
14 (Laughter.)
15 DR. BARON: But I disagree and I would like
16 to show that perhaps there is some sense in what we
17 can learn from this. But, look, we had access to
18 all the data of this particular trial of Grunenthal
19 with tapentadol in patients with back pain
20 radiculopathy.
21 There were 46 baseline co-variables, so all
22 the baseline data which were assessed in this

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1 particular trial. We wanted to see whether some of
2 these baseline characteristics may have a
3 predictive effect on outcome.
4 Just briefly, demographic characteristics,
5 you mentioned demographics briefly. Medical
6 history, vital signs, so this is all the normal
7 things.
8 Physical examination, but we also had the
9 PainDETECT score. We used the PainDETECT
10 questionnaire. I will show you the PainDETECT
11 briefly in a minute. And, also, things like
12 qualities of the pain, like burning, prickling,
13 allodynia attacks and so forth. You can read this.
14 And we had all the comorbidities available at
15 baseline, sleep as of 36 EuroQol and HADS.
16 What we did with PainDETECT -- this is the
17 PainDETECT questionnaire. It's a little different
18 from LANSS and DN4, as you know. But we use them
19 the capture neuropathic elements to the pain.
20 These are the seven questions we assess with
21 the PainDETECT. Interestingly, and this is
22 important, we have a grading in our PainDETECT

<p style="text-align: right;">Page 85</p> <p>1 questionnaire from 0-5. So we have some 2 information about intensity of each symptom we 3 would like to assess, which is interesting for the 4 prediction model. 5 Now, this is more for the statisticians. I 6 do not really understand this, but they say this is 7 state-of-the-art prediction models; first, 8 univariate, then multivariate analysis, all these 9 correction things, over-fitting and so forth. 10 This is a very, very conservative prediction 11 model, I have to admit, with all these correction 12 things. 13 In every step, there are corrections and so 14 forth. I think that what falls out of this 15 prediction model is a relatively solid predictor 16 for this particular trial. 17 These are the results and I think these 18 are the learnings we have. If we look for the 19 primary outcome in these clinical trials, this was 20 improvement of pain intensity on the NRS scale, 21 which we discussed extensively, we couldn't find 22 any baseline predictor for this outcome. But we</p>	<p style="text-align: right;">Page 87</p> <p>1 tapentadol, which might be in line with the 2 mechanism of action of tapentadol with these 3 additional NRI components. So we can speculate 4 this. 5 We put this, the data from the model, into a 6 formula. For example, for the quality of life 7 response, you can calculate this formula. You can 8 put in all these baseline values here and then you 9 can calculate the predictive response in this 10 particular individual based on the data and the 11 clinical trial. You can also do nomograms and do 12 this graphically and estimate the response of the 13 patients. 14 I think what we can do in the future -- and 15 scientifically, perhaps there's a problem. I will 16 discuss this in a minute. But clinically, I think 17 this has relevance, because even if this is not a 18 placebo-controlled trial, it's open, it's relevant 19 for daily clinical routine. 20 We can estimate from this prediction what 21 change of quality of life we can expect in one 22 patient who is sitting in front of you in the</p>
<p style="text-align: right;">Page 86</p> <p>1 also looked for different outcomes, because we had 2 all the questionnaires also at the end of the 3 trial. 4 We looked for the improvement of function, 5 functionality, and the improvement of quality of 6 life in this trial. Then we could identify some 7 very stable predictors, and I put them together 8 here. It's a low health state, a good mental 9 state, and a high PainDETECT score, and a little 10 bit male, which is a predictor of the physical 11 function. And if it comes to quality of life, it's 12 low depression, low anxieties, the classical 13 comorbidities which we would think there might be; 14 and again, a high PainDETECT score and few 15 PainDETECTs. So if you have very few of these 16 severely painful attacks, you have a good chance to 17 be a responder in terms of quality of life and you 18 have improvement of quality of life. 19 Also, always the high PainDETECT score. So 20 many, many neuropathic symptoms. If you have many 21 symptoms, burning and so forth, that is a predictor 22 for a good improvement after the treatment with</p>	<p style="text-align: right;">Page 88</p> <p>1 office. 2 Let's look at three different patients, and 3 I've put this data of these patients into the 4 formula. Back pain, a little bit of depression, 5 but also with sunlight. So if you look for 6 PainDETECT, 10 is relatively low; attacks is low 7 and HADS is low. 8 Then the formula will calculate a predicted 9 possible response of 30 percent increase of quality 10 of life after the treatment of tapentadol. 11 I think I can talk to my patients and say, 12 "Well, you have these values at baseline; you can 13 expect 30 percent change, increase in quality of 14 life." 15 There's another one huge neuropathic 16 element. Your burning is really high and so forth. 17 So PainDETECT is high, 21, no attacks and HADS is 18 4. Then the prediction will say, "You can expect a 19 50 percent increase in your quality of life after 20 the treatment." 21 But this is interesting, because it's not 22 only prediction of response, it's also a prediction</p>

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1 of non-response in this model. If you have a
2 patient with huge depressive symptoms, so HADS is
3 really high, and severe attacks, these really
4 intense attacks, he comes into your office with a
5 PainDETECT of 8, it's low, severe attacks, and high
6 HADS level, then the prediction says, "You have a
7 decrease in quality of life after the treatment of
8 tapentadol" and this is due to the -- I think the
9 side effects are more intense than the benefit in
10 terms of reduction of pain.
11 The patient in these trials will rate this
12 as a decrease in quality of life. I have these
13 data available in my office. I think I could
14 choose perhaps tapentadol in some of these
15 patients, perhaps. This is from the precision
16 medicine.
17 There are many limitations to this approach
18 and we discussed this. Nat said it absolutely
19 correctly. There's no placebo arm, so we can't
20 separate general predictive responses, effects. So
21 these are effects everybody has with every
22 medication.

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1 It's independent of the specific medication
2 with tapentadol and the specific predictive
3 effects, which really relate to the tapentadol
4 treatment.
5 But I think perhaps the PainDETECT might
6 be -- is likely be specific, although I don't know
7 this exactly. But I think these approaches, even
8 in open label trials, have some learnings.
9 What we learned is that demographic baseline
10 data are not relevant. I think this is what we can
11 say, even if this is open. There is no association
12 between demographic data and response.
13 Gender has a minor influence, only in
14 functionality and the prediction of functionality.
15 Male are a little bit better in terms of function
16 afterwards.
17 This is, for me, the most important
18 learning. The alternative outcome parameters, like
19 quality of life, functionality, seem to capture
20 this better than the conventionally pain intensity
21 measures. I think we have to think about this a
22 little bit more in detail.

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1 These are my conclusions. I think we are on
2 a good way that the personalized treatment becomes
3 reality. This is what I've shown you and this is
4 my vision on how we can translate this into the
5 practice.
6 I think in the future, every medication has
7 a certain prior profile and then we can profile a
8 patient with QST. And this is the medication
9 profile, one for example, and then you have to look
10 whether your QST key is fitting into this profile.
11 And you'll see this is not really fitting.
12 Then you have another profile. This is
13 another medication you have tested already. It
14 doesn't work. And then you have the right profile.
15 The key is fitting and this the right medication
16 for the right patient.
17 These are, again, a little bit into the
18 future, where, at the moment, prediction analysis
19 are calculated, are performed, which substances,
20 with QST data.
21 I've shown you oxcarbazepine and capsaicin,
22 but there are many, many more, where now, QST is

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1 implemented in particular phase 2 trials and
2 others, PainDETECT, as well, and the NPSI of DD,
3 Neuropathic Pain Symptom Inventory, as well.
4 I think companies did learn a little bit and
5 the best step forward.
6 Then I would like to thank everybody, so all
7 the people, patients who are involved in the
8 networks, the German network, the European IMI, and
9 the Neuropain Network.
10 These are all the academic partners in these
11 networks. Many are here in the room, as you can
12 see. And, of course, all the lab members and
13 patients.
14 Thank you very much for listening. Thank
15 you.
16 (Applause.)
17 DR. MARKMAN: To wrap up this first session
18 of the morning, I invite Dr. Freeman, professor of
19 neurology at Harvard Medical School.
20 I think we're going to hear more about how
21 to take some of this attempt to improve treatment
22 matching and make it more pragmatic and more

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1 applicable to everyday practice with some of the
2 techniques he's going to talk about right now.
3 Presentation – Roy Freeman
4 DR. FREEMAN: Thank you. Thank you, John.
5 I'm going to go from the laboratory to the
6 bedside, and it's a long trip. You've heard, I
7 think, what I'm going to say in the next couple of
8 slides about the trip from mechanism-based
9 treatment of pain to sensory profiling and back
10 again, and you've heard this from a number of
11 different perspectives.
12 Let me give you my perspective on this, and
13 that is that doing a clinical trial with a new
14 chemical entity or even an old one or seeing a
15 patient in a clinic is like being an old-style
16 matchmaker.
17 You need to match the patient with the drug
18 and you'll either be a successful matchmaker or it
19 will be a mismatch. It's a challenge. Ralf, I
20 think, showed it very graphically with his finding
21 the right key to fit the lock.
22 You want to match the patient with the drug,

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1 which is to say that you want to match the pain
2 mechanism with the drug mechanism. But the
3 challenge for the clinical arena is to know what
4 the pain mechanism is.
5 The hypothesis that underlies the mechanism-
6 based treatment of pain based on phenotype is that
7 the phenotype is a surrogate for the pain
8 mechanism.
9 We then want to go back and there are a
10 series of assumptions inherent to this that you
11 will match the phenotype with mechanism, mechanism
12 with drug, and then patient with drug.
13 Now, this is the challenge and in order to
14 accept the challenge, you really have to, as
15 Coleridge said in the 19th century, "Every
16 movie-goer knows and every theatre-goer knows you
17 have to suspend disbelief," as to the, as they
18 said, implausibility of the narrative, because it
19 really is a fairly implausible narrative. And I
20 think all of us who are either believers or
21 agnostic waiting to be convinced need to, for the
22 moment, suspend disbelief.

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1 Now, it's not as implausible as all that.
2 Why that is the case and why one might be willing
3 to suspend disbelief is, I think, embodied in this
4 series of serial nerve biopsies shown in EM.
5 These are patients who all have diabetic
6 peripheral neuropathy and just for purposes of
7 illustration, I want you to imagine that each one
8 of them has neuropathic pain. I actually don't
9 know whether they have neuropathic pain, but they
10 could easily have neuropathic pain.
11 There is absolutely no question, when you go
12 from the normal patient, perhaps a patient with
13 impaired glucose tolerance, to the mild peripheral
14 neuropathy, to the moderate to the severe, in which
15 it's hard to imagine that there's even a large or
16 small nerve fiber there, it is easy to imagine that
17 the generators of pain in these different patients
18 are very, very different and that it seems much
19 more likely -- and here, one invokes the
20 transient etiological approach to the
21 mechanism-based treatment of pain -- it's much
22 easier to imagine that what is more important in

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1 the therapeutic intervention is the mechanism and
2 not, as is currently viewed by at least the
3 American regulatory authorities, the disease.
4 Now, this has lent some support, and I'm
5 taking you back to an older paper from the Danish
6 group, because I'm going to begin to introduce the
7 notion of timelines, this has given some
8 support-- and I am sorry for the shift of
9 data -- by a comparison -- this is much worse than
10 it was in my computer -- if you can sort of imagine
11 the non-DPN moving above this column over here, I
12 think it's kind of clear, and the DPN coming down
13 over there and that moving across over there.
14 (Laughter.)
15 DR. FREEMAN: Well, the theme is suspension
16 of disbelief.
17 (Laughter.)
18 DR. FREEMAN: Of course, this is accurate,
19 isn't it? I don't know what Ralf said about the
20 Danes and what he implied by it, but there's
21 something there.
22 But to get back to this slide. There are,

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1 apart from the one asterisk, non-DPN and DPN
2 patients, in terms of symptoms, have actually very
3 similar profiles. And this is not quite as bad,
4 the same thing with clinical science.
5 I won't go into the details, but this formed
6 the basis for a discussion that I had with Pfizer
7 over a decade ago. And here, I want to introduce
8 the timeline. I actually gave this talk, I think,
9 three years ago to an audience just like this. In
10 fact, some of you may have been there.
11 I had some -- I call them historical slides,
12 Washington-based historical slides which
13 illustrated the timeline, and I'm going to use
14 those slides again in this talk.
15 Now, at that time, Clifford convened his
16 meeting shortly after coming to the U.S. and had
17 published that article he showed yesterday.
18 Clifford and Mitchell Max had written that piece in
19 Anesthesiology. The German network was up and
20 running. And I was agnostic about the notion of
21 mechanism-based therapy based on phenotype. But I
22 said to Pfizer that, "Look, if this really is going

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1 to work, if this is true, we cannot do this based
2 on having every clinician spend two weeks in
3 Mannheim with Rolf-Detlef Treede, be trained by a
4 German technician in a white coat, get a
5 certificate."
6 (Laughter.)
7 DR. FREEMAN: And I don't wish to denigrate
8 what happens in Mannheim. This is the gold
9 standard. This is the BMW 7 Series. But I thought
10 we needed to do something, I don't know, a litter
11 greener, a little ecologically-friendly, a little
12 shorter.
13 I proposed -- I don't know, the Prius, the
14 new Tesla -- something that was a little shorter
15 than the two-hour and \$25,000-piece of equipment
16 that is necessary to do the full German battery,
17 which I think all of us will regard as the gold
18 standard.
19 This was at the time when Bill Clinton was
20 president and Obama was a community organizer, so
21 quite some time back. So it took a long time.
22 Clifford gave some well-needed support and

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1 eventually mission was accomplished. And that
2 actually took place round about there when George
3 Bush president, and this is, I don't know, an
4 iconographic slide of mission accomplished.
5 Pfizer agreed to incorporate a relatively
6 simple, quantitative sensory test battery in a
7 clinical trial. As it transpired, they actually
8 did it and more. And they also thought that a
9 symptom inventory was a good idea and they agreed
10 to incorporate the NPSI.
11 As many of you are familiar with the NPSI,
12 this is a self-administered questionnaire, 10
13 different descriptors and you know them well,
14 superficial and deep spontaneous ongoing pain,
15 burning, squeezing pressure, brief pain attacks,
16 paroxysmal pain, evoked pain provoked by brushing,
17 pressure, and contact with cold, abnormal sensation
18 in painful areas. And there are, in the
19 questionnaire, temporal items which were not
20 included in any of the clinical trials.
21 The QST battery that I proposed was one
22 which looked at sensory threshold using the graded

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1 Von Frey hairs. It looked at static allodynia,
2 dynamic allodynia, punctate hyperalgesia, temporal
3 summation to tactile stimuli, cold allodynia and
4 cold hyperalgesia.
5 This has changed somewhat over time. It's
6 not exactly what we do at the moment, but this is
7 what was done in the trials that I'm going to talk
8 about.
9 What I call the QST method was proposed and
10 presumably implemented in these trials, as well,
11 which is to say the testing needed to be performed
12 in a quiet environment, patient lying quietly,
13 testing performed on the area of maximal pain,
14 supplied instruments needed to be used, the test
15 needing to be performed in the same area, and the
16 exact wording needed to be used and so on.
17 I also want to say that in contrast to the
18 \$25,000-piece of equipment that -- at least that's
19 what they cost in the U.S. -- that the German
20 network -- and that is used for all our
21 laboratories for QST -- all of the equipment was
22 bought at Home Depot, with the exception for the

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1 Von Frey hairs, which cost a little bit more. But
2 the rest of the equipment is less than \$10.
3 So the QST method, and this is really how we
4 do the sensory threshold determination, using an
5 up-down method with the Von Frey hairs. I'll show
6 you graphically. You start with 4.31. After the
7 patient perceives it, you go down. If the patient
8 doesn't perceive it, you go up.
9 When you go down, more than one trial was
10 required, three trials, and we did this three times
11 initially just to be sure that this was done well,
12 and that the aim of this was really to assess the
13 state of afferentation, and, of course, this is a
14 large fiber measure.
15 These were the instructions and the
16 instructions -- and even though this is bedside and
17 simple, the QST method was important and the
18 paradigm was important and the instructions needed
19 to be identical. No, it was not translated
20 differently when this was done in the various CROs
21 that did the trials.
22 We looked at static mechanical allodynia

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1 evoked by the base of a Von Frey hair, as you see
2 over there, for the 10 seconds, and the tester read
3 the identical instructions to the subject each
4 time.
5 Same thing with dynamic mechanical
6 allodynia. There are the instructions. I won't go
7 through the instructions in detail. And identical
8 reading of the instructions.
9 I show this just because I want to make the
10 point that there is not punctate hyperalgesia, that
11 even though this is a \$10-equipment and there is no
12 training by Rolf Detlef, that we tried to make this
13 rigid and identical across sites. I say tried,
14 because this was at clinical trial.
15 Same instructions, temporal summation. This
16 is the largest Von Frey hair, the 6.65. See the
17 timer, approximately 2 hertz, same instructions and
18 cold allodynia.
19 The rod is placed in cold water, cooled in
20 ice. So using equipment available in any clinic
21 and any lab, make sure that it's for 4 degrees
22 Centigrade and applied.

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1 The biggest debate with these videos was
2 whether we should use one of the male feet or a
3 pedicured female foot, and the male one, as you
4 see.
5 We are now at this point. Obama is debating
6 John McCain. And I, to be honest, had forgotten
7 all about this. I spent a lot of effort persuading
8 Pfizer to do it. You know how long these clinical
9 trials take. They did what they did and I was
10 doing other things.
11 I was at one of Bob Dworkin's meetings, at
12 the time when they used to have these things in
13 Bermuda, and David Simpson comes up to me and he
14 says to me, "Do you remember that cumbersome QST
15 thing that you made us do in the HIV
16 trial" -- David Simpson was the PI on the HIV
17 pregabalin trial -- "what ever happened to that?"
18 I gave that gesture and we went to the
19 people involved at Pfizer and said, "What ever
20 happened to it," and as you may know, that was a
21 negative trial, that pregabalin for HIV neuropathy
22 was negative. But when -- and there was no pre-

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1 specified hypothesis at all, but when the data were
2 examined -- and I'll underline it over here -- the
3 treatment effects differed greatly in subjects with
4 a greater sensitivity to pinprick at baseline, so
5 the punctate hyperalgesia score.
6 Maybe I didn't explain. Other than with the
7 sensory threshold testing, we do not test
8 threshold, but we ask patients or subjects to rate
9 the pain to the punctate hyperalgesia. So all of
10 the evoked pain assessments are not done looking at
11 a threshold, but are measuring an evoked pain.
12 So those that rated punctate hyperalgesia,
13 and you saw how it was done, greater than 10, and
14 this was a negative study, 2.14 greater improvement
15 in pregabalin compared to placebo.
16 Now, Pfizer wishes that they said, "Okay,
17 we, just as the EMA, may be moving in that
18 direction," with their phase 2 and hopefully phase
19 4. Of course, it was a negative trial, but the
20 punctate hyperalgesia group were dramatically
21 different.
22 Where are we? Now, Obama is president and

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1 Bill Clinton looks like that. So there has been a
2 change. And we have the results of what I'm
3 calling the primary analysis trial.
4 What Pfizer did -- and they actually did
5 this in four trials. Some of them were not as
6 intensely trained. The first one or two, I was
7 actually involved and people from my team came and
8 trained the investigators really well.
9 One or two of them were not as well trained
10 as I would've hoped, but Pfizer had the video and
11 trained the investigators. The results of this
12 actually have been reported in Pain. I'm not going
13 to take you through the details of this, but this
14 is the first paper which looks at the sensory
15 profiles or the phenotype.
16 Here, you see the results of the clinical
17 QST across all of the various measures, static
18 mechanical allodynia, dynamic mechanical allodynia,
19 cold allodynia. I can take you through all of
20 them.
21 But there is a bottom line over here and
22 that bottom line is actually very, very similar to

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1 the point Andrew made, and that is that, first of
2 all, there are more similarities than differences;
3 and, second of all, that the prevalence, the
4 frequency of evoked pain in DPN and HIV peripheral
5 neuropathy is actually rather low compared to the
6 other groups.
7 What I would ask you to do is to focus on
8 the severe, which is in blue. So if you look
9 at the key to this, it's saying that a mild
10 response to the stimulus, which is 0-3, is in red;
11 a moderate response is 4-6, is in green; and, a
12 severe response, 7-10, is in blue.
13 So there are subtle differences, but the
14 message is that overall, in these three disorders,
15 central post-stroke pain, HIV peripheral
16 neuropathy, and diabetic peripheral neuropathy,
17 there are many more similarities than differences.
18 In the same way, looking at the NPSI -- now,
19 the NPSI was used in four of the trials, whereas
20 only three QST were used -- you see very much the
21 same, with the exception of -- here, I want to take
22 you to the bottom row. Remember, the same key and

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1 as you see, there is somewhat more burning pain,
2 electric shock, stabbing pain, pins and needles,
3 and tingling in the peripheral groups, HIV and DPN,
4 and less so in the post-traumatic pain. And this
5 is the NPSI. But again, overall message, more
6 similarities than differences.
7 What was really interesting, and I want you
8 to focus purely on this rather complex figure, on
9 the top panel, in which the QST is actually
10 compared to the -- and it is a little hard to see,
11 I know -- the QST is actually compared to the NPSI,
12 what is really interesting is if you look at the
13 somewhat darker blue -- and again, we're looking in
14 the A, the top left panel -- what you'll see is
15 that pain provoked by cold actually correlates
16 reasonably well -- to me, the fact that there's any
17 correlation is surprising -- reasonably well with
18 the cold hyperalgesia and cold allodynia test and
19 that the static allodynia, dynamic allodynia
20 correlate reasonably well with pain evoked by
21 pressure and with pressure pain and squeezing pain.
22 To me, this is, to some extent, internal

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1 validation of both techniques in that both the
2 questionnaire and an evoked pain measure show
3 acceptable correlations.
4 Well, what about pain phenotype as a
5 response predictor? Pfizer actually did a fourth
6 study or a fifth study, depending on whether you
7 are counting the post-traumatic neuropathy study in
8 which only the NPSI was done.
9 We now have data with what I call the
10 primary analysis, which was the thesis, and then
11 the confirmatory analysis study. These are the
12 results of a multivariate analysis.
13 With respect to NPSI, moderate-to-severe
14 pain provoked by cold, moderate pain provoked by
15 pressure, and mild pain provoked by brushing, was
16 associated with a significantly better response to
17 pregabalin than placebo in both primary and
18 confirmatory analyses.
19 Now, of these primary analysis studies, only
20 the post-traumatic pain study was positive. All
21 the other three were negative. If you look at the
22 difference between the effects of pregabalin

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1 placebo, the mean value was 0.77. In the
2 confirmatory analysis, the difference between the
3 effects of pregabalin placebo, that was the spinal
4 cord injury study, which was a positive study, the
5 mean value was 1.40.
6 So some support to the notion that sensory
7 profiling using a questionnaire can predict
8 treatment response and, in particular, in a
9 negative study.
10 What about the bedside QST? Here, we show
11 severe punctate hyperalgesia, moderate-to-severe
12 cold hyperalgesia, and moderate-to-severe temporal
13 summation to tactile stimuli were associated with a
14 better response to pregabalin in both the primary
15 and confirmatory analysis.
16 It's important to note that the degree of
17 afferentation or deafferentation made no difference
18 at all. It was not a predictor.
19 The primary analysis showed a difference
20 between the effect of pregabalin placebo using
21 those criteria was 1.34. The mean difference,
22 statistically significant, the confirmatory

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1 analysis 1.88.
2 Now, for negative studies, these are
3 reasonable values and one -- again, these were not
4 pre-specified hypotheses, but certainly formed the
5 grounds for a pre-specified hypothesis.
6 This is what the punctate hyperalgesia looks
7 like. As Ralf implied, the DPN, bottom right; HIV,
8 bottom left; central post-stroke pain, top; and,
9 all of them grouped together, there really does
10 seem to be a difference between those patients that
11 had a peripheral cause of pain and the central
12 cause of pain.
13 Here's the temporal summation, not quite as
14 dramatic, but still the same and still a difference
15 between central and peripheral.
16 I want to just look at selected other
17 studies. Now, I'm not going to refer to it -- it's
18 been referred to several times -- the two Danish
19 studies looking at sodium channel antagonists.
20 I'm going to look at the study by Jim
21 Campbell using the alpha-2 agonist clonidine
22 topically. This was a randomized, double-blind,

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1 placebo-controlled trial. They received
2 0.1 percent clonidine gel. The study was
3 borderline negative.
4 But he -- by he, Jim Campbell -- and his
5 group decided to look at nociceptor function by
6 looking at the degree of pain evoked by 0.1 percent
7 topical capsaicin applied in a 1-centimeter area on
8 the anterior tibia.
9 Subjects who experienced any degree of pain
10 to capsaicin or clonidine were superior to placebo
11 and this showed more and more an effect the more
12 pain subjects perceived. And it was only related
13 to the capsaicin test. No other measure of sensory
14 function showed this difference.
15 Here, you see the ITT, top left; the
16 capsaicin, no response, to the right; capsaicin
17 response greater than zero; separation, greater
18 than 1; separation. And as you go from 2, to 3, to
19 4, to 5, the separation increases, so lending some
20 support to the notion that some kind of sensory
21 profiling could make a difference in the assessment
22 of a response in a clinical trial.

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1 Here, you'll see the relationship between
2 the capsaicin response, going from 0-7 on the
3 X-axis, and the intraepidermal nerve fiber density,
4 shown on the Y-axis. And the more intraepidermal
5 nerve fibers, the greater the capsaicin response,
6 so providing some structural support to the
7 physiological test.
8 I now want to talk about this trial or this
9 meta-analysis, a retrospective analysis, which
10 comes from the Danish group. I see Ralf and Troels
11 having a sidebar and I think it's important and I'd
12 love to hear what the two of them say to one
13 another, because this was a retrospective analysis.
14 And the conclusion of the retrospective analysis
15 was the following.
16 This post-hoc analysis of 8 drugs with
17 mainly non-selective action on neuropathic pain
18 mechanism, arguably, found limited usefulness of
19 sensory phenotyping in pain as the basis for
20 individualized treatment. And that was the
21 conclusion of the paper.
22 I've left this area blank because I think

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1 that area is the [indiscernible] en bloc. You can
2 see a glass over there which can either be half
3 full or half empty or one of those figures, the old
4 lady, the young girl.
5 Depending on how you look at this, the data
6 can be interpreted differently. Here are the data
7 taken from the trial and I'm going to focus just on
8 one of these forest plots, one confidence interval
9 and that is the -- this doesn't seem to be working
10 anymore -- this is the one over here which looks at
11 gain.
12 Sure, the confidence interval is rather
13 large but -- and we are looking at pregabalin. As
14 Rolf and Tony Dickinson said in their editorial,
15 that the sample size was rather small, but gain
16 does seem to be a factor.
17 I want to make a point over here. If we
18 think back to the talk maybe given by many people,
19 Clifford, Nat Katz, where they spoke about the many
20 factors that go into a single individual's response
21 to a drug, we are talking about age, we're talking
22 about gender, we are talking about PK, we're

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1 talking about genetic factors, the sensory profile
2 is just one of those factors.
3 When we are seeing a patient in the clinic
4 or doing a clinical trial, you just want to give
5 your therapeutic intervention an edge. You want to
6 improve the likelihood that your intervention is
7 going to be effective.
8 It seems to me that my interpretation -- and
9 I'm not particularly a glass-half-full kind of
10 person -- my interpretation of this is that the
11 presence of hyperalgesia, of gain of function, call
12 it what you will, gives you an edge and this, of
13 course, is consistent with what we saw, without
14 being specific, in those pregabalin clinical
15 trials.
16 When I gave this talk three years ago, it
17 was, I proposed a road map. That road map still
18 exists and I said that we need a dynamic approach
19 to sensory profile using QST.
20 This should be in specialized clinical
21 centers, where I think we need to be dynamic in how
22 we use these tests. We need to have international

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1 within-nation approaches to QST, laboratory-based
2 QST and we need to begin to do the same in the
3 community.
4 I also said that there should be obligatory
5 phenotyping for all phase 2 and phase 3 studies. I
6 think, then and now, I think one should still be
7 critical or agnostic as to how valuable this will
8 ultimately be. But I certainly -- and I was
9 agnostic at the start -- am leaning in the
10 direction that this gives an edge. This does
11 impart some value. I thought it was an important
12 opportunity for academia, industry interaction.
13 I thought this is the way, whether it'd be
14 open label or double-blind, randomized,
15 placebo-controlled, a way for pooling data across
16 studies, because what we looked at was purely
17 pregabalin. And I think we need to do the same
18 thing with other drugs with different purport of
19 mechanism of action.
20 I said then -- and remember this was three
21 years ago -- that I hope this would be
22 accomplished. This was three years ago. Before

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1 the circus that was the Republican nomination of 16
2 candidates and before we had any idea who was going
3 to be the Democratic candidate, I said I hope this
4 would be accomplished before our next president
5 looks like this.
6 (Laughter.)
7 DR. FREEMAN: Well, times have changed and
8 so I do need to say "or."
9 (Laughter.)
10 DR. FREEMAN: Thank you for listening.
11 (Applause.)
12 DR. MARKMAN: I want to take two questions
13 and then we'll take break for about 45 minutes.
14 DR. COLOCCA: Yes, I have a question. Luana
15 Colloca. Why Baron and Roy didn't talk about the
16 bedside kit? I mean, it seems like they already
17 had one very cheap, Home Depot. I wonder why, when
18 the European Agency asked about money and the time,
19 you didn't suggest, well, there already one in the
20 literature or --
21 (Laughter.)
22 DR. FREEMAN: We can talk offline about

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

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

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

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

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1 phenotyping, the distinction between state and
2 trait.
3 A question for all of the speakers today and
4 Troels, as well. As far as I could tell, I think
5 that some of the patients that have had phenotyping
6 done with respect to sensory testing may have been
7 on neuropathic pain treatments.
8 Do we know whether QST parameters change on
9 or off these different treatments and whether it's
10 necessary, first, to answer that question? And
11 secondly, do we have to have people off treatment
12 when the phenotyping is done?
13 DR. FREEMAN: Yes. It's a very important
14 point. It's a point that we've discussed several
15 times with respect to the German network data,
16 which I understand is acquired while patients are
17 on treatment. They are not taken off treatment.
18 Rob, correct me if I'm wrong about that.
19 I want to say one more point, and that
20 is -- and this refers purely to pregabalin. I did
21 not show you, but this was done at the beginning
22 and at the end of the clinical trials, and the

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1 measures did not change.
2 The aim was to see whether, of course,
3 pregabalin made a difference to these evoked pain
4 measures. They did not.
5 DR. GILRON: At the end on treatment or the
6 end off treatment?
7 DR. FREEMAN: Sorry. At the end of
8 treatment. So the last visit, it was.
9 DR. GILRON: They were still on pregabalin?
10 DR. FREEMAN: They were still on pregabalin,
11 yes.
12 DR. MARKMAN: Well, I'd like to thank
13 Dr. Freeman, Dr. Baron, Dr. Katz.
14 (Applause.)
15 (Whereupon, at 10:22 a.m., a recess was
16 taken.)
17 DR. MARKMAN: Our next speaker needs no
18 introduction, so this is very easy. If everybody
19 would join us to hear Dr. Turk, who will be
20 speaking about Non-Pharmacologic Treatments in
21 Precision Pain Medicine: The Rationale for Lumping
22 Versus Splitting.

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1 Presentation – Dennis Turk
2 DR. TURK: Thank you. In listening to the
3 presentations the last day and a half, when I first
4 got interested in the area of pain, I got
5 frustrated, because we were so dependent upon what
6 patients tell us and their way of interpreting
7 whatever treatments we're offering them.
8 I tried to get over that by switching into
9 another area, I worked in diabetes for a while, and
10 then I found out it wasn't any different. So we're
11 in the same situation.
12 As I heard the presentations here, though,
13 yesterday, I heard a lot about ion channels and
14 different chemical agents and I started thinking
15 about, well, there's another part of this. There
16 are subjects, people.
17 Then I heard Nat this morning say he's not
18 going to talk about that stuff, people thinking,
19 oh, my God. I don't want to think about it.
20 But then I heard Andrew Rice yesterday
21 talking about how the mice and the rats use their
22 environments and respond in different ways when

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1 they're afraid of something.
2 So maybe we can't get away from the fact
3 that our subjects do think, they're conscious, and
4 maybe the problems that we keep running into is we
5 keep looking for the very narrow, subtype people or
6 animals on the basis of the physiology, or the
7 neurophysiology, or the sensory processing.
8 Maybe that's an important part, but maybe
9 it's not all. So I'm going to try something maybe
10 a little different for some of you to help you
11 think some of these things.
12 There's how birds see the world, and they
13 see things differently than we do. There are two
14 kinds of people in the world, those who think there
15 are two kinds of people and those who don't.
16 (Laughter.)
17 DR. TURK: The first group we can call the
18 splitters and the second group the lumpers. In
19 listening to -- and the title of this presentation,
20 the title of the whole meeting is really -- I think
21 we all have a similar perspective on splitting may
22 be important. We may want to be splitting in

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1 different ways. Now, you could decide whether the
2 splitter is the bird or the target, that's up to
3 you. But I think this is important because that's
4 the whole purpose of what this meeting is.
5 There are a lot of different ways we might
6 go about splitting or stratifying patients, and
7 we've heard about a number of different ones, some
8 of which we're going to pay attention to, some
9 we'll not. We spend a lot of time on biomedical
10 factors, most of the time on mechanisms. There's
11 also symptom presentations.
12 We heard a little bit about that, that it
13 actually could alter people possibly into subgroups
14 based on their symptom presentations. It's
15 possible we could also look at the etiology,
16 whether it's the actual etiology or the perceived
17 etiology that might explain it. There may be
18 psychological factors that contribute.
19 We could possibly could end up finding ways
20 to phenotype, stratify, psycho-type patients and it
21 may be important to know something about those and
22 that may explain why we see some of the results we

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1 do.
2 We could also look at response to treatments
3 and are there differences in how people, how
4 animals respond to treatments, and that goes to the
5 subtype, and we've heard a lot about that in a lot
6 of these discussions.
7 I'm going to focus on the bottom three of
8 these, because we've heard a lot about the other
9 ones. Mostly, I'm going to focus on these in a
10 sequence, and, hopefully, these are related
11 sequence.
12 We could think about it, as I said, as
13 stratifying, subtyping, phenotyping people on the
14 basis of the nature of their symptom, on the basis
15 of the etiology.
16 The reason I said actual or perceived is
17 because it may be that the perception of those
18 subjects of how their symptoms began or what their
19 symptoms are like make a difference. And whether
20 it's the actual cause of their symptoms, it's a
21 trauma of some kind, it was a disease of some kind
22 is only part of the action.

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1 So just to show you some slides as I go
2 along to illustrate some of these points. This was
3 a study that we were involved with that looked at
4 569 patients who had fibromyalgia.
5 We asked them -- and a bunch of other
6 things -- but one of the things we asked them was
7 the perception of how their symptoms began, was
8 there a trauma of some type, was it an accident,
9 did something happen to you, was it an illness, was
10 it just, who knows, I woke up one morning and had
11 the flu and it just got progressively worse.
12 You can see that the percentages of patients
13 who could be split here and those who thought there
14 was a precipitating event, that was about 36
15 percent of the sample, and 39 percent who said
16 there was no cause, they don't know, it just seemed
17 to come on, it got worse over time, and eventually
18 they had all these other things going on, and then
19 about 21 percent said it was something else. So it
20 wasn't our two. But if we just seem to split
21 patients on the basis of their perception of their
22 symptoms, does that make any difference and that

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1 will help us understand something about them? And
2 can we be thinking about precision health care,
3 precision medicine, not only on the basis of some
4 of the things we saw for the last day and a
5 fraction, but also for some of these other factors?
6 So we split those people in a study into
7 those who said there was a traumatic onset and
8 those who said it was idiopathic onset, or it's
9 something else.
10 You can see that there's no difference on
11 age, sex, high school education, marital status,
12 duration of their symptoms. They didn't differ on
13 those factors. So we were interested in what does
14 differentiate these people.
15 Based on biomedical findings -- and we had a
16 whole range of different tests, which I'm not going
17 to go into -- we found that there's really nothing
18 that we can find different between those who said
19 their symptoms began following a trauma and those
20 who didn't.
21 There was nothing different on the pain
22 severity, nothing different on how much they said

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1 the pain interfered with their life, nothing
2 different in the level of affective distress. So
3 what's different about these people?
4 Well, we also want to look at these people.
5 What about physical function? Maybe there's
6 something different in their actual physical
7 function.
8 I'm only going to show you one of many
9 physical tests that we performed and these are by
10 physical therapies and functional capacity exams.
11 They found that they can find nothing different in
12 these groups whether they had traumatic onset or
13 not a traumatic onset based on physical function
14 that they could do in these tests, not significant.
15 Then we say what about perception of
16 disability. How did these people think about their
17 circumstances and what happens to them? Does that
18 differentiate among those who had a traumatic onset
19 and those who didn't?
20 What we found that is, yes, in fact, if the
21 patients said that they believe their symptoms
22 began following a trauma, even though we have no

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1 evidence that there's anything different, they were
2 significantly different in how they perceived their
3 disability. We also looked at their quality of
4 life and other things.
5 Those were things that they consistently
6 seem to differ on. So it wasn't anything on
7 demographics. It wasn't anything on physical
8 factors that we could find. It doesn't mean that
9 we couldn't have looked at other things, but at
10 least we couldn't find anything.
11 Interestingly, we also looked at how were
12 these patients treated by those who are clinicians
13 in the room. If the patient comes to you with
14 fibromyalgia, or to a practicing physician, and he
15 or she says that they're diagnosed with
16 fibromyalgia, what kind of treatment would they
17 receive?
18 We found out that if the patients said they
19 had a traumatic onset, there's no objective
20 evidence they truly had, that this is the patients
21 saying it, they are more likely to get nerve
22 blocks, physical therapy, TENS or opioids. This is

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1 if the patient said it, not because they were
2 different than anything.
3 What is the physician making the decision on
4 why he or she is providing these different
5 treatments? They're also interacting and
6 responding to the patient.
7 Therefore, there's a whole social
8 interaction that's going on that's also important
9 when we think about this.
10 Let's switch gears to another sample, and
11 I'll be looking at different kinds of populations.
12 This is a study that looked at people with
13 whiplash-associated disorders. We had 108
14 patients. We're interested in seeing can we find
15 differences among these groups that might be
16 meaningful to understand how well people are
17 responding to different treatments, how they're
18 adapting to their condition, who goes on to develop
19 these chronic conditions, looked at cervical range
20 of motion, neck strain, shoulder range of motion,
21 shoulder strength, elbow flexion-extension, grip
22 strength, pinch strength, plain x-rays.

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1 We have neuropsychological tests that we
2 did. Is there anything that's unusual about people
3 who have mild symptoms following a motor vehicle
4 collision and those who had more severe symptoms?
5 We have split the group based on the
6 severity of their symptoms. What we found is
7 there's nothing different among these people on the
8 severity of their symptoms in any of the measures
9 that we had.
10 Now, these are gross physical examination
11 measures and neuropsychological tests, but we
12 couldn't find anything different among these
13 people.
14 So what might differ? Well, we were
15 interested in patients', again, perceptions,
16 expectations and how does that influence the
17 perception of their symptoms.
18 I have to show you a measure we developed so
19 you'll understand this. We had something called
20 the Pictorial Fear of Activity Scale for the
21 cervical region. There are 78 photographs of
22 movements and five controls. They manipulate or we

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1 manipulated arm position, manipulated whether they
2 were lifting something or not lifting something.
3 We looked at the extent of the motion that they
4 were engaging in. Was it extension, was it
5 flexion, lateral bending or rotation?
6 We looked at the degree of exertions. So
7 was it an extreme change or was it a minor movement
8 about these individuals? We then showed these
9 people photographs to ask them how much these
10 activities would bother them, that would be
11 distressing to them and cause their symptoms to get
12 worse.
13 So just an example, this is a sample of one
14 of the pictures, which is arms on the side,
15 unloaded, left rotation, extreme. That's just
16 showing you what we're manipulating.
17 I'll just show you another one. I won't
18 read them off to you, just so you could get a sense
19 of what we're asking the patient to do. So they're
20 looking at this set of pictures and they're
21 responding to how concerned, worried, fearful that
22 they would be of doing this because it might even

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1 make them have more damage, more injury, or might
2 make their symptoms worse.
3 We started saying what predicts pain
4 intensity, what predicts the number of symptoms,
5 what predicts the Neck Disability Index, which is a
6 scale that's used in whiplash in the neck and
7 shoulder area for disability.
8 What you can see is that age didn't matter,
9 range of motion didn't matter, whether it was pain
10 for severity it didn't predict, for number of
11 symptoms for disability, but what it did predict
12 was TSK, which is the Fear of Movement scale, and
13 the Pictorial Fear of Activity.
14 Their concern and their worry about movement
15 was what predicted the severity of the perceived
16 reporting of their symptoms. Not a big surprise to
17 you.
18 This is the same thing that occurred for
19 each one of these measures. So that the subject,
20 patient, is interpreting their own symptoms and
21 responding to those symptoms, even though, on
22 objective measures, we can find nothing different

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1 among these individuals.
2 We could also think about looking at maybe
3 there's some psychological characteristics that are
4 different. And Nat listed some of those quickly in
5 his slide. Maybe we can look at some of these.
6 Bob Kerns is in the room, so I have to pull
7 out an old measure he developed called the
8 Multidimensional Pain Inventory, which, if you're
9 familiar with it, has three different parts.
10 It asks about pain severity, interference,
11 life control, affective distress, support from
12 significant people, and the environment, how do
13 other people respond to you when you experience
14 pain, and what do you actually do with your actual
15 activities.
16 So there's a 52-item, one version. There's
17 a 60-item version of this questionnaire. So the
18 question is, do these people respond differently.
19 Can we subtype, psycho type, however we want to say
20 it, for these individuals, stratify them in some
21 way on how they respond to this type of
22 questionnaire?

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1 What we looked at was one group of these
2 individuals using cluster analysis. You've heard a
3 bunch of things about one group identified. These
4 all started out as people getting referred to a
5 tertiary care pain facility.
6 So these are not your mild problems you see
7 in primary care. We found that one subset of these
8 patients reported high pain, high levels of
9 emotional distress, low sense of control, and
10 little activity.
11 When I looked at Ralf Baron, when he showed
12 some of the patterns that he had, gee, a lot of
13 pain, a lot of emotional distress, it sort of
14 looked like this was important in the subtypes that
15 he was looking at, as well.
16 Another group we referred to as
17 interpersonally distressed, despite having pain
18 severe enough to be referred to a pain clinic, what
19 was most characteristic was they said they had low
20 support from significant people in their
21 environment.
22 People around them were very negative toward

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1 them, they didn't try to help them, they didn't try
2 to distract them, and they never did things to help
3 them out.
4 We use the term interpersonally distressed.
5 So although they had pain, what was most
6 characteristic was that they were interpersonally
7 distressed.
8 The third group of people -- remember, these
9 are all people coming to a pain clinic. So they
10 had to have sufficient level of pain. Relative to
11 the other groups, they were doing pretty well.
12 They were very low emotionally distressed.
13 They felt some control, and they tended to be
14 somewhat more active than the other populations.
15 So these were three subgroups we identified in this
16 initial early study.
17 That has been replicated, those three
18 subgroups, across patients with chronic low back
19 pain, with headaches, temporomandibular disorders,
20 lupus, metastatic cancer, local cancer, and
21 fibromyalgia. We see the same three patterns of
22 adapting to having their symptoms.

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1 Now, interestingly, if you look at these, if
2 you look across these, for the dysfunctional
3 patients, the percentage of patients is different
4 in these different groups.
5 For example, the back pain patients had a
6 much higher percentage of people who are, quote,
7 "dysfunctional," high pain, high distress, low
8 activity levels.
9 For the lupus patients, that was a
10 relatively small number. If we look at the
11 metastatic cancer patients, interpersonally
12 distressed group, they're pretty well, a pretty
13 small group of these people.
14 If you have metastatic cancer, people tend
15 to be supportive of you. However, if you happen to
16 have fibromyalgia, these patients are saying, "We
17 don't get attention, don't get support. People
18 don't help us. We have interpersonal problems."
19 For the adaptive copers, it's quite
20 variable, very few -- relatively small percentage
21 in the low back pain samples and a much higher
22 proportion in the lupus samples. By the way, the

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1 sample size is that these run anywhere from 300 to
2 400, 500. So these are pretty decent sample sizes.
3 Now, maybe what's different among these
4 three groups is there's really something physically
5 different about them. The people who are
6 dysfunctional have a lot more physical findings
7 that contribute to their particular problem. Maybe
8 that's what's really important here.
9 So here, we are looking at a sample of
10 people with temporomandibular disorders. We've
11 used this MPI clustering procedure for that. We
12 looked at pain duration, looked at symptoms based
13 on examinations, muscle palpations our dentists
14 have performed.
15 We have looked at intercuspal opening, how
16 much they can open their mouth, which is a
17 characteristic of temporomandibular disorders, it's
18 restricted. We looked at abnormal CT scans.
19 We
20 had CT scans in all these patients.
21 Interestingly, if you look at that, the
22 dysfunctional, the interpersonally distressed, and
the adaptive copers, there's no difference in any

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1 of those findings.
2 The findings that one might think would be
3 related to having TMD, these groups don't differ,
4 but yet they do differ on the things that I showed
5 you earlier.
6 We also had another sample of patients that
7 we've looked at who had -- this is chronic back
8 pain patients -- no, this is a heterogeneous
9 chronic pain sample.
10 And we looked at these three different
11 groups, dysfunctional, interpersonally distressed,
12 and adaptive copers. They don't differ on lumbar
13 flexion, they don't differ on fingertips to floor,
14 straight leg raising, cervical range of motion.
15 So there's something here that's potentially
16 important for us to understand, in addition to
17 whatever we know about them physically. And it may
18 be that when we start thinking about phenotyping
19 and genotyping, we may be thinking about
20 psychotyping, if you will, and then maybe some
21 combination of these factors are going to become
22 important to us.

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1 This is a study that Kati Thieme did, who's
2 from Germany. She looked at those same subgroups
3 of patients that she identified, and this was -- I
4 think this is fibromyalgia patients -- on
5 fibromyalgia patients. And she said, "Okay, let me
6 see on the MPI what subgroups do we find."
7 She finds dysfunctional, interpersonally
8 distressed, and adaptive copers. Then she looked
9 at measures of anxiety, depression, and without any
10 kind of emotional disorder.
11 Each of these three different subgroups
12 showed three different patterns of psychological
13 distress; in particular, depression and anxiety.
14 You can also think about response to
15 treatment and Nat, I think, gave us some ideas
16 about thinking about response to treatment.
17 Well, this is my collection. As of 2004, I
18 stopped, because I ran out of room on my slides.
19 These are pharmacological treatments that are in
20 the literature that have some beneficial effect and
21 some symptoms for some patients with fibromyalgia.
22 A lot of stuff.

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1 As a matter of fact, that's 57 different
2 pharmacological treatments. But I'm going to
3 prescribe something that works better than aspirin,
4 but it costs a lot more.
5 We have a lot of new drugs and maybe we're
6 getting better with the newer drugs. This was a
7 study that was looking at a whole range of
8 different treatments for fibromyalgia, duloxetine,
9 milnacipran, pregabalin, and the others which I
10 can't quite read from where I'm standing.
11 But the ones that are at the top are the
12 ones that are approved by the FDA for the treatment
13 of fibromyalgia. If you look at that, the
14 beneficial effects that the patients are
15 reporting with that is 50 percent pain reduction.
16 It's not particularly great, even though we have
17 three FDA-approved drugs for fibromyalgia.
18 All you know is because we've been hearing
19 about this for every other kind of treatment out
20 there, the range of beneficial effects we're seeing
21 for the patients is 30, 40 percent, and those
22 50 percent, but rarely do we see it that high.

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1 Substantial numbers of patients are not getting
2 better.
3 Is it because we just need to find subtypes
4 of physical factors that might explain this or
5 might it be the case that we should be thinking
6 about other ways of subgrouping patients?
7 This is a paper that Henry McQuay reported.
8 He looked at very interesting reductions in pain
9 from duloxetine. He looked at the placebo
10 response, and he looked at the drug response.
11 This is for fibromyalgia patients and what
12 you see is almost a bimodal distribution both for
13 the placebo and for the active treatment. He also
14 did that for OA and for chronic low back pain and
15 for DPN.
16 So we're seeing differential responses and
17 now maybe there are subtypes of patients who will
18 respond differently, as we heard about, based on
19 the physical factors that we've been seeing.
20 But there are also a whole bunch of
21 psychological -- or non-pharmacological, I should
22 say, because there's a lot of non-pharmacological

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1 treatments. This was my list as of 2004. I ran
2 out of room on the sides.
3 There's published studies as of 2004 that
4 every one of these different treatments has had
5 some beneficial effects for patients of
6 fibromyalgia. By the way, they happen to be 57 of
7 those, nice balance there. That's 114 treatments
8 for fibromyalgia, all of which have some beneficial
9 effects.
10 I really was kind of curious about what the
11 physical mechanism are going to be to explain all
12 those different -- and the treatments are extremely
13 wide range, from ECT, electroconvulsive shock
14 therapy, to hot baths, pretty extreme difference.
15 Now, the hot baths tend to be in Germany.
16 My understanding is that in Germany, if you have
17 fibromyalgia, you get several weeks in a spa and it
18 tends to have very beneficial effects. If anybody
19 want wants weeks in a spa, just go to Germany and
20 say you have fibromyalgia.
21 (Laughter.)
22 DR. TURK: There are a lot of psychological

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1 treatments. There are other kinds of treatments
2 out there that had some effects. But notice that
3 the effects are still fairly modest that we're
4 seeing. We're not seeing huge benefits to these
5 different kinds of treatments.
6 Let me show you a treatment protocol that we
7 did. It starts explaining some of the
8 possibilities. It's because what we're doing is
9 these are giving generic treatments to everybody.
10 Every patient who comes in with that diagnosis, we
11 lump them.
12 They have fibromyalgia, they have back pain,
13 they have TMD, they have IBS, whatever that happens
14 to be, we lump them together and we give them the
15 same treatment.
16 Obviously, this meeting wouldn't have to go
17 on very long, because all of you are the believers
18 that that's the wrong way to go about it. So this
19 was a study that was a rehabilitation-oriented
20 study. You don't need to know the details but it
21 was -- just in general, it was a six-week,
22 three-hour sessions once a week.

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1 They had attention from a physician who
2 talked to them about their condition, gave them
3 reassurance about they weren't going to have a
4 condition that was going to be terminal, and that
5 they really needed to start taking control of their
6 lives and get going.
7 They had physical therapy, aerobics, and
8 stretching exercises. This is a heterogeneous
9 group of patients. Occupational therapy, focus on
10 pacing and body mechanics, and the psychologists
11 focus on pain and stress management.
12 So that's what the treatment was and you
13 don't need to know the details, but I want to show
14 you this. What happens if we go back to those
15 three subtypes of patients?
16 So we have dysfunctional, interpersonally
17 distressed, and adaptive copers along the bottom.
18 So at the bottom, this is where the patients
19 started prior to treatment. Those are the patients
20 in each one of those groups. Now, at the end of
21 the treatment, what happens to these groups?
22 Do they switch? Well, we found out that

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1 62 percent of the patients who were dysfunctional
2 turned out to look like adaptive copers by the end
3 of the treatment. You can look at the other
4 percentages.
5 If we look at the interpersonally distressed
6 patients, they didn't do nearly as well. Now,
7 remember there was nothing in this treatment that
8 dealt with interpersonal problems, or family
9 issues, or how you interact with people at all and
10 that treatment didn't have nearly the same
11 beneficial effect.
12 The adaptive copers didn't need the
13 treatment. They were already doing pretty well
14 already. We are wasting our time and their money
15 and their time in putting them in this treatment.
16 But everybody got the same treatment,
17 because they were sent to the rehabilitation
18 program. So maybe that's not the way we should be
19 going.
20 This is looking at another study that Kati
21 Thieme did in which she looked at differential
22 responses of patients. What kind of patients were

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1 these? I think they were fibromyalgia -- to an
2 operant conditioning type of treatment, very
3 behaviorally-oriented, reinforced the appropriate
4 behaviors, ignored the pain behaviors, a cognitive
5 behavior therapy type of intervention which focused
6 more on thinking and an attention control, a
7 relatively small study.
8 What she wanted to look at is what did the
9 responders look like. So if some patients
10 responded to all of these three treatments, are
11 there any characteristics of who the responders
12 were?
13 So she looked at the baseline
14 characteristics and she found out that if the
15 patients reported having higher physical impairment
16 at baseline, greater pain, more pain behaviors,
17 more negative responses from significant others,
18 they were low physical functionally, they had more
19 physician visits, and high catastrophizing, they
20 did much better with the operant treatment than the
21 other two treatments.
22 If, in fact, they happened to have high

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1 levels of affective distress, low solicitous
2 behavior, low pain behaviors, and inadequate or
3 poor coping on the scales that she was using, they
4 did better with the cognitive behavior therapy.
5 The same patients all going to the clinic for
6 fibromyalgia, but they're responding differently to
7 these treatments.
8 Interestingly, the attention control group,
9 if they have a lot of negative support, they did
10 well in a group treatment. They got to spend time
11 talking to and being with other people who had the
12 same kind of problem.
13 So even the people who got what she thought
14 was her placebo treatment, there were some who got
15 a beneficial effect, a relatively small number of
16 people, but that's where the benefits were.
17 Let's think about what I very quickly went
18 through. Obviously, all of you know there are
19 predisposing and protective factors. We talk about
20 genetics. You talk all the time about genetics,
21 prior stresses, prior learning history.
22 We also could talk about precipitating

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1 factors. Is there a physical trauma, is there
2 disease, is there an illness, is there some sort of
3 emotional trauma, as I tried to show you with the
4 patients in some of the studies we had.
5 You can look at perpetuating or protective
6 and alleviating factors. It could be the symptoms,
7 could be attitudes, beliefs, meaning, coping
8 responses, social support, financial resources,
9 behavioral responses, consequences.
10 Maybe one of the problems is that we tend to
11 think of people at the time they come in for
12 treatment. So it's so sort of a cross-sectional
13 perspective.
14 So what we did was we were interested with
15 looking at what happens over time with patients.
16 This is extracting literature from some other
17 areas. The age of onset -- this was a
18 meta-analysis we did a number of years ago.
19 [Indiscernible] was the lead author on this, in
20 which there were no -- patients who go to pain
21 clinics, what was the average age when they say
22 their pain began.

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1 Interestingly or not so interestingly, it
2 was when they were age 37. By the time they got to
3 the pain clinic, that means they've had 37 years of
4 history to be the kind of person they are.
5 But prior learning history, their genetic
6 factors all preceded what happens to them at the
7 time they say their pain began. We then say when
8 do they actually get to the pain clinic.
9 The mean age of patients being treated in
10 these 54 different pain clinics that they looked at
11 was 44 which means that the patients have had had
12 their pain seven years before they got to the pain
13 clinic.
14 So what's happened in those seven years to
15 these people? That's the current age of change or
16 their changes in pathology. What's happened in
17 that time frame? And they're going to live for 30
18 more years. To my knowledge, at least, since I've
19 had black hair when we're looking for cures for
20 people with chronic pain, those same patients who I
21 saw 30 years ago are still waiting for the cure for
22 their pain.

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1 I have a hunch -- I don't want to say this
2 too loud, because you'll stone me, but if I come
3 back in 30 years, I think we're still going to be
4 looking for the cure for pain. We're going to find
5 better treatments. We're going to find ways that
6 we reduce the symptoms. But I'm not confident
7 we're going to have a cure, at least definitely not
8 in my lifetime. I'm planning on living 30 years,
9 in case you were wondering.
10 Maybe we should also look at what's
11 happening to them over those 30 years, because now
12 their pain is maybe reduced, hopefully, but they're
13 still not cured. So things have changed.
14 These people have a whole range of resources
15 available to them. I mean, there's support,
16 economic factors, the environment, the culture, all
17 these things are going on around them.
18 Interestingly, we tend to forget that these
19 people don't live in isolation. They live in
20 social context, people around them. So if you take
21 this perspective instead of just looking at the
22 patient at age 44 when they come in the door and

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

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

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

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1 others are, in fact, important, as well.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 people. It was a radical idea to pharmaceutical
2 industry. What do you mean? We want you to give
3 you a treatment. What do you mean, this
4 combination of treatment? What combination?
5 Then we have people like Ian who did some
6 work to demonstrate the value of combinations of
7 pharmacological treatments. Sometimes, 1 and 1
8 does equal 3.
9 It may be you'll get better outcomes if, in
10 fact, you have more than one treatment. When you
11 think of fibromyalgia, we have a symptom checklist
12 and the mean of 38 items on our symptom checklist
13 and the mean number of symptoms that the patients
14 report is 22.
15 I don't know about your best treatment, but
16 to think that you're going to take care of all the
17 fibromyalgia patients with a single treatment, I
18 don't care what your treatment is, you're probably
19 going to end up seeing your 20 to 30 to 40 percent
20 benefit on some symptoms for some of those
21 patients. But you're not going to get them all and
22 maybe we shouldn't expect it to.

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1 These should be matched to the patients
2 based on whatever characteristics we think are
3 important, whether we think it's genes, whether we
4 think it's sensory profiling which may be affected
5 by genes, whether we think it has some biological
6 or psychological characteristics.
7 But we need to be thinking about splitting
8 these patients apart and that maybe it's not -- is
9 it a psychological treatment, is it a physical
10 treatment, is it these two physical treatments, is
11 it physical therapy in this drug?
12 But maybe what we're looking for is what's
13 the combination of physical, biomedical factors,
14 and psychosocial factors. And do we look for
15 what's the best combination of treatments that'll
16 match those patient characteristics?
17 I showed you just one slide and that made an
18 important point. You've got to demonstrate -- it's
19 one thing -- we can identify an infinite number of
20 subgroups, no question. Cluster analysis will find
21 something even if there's nothing there.
22 Replicating a cluster analysis doesn't

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1 always occur. But if, in fact, we find some
2 differences that are meaningful, then we've got to
3 test out, do the treatments match those patient
4 characteristics, really make any difference.
5 Therefore, you're going to have to have
6 treatments that are beyond what you expect to see
7 with the placebo drug. If we start getting
8 combination treatments, the reason that people shy
9 away and get scared about this is the complexity of
10 doing the research, because now you need a lot more
11 arms to your studies.
12 If I got three subgroups based on
13 psychosocial factors and three subtypes based on
14 sensory profiling, so the number of possible
15 treatments in your study is going to be pretty
16 outside what you're going to be able to do.
17 That's one of the dilemmas when we talk
18 about trying to match patients with different
19 characteristics, is it gets to be very big and
20 complicated kinds of studies.
21 So all I wanted to hopefully just do in the
22 short time I had was not to say there's anything

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1 wrong with all the things we've been trying to
2 identify, these subtypes of patients, the
3 stratification of patients. But at the same time
4 that we're looking at a range of those different
5 biophysical factors, the genetic factors, we might
6 also want to pay attention to that unfortunate
7 conscious individual who is paying attention to
8 what you do to him, and what you say to him or her,
9 what treatments you're providing to him.
10 That may explain a great amount of what we
11 see with every treatment having some beneficial
12 effect, because we're not spending enough time with
13 those individual patients and customizing,
14 tailoring, matching the treatments with the patient
15 characteristics.
16 Thank you.
17 (Applause.)
18 DR. MARKMAN: Question? [Inaudible - off
19 microphone].
20 DR. TURK: Only an easy one. I won't let
21 Nat -- Nat never asks an easy question. I can't
22 see Dr. Katz. I think we need to be fair to the

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

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

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

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

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

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

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

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

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

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

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

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

22 In that manuscript, we tried to summarize a

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

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

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

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

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

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

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

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

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

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

22 These are predictive effects and studies in

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1 which there isn't a control group. So the
2 phenotype of interest — or, if there is a control
3 group, the phenotype of interest predicts equally
4 in the active and the placebo treatment groups. If
5 there's no placebo group, then it just predicts in
6 the active group, of course.

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

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

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

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

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

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

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

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

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

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

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

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

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1 were none at all.

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

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

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

22 These psychosocial forces are important both

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

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

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

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

22 I could easily spend a whole talk discussing

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

7 But that's not quite as relevant as I'd need
8 it to be for our discussion of phenotyping here.

9 Just know that there's a vast literature, probably
10 most of you know this already, on the importance of
11 psychosocial forces in shaping the trajectory of
12 all sorts of chronic pain conditions, nociceptive,
13 neuropathic, inflammatory, you name it.

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

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

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1 predictors.

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

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

12 This has been used a lot to phenotype
13 psychosocial aspects of chronic pain patients.

14 This is just some data from a hydromorphone study
15 that Bob Jamison and I were able to get our hands
16 on.

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

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

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

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

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

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

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

4 This is a fairly large and profound effect,
5 40-50 percent less analgesic response in the high
6 negative affect group relative to low.

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

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

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

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1 morphine and placebo than the high negative effect
2 group, so an important sort of finding when
3 considering what patients you might select for a
4 future opioid trial.
5 We had actually done some work as part of
6 Ajay's oral opioid study administering quantitative
7 sensory testing measures. You heard a nice talk by
8 Roland earlier about conditioned pain modulation
9 and other pain modulatory processes.
10 We had the chance to take a look in this
11 study at whether opioid's effects on QST or pain
12 modulatory measures might vary as a function of
13 patient's psychosocial phenotype.
14 What you can hopefully see in that graph
15 there is at baseline, the low negative effect and
16 high negative effect, the patients don't differ in
17 CPM, or conditioned pain modulation, but by
18 mid-treatment, the high negative effect patients
19 have a reduced CPM effect.
20 I think several folks have mentioned there
21 is some data on opioids impairing CPM and other
22 endogenous pain modulatory processes in patients.

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1 We observed this selectively in the high negative
2 effect group.
3 There are yet more effect modification
4 findings to measures of negative effect or
5 depression and anxiety. These are some data for
6 that, which I won't go into great detail.
7 These are patients with chemotherapy-induced
8 peripheral neuropathy who are randomized to either
9 duloxetine or placebo.
10 What you might be able to see in the lowest
11 rows of that table is that the response to
12 duloxetine and placebo was partly related to
13 patient's level of baseline emotional functioning.
14 There were more than twice as many pain
15 responders in the high emotional functioning group
16 in the duloxetine arm, but that was not true in the
17 placebo arm.
18 This effect modification finding, if you
19 want to get the largest difference between the
20 duloxetine and placebo, you should take individuals
21 with, in this study, high emotional functioning or
22 you could think of it as low levels of depression

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1 and anxiety.
2 Now, maybe most fascinatingly, there are a
3 couple of recent studies on this sort of question
4 in animals. I had no idea, but apparently you can
5 induce a depressed phenotype in rats by giving them
6 a bilateral olfactory bulbectomy.
7 When you do that, if you take rats who are
8 then subjected to spinal nerve ligation and you
9 compare the analgesic effect of amitriptyline with
10 analgesic effect of a vehicle or saline, you only
11 get an analgesic benefit of amitriptyline in the
12 non-depressed rats who did not get the olfactory
13 bulbectomy.
14 Those dark bars are the rats who did get the
15 olfactory bulbectomy and in that group of rats,
16 amitriptyline does not beat placebo in the way that
17 it does in the non-depressed group.
18 This should come with dozens and dozens and
19 dozens of caveats. But it's a fairly interesting
20 conceptual parallel to some of the human findings.
21 Now, I get to talk about catastrophizing for
22 a few minutes. Some of you have probably heard me

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1 ramble at length about pain-related catastrophizing
2 before.
3 In catastrophizing, as I said, of negative
4 cognitive and emotional and attitudinal processes
5 related to pain and patients who catastrophize
6 about pain, which we measure via self-report on
7 questionnaires like the PCS, or the pain
8 catastrophizing scale, those patients tend to
9 ruminate about pain, they tend to magnify the
10 threat value of pain, and they tend to feel
11 helpless in the face of pain.
12 Now, I can let you know what the acronym
13 IMMPACT actually means. So IMMPACT is an Insidious
14 Mechanism for Massachusetts-based Psychologists to
15 Advance Catastrophizing Theoretical Importance,
16 IMMPACT.
17 (Laughter.)
18 DR. EDWARDS: We'll have to add that in for
19 future meetings.
20 So we've done a fair amount of work on
21 catastrophizing and there are fairly broad
22 individual differences in any group that you would

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1 care to study. Even healthy adults or kids show
2 individual variability and catastrophizing.
3 These are some data from patients seeking
4 treatment at the Brigham and Women's Pain
5 Management Center, patients with low back pain.
6 You can see that in these nearly 300 individuals,
7 there's a normal looking distribution. The mean
8 score is about a 25, and there are some people who
9 are down very close to zero and some who are very
10 close to the top end of the scale. And you get
11 this nice sort of variation in how much people say
12 they catastrophize about pain.
13 There are, at this point, a bunch of general
14 predictive studies in both nociceptive and
15 neuropathic pain conditions.
16 This is some summary data from a few
17 different trials, patients with diabetic painful
18 neuropathy, PHN; or persistent neuropathic
19 post-operative pain who are in trials for a variety
20 of topical preparations.
21 When you split them by their baseline
22 catastrophizing score -- and this is Mick Sullivan

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1 and crew dividing them into catastrophizers and the
2 non-catastrophizers -- the non-catastrophizers are
3 quite a bit more likely to get at least two points
4 or more greater reduction on a 0-10 pain intensity
5 scale in their neuropathic pain with treatment and
6 quite a bit more likely to get an even larger
7 reduction as well.
8 There are even now a couple of effect
9 modification findings in catastrophizing -- I don't
10 know how that interesting orange bar got there.
11 But it probably prevents you from reading a bit of
12 the description of the study.
13 So this is work by Bob Rakel and colleagues
14 in the University of Iowa who are doing a TENS
15 study in patients with severe knee osteoarthritis
16 who had just gotten a joint replacement and were
17 rehabbing after that.
18 What you can see there is that in this
19 randomized controlled study, if you look at
20 patients who got active TENS versus those who got
21 placebo TENS, in the active TENS group, the low PCS
22 patients do better than the high PCS patients.

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1 So catastrophizing level at baseline
2 predicts response to this analgesic treatment but
3 that is not true in the placebo arm. There are
4 other effect modification findings, as well. I
5 won't go into this in detail
6 But in this study of low back pain patients
7 randomized to either placebo or an
8 acetaminophen-tramadol combination, you get the
9 same sort of effect modification result, where low
10 catastrophizing is associated with good response to
11 active treatment but not placebo.
12 So negative effect, catastrophizing, seems
13 to at least have some phenotypic importance for
14 predicting responses. There are a variety of other
15 psychosocial processes, as well, which may be
16 related to both these features.
17 Individuals who catastrophize quite a bit
18 about pain, who are depressed and anxious tend not
19 to sleep particularly well. And there is
20 substantial overlap between sleep disruption and
21 the experience of chronic pain.
22 There are some really neat animal studies

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1 looking at the effect of sleep deprivation on
2 impairing opioid analgesia -- or maybe I should say
3 anti-nociception in rats and a little bit of data
4 in humans suggesting the same sorts of effects.
5 That is, when you help people who are not
6 sleeping well at night and who are very sleepy, in
7 this study, codeine does not beat placebo, but it
8 does in the non-sleepy individuals. This is a
9 laboratory study of heat pain responses rather than
10 a chronic pain trial.
11 But you get some really interesting data
12 from this summary of thousands of patients in a
13 number of pregabalin trials. In this case, the
14 researchers split people by their baseline level of
15 sleep disturbance from mild to severe and looked at
16 the relative pain improvement with pregabalin over
17 placebo.
18 So this would be an effect modification sort
19 of findings. Those with the most sleep disturbance
20 got the most benefit from pregabalin over placebo.
21 Then that little figure on the bottom right
22 when you did some fancy structural equation

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1 modeling sorts of statistics, they concluded that
2 over 80 percent of the benefit of pregabalin, in
3 terms of the improvement in pain, was due to
4 improvements in sleep.
5 This seem widely implausible to me. That
6 would be the vast majority of the benefit that
7 people get from pregabalin, but it does at least
8 highlight the potential importance of sleep and
9 sleep disruption as a phenotype.
10 The last five to seven minutes or so, I want
11 to cover not so much psychosocial factors but
12 characteristics of patients' report of their pain
13 and pain qualities as a potential important
14 phenotypic predictor.
15 There's been some interesting work on
16 individual patient variability in how variable
17 their pain reports are. So you can do diary-style
18 of the studies where you have people rate their
19 pain on a daily basis and then measure how much it
20 varies for an individual patient across days.
21 You can see there are a couple of sample
22 participants, one with very low variability. So

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1 that person's got really stable pain ratings and
2 the other with the same average pain level but
3 quite a bit more variability.
4 I think this might have been the first study
5 published on the topic. It was in patients with
6 fibromyalgia as a randomized controlled trial of
7 Savella.
8 What the Michigan group found in this study
9 was that the more variable patient's pain was at
10 baseline, the more they tended to respond to
11 placebo.
12 Now, a quick plug for ACTTION here. This
13 had been followed up by an ACTTION meta-analysis
14 done by lots of people in this room. John Farrar
15 is the lead author.
16 They have found that for randomized
17 controlled trials of, I think, gabapentin and
18 pregabalin in both diabetic painful neuropathy and
19 PHN, you get exactly the same sorts of effects.
20 That baseline variability in pain intensity ratings
21 on diaries is associated with placebo effects in
22 these studies.

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1 The more variable patients' pain ratings are
2 day-to-day before you start treatment, the more
3 they're likely to respond to placebo, which seems
4 like a fairly important thing to know if you are
5 designing a trial.
6 I have not seen any report in the trial's
7 literature on other sources of daily variability,
8 but I just took a look this morning at some of our
9 data in knee OA patients, and you get just as much
10 day-to-day variability in catastrophizing ratings
11 as you do in pain ratings. Just for fun, I looked
12 at what that daily variability and catastrophizing
13 might be related to.
14 You can see there are moderate correlations
15 between how variable patients' catastrophizing
16 scores are day-to-day and their overall PCS level.
17 There are moderate inter-correlations
18 between daily variability and catastrophizing and
19 daily variability and pain. You can, I suspect,
20 easily imagine that you could compute daily
21 variability for dozens and dozens of other
22 potentially important variables, which I don't

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1 think anyone has done yet but might neat to look
2 at.
3 Outside of variability, it's probably
4 important to consider a patient's pain
5 characteristics or pain phenotypes. We have a
6 number of measures that can do that quite well.
7 I think you've seen the PainDETECT already.
8 And as Ralf and others have shown a very nicely,
9 you can phenotype and subgroup patients using, for
10 example, cluster analysis on some of these
11 measures.
12 You get interesting, and neat, and fairly
13 consistent clusters across pain conditions. So
14 when you characterize people according to the
15 degree of burning pain that they have and
16 mechanical hyperalgesia, thermal hyperalgesia that
17 they report on these instruments, you can subgroup
18 or cluster patients into these roughly five
19 different categories in most of the very large
20 German studies.
21 You can also use measures of pain quality
22 like the PQAS or the Pain Quality Assessment Scale

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1 which asks patients to rate the degree to which
2 various adjectives apply to their pain, burning,
3 tingling, cold, sharp, et cetera, et cetera.
4 There have been some effect
5 modification-style analyses of these sorts of
6 measures. This is a PQAS study in patients with a
7 variety of neuropathic pain conditions.
8 They're randomized to pregabalin or placebo
9 and what you can hopefully see in that slightly
10 yellow highlighted column on the left is that there
11 are some nice positive correlations between a
12 number of PQAS items. So patients with more
13 paroxysmal pain and intense electrical pain tended
14 to respond more to pregabalin. But those PQAS
15 items didn't predict the response to placebo.
16 If you categorized people in these ways, you
17 could get better looking pregabalin effects over
18 placebo in that subgroup of PQAS responders.
19 I think I actually will probably not spend
20 any time on that study, which is a short-form MPQ
21 study. The neuropathic pain symptom inventory is a
22 measure that you've heard about before and I'm just

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1 going to hurry along in the interest of time here.
2 This is another measure on which patients
3 can self-report the degree of neuropathicity, if
4 that's the word, of their pain.
5 In this particular combo diabetic neuropathy
6 study out of France, which had a really interesting
7 and complex design, patients were randomized in an
8 initial phase of treatment to either duloxetine or
9 pregabalin and then randomized again to either
10 high-dose mono therapy or combination therapy,
11 which we don't have to worry about.
12 But in that initial period, if you look at
13 the cluster of patients with the lowest level of
14 neuropathic pain symptoms -- this is cluster 3, the
15 greenish-looking lines and symbols -- duloxetine
16 beats pregabalin significantly only in that cluster
17 of patients with the lowest level of neuropathic
18 symptoms.
19 In the Demant study, which we've heard
20 mentioned a number of times -- I think possible
21 every speaker has mentioned it -- you can also
22 subgroup patients as a function not of the QST

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1 findings, but on the NPSI.
2 They find that the subgroup of patients
3 reporting more paroxysmal and burning pain symptoms
4 show better pain relief with oxcarbazepine over
5 placebo.
6 You can all see the summary up there. I
7 won't go into great detail, but this is my plug for
8 phenotyping and assessing psychosocial processes as
9 potentially important predictors and even effect
10 modifiers in these sorts of studies.
11 Other measures like pain variability or
12 patient's report of the quality or degree of
13 neuropathic-ness of their pain symptoms might also
14 be fairly important.
15 But a question that comes up, and these are
16 my last couple of slides, exactly how
17 phenotypically-selective do we want to be in these
18 trials?
19 If we know there are a dozen or a couple of
20 dozen factors that predict response, how small a
21 slice of the population of patients that we might
22 be studying are we willing to get?

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1 I just want to illustrate -- this is a
2 really nice study of painful diabetic neuropathy, I
3 think, done by Andrew Rice among others, the PiNS
4 study, just a cross-sectional observational of
5 phenotypic study.
6 They recruited over 200 patients with
7 diabetes and possible, probable, clinical
8 neuropathy, split them into groups who don't have
9 any neuropathic pain, who have mild neuropathic
10 pain, or who have moderate-to-severe neuropathic
11 pain, and you can see them characterized there.
12 But when you run their actual breakdown, so
13 of 209 initial folks, a little over half of
14 neuropathic pain consistent with the literature,
15 about a third have neuropathic pain of the
16 intensity that would get you into a trial.
17 If you do some deeper sensory and
18 self-report phenotyping and look for patients who
19 both have moderate-to-severe neuropathic pain and
20 have what we could have I guess casually called an
21 irritable nociceptor subtype of pain, where that is
22 present both on their report of hyperalgesia sorts

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1 of symptoms and on sensory exam, then you wind up
2 with five subjects out of the initial 209 or a
3 little over 2 percent who actually meet those
4 phenotypic criteria.
5 That's not even looking at things like
6 psychosocial functioning, sleep and a number of the
7 other things that we've mentioned as potentially
8 important.
9 So if we're putting up wanted posters in
10 order to recruit individuals for our clinical
11 studies, exactly how picky do we want to be?
12 Do we want to have a list of two dozen of
13 these criteria, people have to have high intensity
14 pain, low pain variability, low catastrophizing,
15 but high sleep disturbance, low negative effect and
16 some mechanical hyperalgesia, as well as specific
17 qualities of their pain, et cetera, et cetera.
18 That sounds challenging to pull off and
19 should make us wonder if we're going to be running
20 our clinical studies on an ever smaller number of
21 individual patient needles in the giant haystack of
22 the population.

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1 There's probably an interesting debate about
2 where the line is that we're going to want to draw
3 and, presumably, we'll get to do a little bit of
4 that when we work out a consensus and write the
5 paper.
6 Thank you, guys, very much.
7 (Applause.)
8 DR. MARKMAN: Thank you, Rob. We're going
9 to break here and have an hour lunch, and we'll be
10 back at 1:00.
11 (Whereupon, at 11:58 a.m., a lunch recess
12 was taken.)
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14
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21
22

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1 AFTERNOON SESSION
2 (1:26 p.m.)
3 Q & A and Panel Discussion
4 DR. MARKMAN: Good afternoon, everyone. I
5 hope you had a good lunch. We're going to get
6 started. The goal of the next 30 minutes or less
7 is going to be clarifying questions for this
8 morning's presentations. So we're just going to
9 try and wrap it up.
10 Then the closers, if you will, Dr. Edwards
11 and Dr. Dworkin, will come up here in the spirit of
12 Mariano Rivera and another great Yankee, Sparky
13 Lyle and --
14 MALE SPEAKER: Boo.
15 (Laughter.)
16 DR. MARKMAN: -- close it out. Any Boston
17 fans, this might be your time to leave the
18 underground, because we've got a history of doing
19 this very, very well. Okay, great.
20 Does anyone have any questions regarding the
21 four presentations this morning that we can have
22 clarifying -- actually, I think it might make sense

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1 to have the speakers come up to the table actually,
2 also, just so you can be mic'd up.
3 If I could ask Dr. Baron, Dr. Freeman,
4 Dr. Turk, and Dr. Staud to join us, that'd be
5 great. Please. Why don't we start with the
6 questions as these gentlemen come forward? Yes?
7 In the very back -- oh, is that Bob? Bob Kerns.
8 DR. KERNS: So I really am interested in
9 hearing folks that are more on the basic
10 preclinical science biological end of things
11 reflect on the discussion about the importance of
12 the psychosocial context and how that could be
13 better integrated or where the opportunities for
14 integration of at least the concept of a
15 psychosocial context for your work.
16 DR. MARKMAN: There seems to be some
17 uncertainty among the panelists regarding who
18 should take this question.
19 (Laughter.)
20 DR. MARKMAN: Does anyone want to step up?
21 I thought Serge gave a beautiful, eloquent answer
22 to this question, but I defer to the gentlemen

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1 here.

2 DR. TURK: Direct it more specifically, Bob

3 Kerns, to who you'd like, because if you say to the

4 panel, we'll all sit there going at that.

5 DR. KERNS: Maybe to Ralf in terms of QST.

6 I'm wondering in terms of profiling of QST, how

7 much psychosocial variables, anxiety, in

8 particular, maybe as a construct. Doesn't that

9 affect results in that domain and do you take that

10 possibility into account?

11 DR. BARON: I think nobody really has looked

12 into these issues very closely. But we discussed

13 this with others over lunchtime. I think all the

14 evoked types of pain, in particular, those

15 depending on central sensitization like dynamic

16 allodynia or pinprick allodynia, might be dependent

17 on psychosocial factors, as well, because this is

18 influencing descending control mechanisms and so

19 forth. It might very well be that there is an

20 influence for these measures, obviously not for the

21 negative phenomena and so forth, so they are

22 stable.

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1 DR. MARKMAN: I think Dr. Carr and then

2 Dr. Dworkin had a question.

3 DR. CARR: Dan Carr. First, a question,

4 then an observation. The question is I'm thinking

5 back to my endocrinology days when if one were to

6 study something like athletic performance in women

7 and their ability to reach a certain aerobic

8 capacity, generally, these would be controlled for

9 phase of the menstrual cycle.

10 I wonder -- I know there has been some pain

11 literature, but I didn't hear much about that in

12 the last day or two and wondered whether that might

13 be a factor, also, in influencing individual

14 testing responses.

15 DR. FREEMAN: I think these two questions

16 are really good questions. I think when I spoke, I

17 tried to make the point that what sensory

18 phenotyping is doing is really just giving you an

19 edge, increasing the statistical likelihood to some

20 extent over what would be just a patient walking in

21 without having sensory phenotyping.

22 I think both of these two questions answer

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1 some -- and that needs to be viewed within the

2 context of the many other factors, age, gender,

3 genotype, all of those other factors that go into

4 pain processing and pain perception.

5 When we look then at the sensory phenotype,

6 there are going to be many, many factors that go

7 into the response, as well, including, as you say,

8 the menstrual cycle, the psychometric issues that

9 Dennis spoke about, and, also, circadian

10 variability of pain processing, as well.

11 I think we can begin to take a more granular

12 approach to sensory profiling, sensory phenotyping

13 and this probably -- we are still at, I think, the

14 very, very early stages in understanding these

15 measures and what they work and how they work.

16 It would be wonderful if we could

17 standardize them and do them at a particular time

18 of day, a certain amount of time after a meal, with

19 certain degree of hydration, with certain ambient

20 temperature, and I could go on, and on, and on.

21 Many of those factors are not implemented.

22 I think with time, they will be.

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1 DR. MARKMAN: Sounds like a

2 factors-to-consider section for a manuscript

3 perhaps.

4 Dr. Dworkin?

5 DR. DWORKIN: Yes. So I have a question for

6 Nat, who I think should be up on the stage. Or are

7 you playing hooky?

8 DR. KATZ: I'm wondering if somebody would

9 outman it.

10 (Laughter.)

11 DR. DWORKIN: I won't.

12 DR. MARKMAN: It's a Red Sox boycott, I

13 think.

14 DR. DWORKIN: I'll decline the opportunity

15 to out Rob Edwards, who should actually also be up

16 on the stage.

17 (Laughter.)

18 DR. DWORKIN: So Nat, if I understood your

19 naproxen clinical trial correctly, the more

20 abnormal the conditioned pain modulation, the

21 sensory profiling -- should I start over or

22 you -- so the more abnormal the sensory profile and

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1 the CPM, the greater the separation of naproxen
2 versus placebo.
3 Couldn't that simply be result of the fact
4 that the patients with the more abnormal profiling
5 CPM had greater pain intensity and that what you
6 found, unless you control for pain intensity, is
7 that pain intensity is associated with signal
8 detection?
9 DR. KATZ: I know that we talked about that
10 internal and I think we looked at that and that
11 didn't explain the findings. But I don't remember
12 exactly. So I'll have to get back to you on that.
13 DR. DWORKIN: I think this is important,
14 because the same question applies to Dennis' MPI
15 profiling, to Ralf's profiling, and to Roy's
16 profiling.
17 I think we need to demonstrate that
18 profiling, phenotyping, whatever we call it, has an
19 incremental benefit on predicting the analgesic
20 signal over and above pain intensity, because if it
21 doesn't, let's just have patients rate their pain
22 on a 0-10 scale and we don't need to do all this

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1 fancy expensive stuff.
2 DR. MARKMAN: Dr. Woolf?
3 DR. CARR: It's Dan. I got to ask my
4 question, but I didn't make the observation.
5 DR. MARKMAN: Please.
6 DR. CARR: The observation is that in
7 discussing factors like we just are looking at many
8 of the graphical representations of one or another
9 finding, there are often swarms of points rather
10 than a small bullet hole-size to point in
11 aggregate.
12 It seems to me that the word "accurate pain
13 medicine" might be a better word than the word
14 "precise pain medicine," because precision, to me,
15 implies the reduction of variance.
16 Yet, as we drill down to more and more
17 granular knowledge, we don't diminish the variance.
18 There is still a lot of variance. But the
19 attraction of the approach lies, for example, in
20 matching mechanism to clinical response, which
21 would, to me, be more in tune with the word
22 "accurate."

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1 DR. MARKMAN: Okay. That's helpful. I
2 think it'll come back. Dr. Woolf, and then
3 Dr. Gilron.
4 DR. WOOLF: I'd like to come back to the
5 issue that was touched on Ralf and Roy, where the
6 treatment changes the signature of the profile,
7 because if it doesn't, then the whole basis for
8 this discussion is rather moot. The mechanisms
9 driving tactile allodynia or normal hyperalgesia,
10 we target them with a treatment, that should
11 change, that should disappear so that the profile
12 is not a fixed fingerprint of the patient's pain,
13 but should be dynamic reflecting the relative
14 presence of different pain drivers which will
15 respond to different treatments.
16 DR. BARON: Perhaps I could start. You say,
17 well, your guess would be that if one particular
18 medication will affect one mechanism, like central
19 sensitization, then we should see something in the
20 allodynia, in reduction of allodynia. But all the
21 trials we are talking about, our endpoint is
22 spontaneous pain.

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1 We look at baseline for the existence of
2 allodynia. And if you have a predictor for this,
3 it doesn't necessarily mean that also your
4 allodynia is going down.
5 DR. WOOLF: What I was getting is that the
6 patients on therapy, say pregabalin, for argument's
7 sake, let's assume pregabalin has a specific effect
8 on central sensitization, but --
9 DR. BARON: Then we should assume that
10 allodynia has.
11 DR. WOOLF: You would assume that -- what
12 I'm trying to say is the phenotype should be
13 dynamic and reflect the activity of different
14 treatments.
15 DR. BARON: We had this discussion earlier.
16 But what we know is that opioids have an effect on
17 the evoked types of pain in our QST profile. This
18 we have shown, allodynia and hyperalgesia, for
19 example.
20 All the negative phenomena are stable,
21 obviously, because they are negative. They are not
22 influenced by the therapy. Other therapies have a

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1 minor effect on the positive phenomena, as you
2 observed, as well.
3 DR. WOOLF: Just to reconcile, because
4 bringing Roy in this, that if, from your studies
5 with Pfizer, there is the predictor of the presence
6 of punctate hyperalgesia as a predictor of efficacy
7 signal with pregabalin, then is the assumption that
8 it's going to work, but without affecting the
9 pinprick hyperalgesia?
10 DR. FREEMAN: I think I would answer it by
11 saying the data are what the data are, and it
12 didn't. We need to deal with that.
13 What you say is logical, that you would
14 think that a drug that its efficacy is predicted by
15 the presence of hyperalgesia and results in an
16 improvement in a specific measure, as Rob said, not
17 punctate hyperalgesia, but a specific measure of
18 pain, patient self-report, is also going to improve
19 punctate hyperalgesia. It didn't seem to be, at
20 least for pregabalin.
21 Why that is, is obviously not clear. That
22 wasn't addressed in any way prospectively in the

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1 study. I don't think that necessarily it makes the
2 whole process moot. It makes the question
3 interesting and perhaps more multifaceted than one
4 would think at first glance.
5 DR. MARKMAN: Ian? I'm sorry. Turk?
6 DR. TURK: This isn't what I think you were
7 asking, but I think I was showing some data that
8 actually spoke to that. I did it quickly.
9 The rehabilitation program where people
10 started out in one of the three profiles I had and
11 then you gave a generic treatment, what you found
12 out was that the 62 percent of the patients who
13 started out looking as if they were in one profile,
14 a less adaptive one, moved to the adaptive one.
15 The middle group, which was called
16 interpersonally distressed, there was nothing in
17 the treatment that dealt with interpersonal
18 problems, and only 32 percent of them received the
19 benefit.
20 It appeared to be the case that the
21 treatment did have a more beneficial effect on a
22 particular set of characteristics of the patient

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1 and it did not have as great an effect on those
2 individuals who had another unique set of
3 characteristics that wasn't covered by the
4 treatment.
5 DR. MARKMAN: Dr. Gilron?
6 DR. BARON: I can add one more sentence,
7 because this was a question before, whether in our
8 database people were treated, and this might have
9 an influence on this data.
10 Of course, they were treated. You can't
11 collect thousands of patients, do all the things
12 and wash out every treatment. Impossible. This is
13 a KO criterion always. But they were under
14 treatment.
15 DR. MARKMAN: Thank you.
16 DR. GILRON: Ian Gilron. Rob's comment
17 about how thinly we want to slice the pie, it made
18 me think about what precision means to different
19 domains of what we're trying to accomplish here.
20 I think of precision pain care as clinicians
21 who are frustrated because they don't know how to
22 predict which patients do benefit. And they're

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1 treating their low back pain patients with
2 pregabalin and don't understand why it doesn't
3 work.
4 Of course, we know the pregabalin is labeled
5 for post-traumatic neuralgia and diabetic
6 neuropathy. And, of course, Bob and others in the
7 room have authored some ideas about how to
8 extrapolate efficacy to other areas.
9 The question is, does precision pain
10 medicine mean something different than precision
11 drug development? And so I am sensitive to the
12 needs of industry.
13 But if we sort of use precision to get a
14 highly focused, positive result and then get a drug
15 on market, are we doing a service to precision care
16 if the extrapolation is just going to become more
17 widespread?
18 Are we going to be in the same boat, in
19 fact, maybe even more, because we're going to have
20 now drugs that are labeled for a specific
21 indication that are being used more widely?
22 I just don't know how -- and then add the

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1 same thing for precision preclinical drug
2 development, it might be a completely different
3 picture. I don't know how to reconcile that.
4 DR. MARKMAN: Do any of you want to react to
5 that?
6 (No response.)
7 DR. MARKMAN: No? Okay. Dr. Farrar, and
8 then Dr. Rowbotham, Dr. Jensen.
9 DR. FARRAR: I'd like to make one comment
10 and then make another statement about some work
11 that's ongoing at the University of Pennsylvania.
12 The comment is that during one of the
13 breaks, Serge and Roland and I had a conversation
14 about the CPM and the fact that they ought to get
15 invited to Bermuda, as well.
16 There was general agreement amongst the two
17 of them, at least, that the criteria for defining
18 CPM needed to be standardized and that apparently
19 there was an attempt six or seven years ago, but
20 there still remain many ways of doing it. And so
21 I'll just leave that for what it is.
22 There is also some interesting data that

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1 they may want to present with regard to studies,
2 Serge in particular, with some studies that he's
3 done in terms of the continuity of that over time,
4 as well as the variability within normal
5 populations.
6 What I wanted to say about the University of
7 Pennsylvania is that Garret FitzGerald has a center
8 grant that really is looking at personalized
9 medicine and its relationship to COX-1 and COX-2
10 therapeutics.
11 There have been a number of advances since
12 the data that Nat has shown. None of them have
13 been related to pain, unfortunately, because that
14 portion of the grant was left out when the budget
15 was reduced five years ago.
16 But just to make the point that there are
17 now clearly phenotypes, genotypes really, of
18 patients who either rapidly or slowly metabolize
19 and convert the COX-1 and COX-2 into either active
20 or non-active metabolites.
21 There are clearly -- we're beginning to look
22 at whether people who metabolize nonsteroidals more

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1 quickly have as pronounced a response in a setting
2 where -- we're looking at third molar extraction,
3 for instance, and there may actually be ways of
4 getting at some of that.
5 The advantage of that particular paradigm is
6 that they have the ability to look at it in cells,
7 in yeast, in zebra fish, in mice, and then in
8 humans.
9 If you find something in humans, you can
10 look down and see if it occurs in zebra fish. And
11 if you find things in zebra fish that are
12 interesting, you can look up to see if it occurs in
13 humans.
14 That kind of structure, I think, actually
15 provides a way at getting at some of this data that
16 might be very useful and would have applicability
17 to some of what we do here related to looking at
18 animal studies, related to looking at some of the
19 cell structures, cell cultures that Clifford is
20 looking at to try and put it all together as a way
21 of more rapidly advancing some of the precision
22 medicine.

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1 I just wondered if any of the panelists knew
2 of other instances where there's sort of the
3 combination of both basic and clinical science to
4 try and look at some of these issues.
5 DR. TURK: I'll respond to your first
6 comment, your statement. Is this another thing for
7 the list on Rob Edwards about desirable things,
8 that is there was a meeting on CPM where they
9 brought the experts together to try to come to a
10 decision, but it wasn't held in Bermuda.
11 (Laughter.)
12 DR. TURK: Now, if in fact we have a meeting
13 in Bermuda and demonstrate that the location of
14 where the treatment was provided, actually, that
15 would mean that location would become another
16 important way to phenotype the studies in the
17 patients in the population, right?
18 DR. FARRAR: I'm all for that. By the way,
19 I have a way of measuring it, as well. I'd really
20 like an invite.
21 DR. MARKMAN: Mike?
22 DR. MARCHAND: I want to react to that after

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1 that.
2 DR. MARKMAN: Okay.
3 DR. MARCHAND: It's for the Bermuda thing,
4 yes.
5 DR. MARKMAN: Bermuda-related, several
6 questions. We'll take them all now.
7 (Laughter.)
8 DR. MARCHAND: It's something else. I think
9 it's quite important, because I know that
10 CPM -- it's Serge, Serge Marchand. With the French
11 accent, it's me. Every time there's a French
12 accent, it's Serge Marchand.
13 What I would like to tell you is when we
14 look at all the literature on CPM, I totally agree
15 that there is like 25 ways of measuring it. But
16 what is nice is most of the people find the same
17 thing.
18 I mean, it's not perfect. There is some
19 variability, but at least it seems that we can
20 predict some treatment or whatever. It's probably
21 just 20 percent of the variability, but at least
22 it's there. I think it's important.

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1 Taking that, when I look at that in the lab
2 and we can separate population very easily in
3 different chronic pain conditions, and it's just
4 one lab.
5 But when I talk with other people and we
6 were together a few minutes, Andrew and I, and he's
7 doing the same in the lab, we found, also, almost
8 the same thing.
9 I think we need a subgroup of people, again,
10 just to sit there and say, "You know, which ones
11 have been used a little more and, also, can we use
12 it in the clinic," because in my lab, it takes me
13 45 minutes or an hour to do it and you will never
14 do that in the clinic. But I'm sure, I'm quite
15 sure, I'm convinced, when you get older and gray
16 hair and white hair, in fact, what you realize is
17 you have some intuition on the research, and I'm
18 quite sure we can do a short test for that, quite,
19 quite sure. But I will need the help of people
20 like you and I would like to thank you either away
21 for being here, because it's people like you that
22 will help us to do something like that.

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1 I want to react to [indiscernible] on the
2 fact that if we're developing some phenotyping just
3 to develop new drugs -- I mean, this is perfect and
4 it's really nice to do, but the phenotyping, it's
5 not for that, I think. We'd like to teach it to
6 other clinicians to understand why they're
7 prescribing the drug, because if we phenotype and
8 we say, "Oh, this subpopulation is responding very
9 well to this drug and let's develop the drug," and
10 it's not going to the clinicians, there's no help
11 at all, because they will prescribe the drug to
12 everyone and will say, "My God, nobody is
13 responding to that."
14 DR. MARKMAN: It's helpful. It's great.
15 DR. STAUD: Let me just respond to this one.
16 I agree that different forms of CPM have similar
17 results shown in multiple different occasions, but
18 I think the importance is that depending on how CPM
19 is structured, different mechanistic changes occur.
20 This is, in my mind, the important part, that we
21 are really dealing with the same analgesic response
22 and not with [inaudible - off microphone].

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1 DR. BARON: I would just comment on your
2 second point. I think we desperately need some
3 back translation from our human world to the animal
4 world again.
5 I strongly believe that the heterogeneity we
6 see in the patients also exists in animals. But so
7 far, animals that do not show pain behavior were
8 thrown away. You know this. They were not tested.
9 I think Frank Porreca was the first who just
10 went into this and looked for neuropathy, animals
11 with pain and without pain and looking in brain
12 stem things.
13 Andrew, you touched upon this issue, as
14 well, that we can do sensory testing with thermal
15 stimuli and cold stimuli. And so in animals, as
16 well, I think we really should do this and we
17 should take this into the manuscript, back
18 translation of these ideas more broad.
19 DR. ROWBOTHAM: This is Mike Rowbotham and
20 I've got a couple of comments and one question. In
21 terms of outcome measures, as Ralf was saying,
22 things that are dynamic, like dynamic allodynia or

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1 even area of pain, an area of allodynia have been
2 used in clinical trials before and are dynamic.
3 There's a possibility, I think, that some of
4 the thermal sensory abnormalities can be reversed,
5 as well, by treatment, although that, I would
6 agree, is a tougher target.
7 I just wanted to mention something that I
8 heard directly from somebody in EMEA some years ago
9 in terms of electing patients, subgroups for
10 pivotal trials and how they would or would not be
11 to a label.
12 This was around using topical capsaicin to
13 either -- like what Campbell did in the clonidine
14 study. Because it's a nonstandard test, in other
15 words, there's not a reference capsaicin
16 preparation and all the other things that go around
17 that, you can't really use that to select that
18 subgroup for an indication. It's got to be
19 something that would be accessible to a clinician
20 in practice.
21 That, I think, needs to be kept in mind in
22 terms of how much profiling you do. If you get to

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1 the point where there isn't a local reference
2 center or there isn't published standards or other
3 things, you can't really use it to develop your
4 population.
5 My question is about the interaction between
6 things like catastrophizing sensory testing and
7 Ralf mentioned that at the beginning of his
8 remarks.
9 But I'd like to hear more about it, whether
10 or not there's an interaction that is adding to the
11 noise that's being seen when you're trying to look
12 just at the sensory phenotype and you're getting
13 quite a bit of spread in the results of treatment,
14 because you're not also looking at things like
15 catastrophizing that might be important either
16 confounders or co-variables.
17 DR. MARKMAN: Ralf, do you want to answer
18 that?
19 DR. BARON: We discussed this. I think it's
20 very important and perhaps we should include these
21 psychosocial measures into our cluster analysis
22 together with the sensory phenotype which you

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1 could.
2 We did this in fibromyalgia patients once,
3 where we included PainDETECT data and the
4 psychosocial data and did everything with a cluster
5 analysis. You get a really different structure and
6 I think this would capture this influence of both.
7 DR. MARKMAN: Dr. Edwards?
8 DR. EDWARDS: Just to expand on that, that's
9 a really good question and I think I have two
10 answers for it.
11 The first, I think, thing to consider is
12 that most of these, we can call them risk factors
13 or phenotypic constructs or whatever it is we're
14 talking about, most of them are not perfectly
15 independent from one another.
16 Measures of catastrophizing and measures of
17 anxiety are quite highly correlated. Measures of
18 catastrophizing and measures of sleep disruption
19 are moderately correlated.
20 In our hands, at least, catastrophizing is
21 associated with the degree of temporal summation
22 that pain patients exhibit, both neuropathic pain

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1 patients and fibromyalgia patients.
2 A lot of these correlations are in the 0.3-
3 0.4 range, but they're not perfectly independent.
4 I think that does raise some interesting
5 statistical challenges when we're trying to figure
6 out which phenotypes predict best.
7 Then just to follow-up on that, it might
8 very well be -- and I'm sure this is the case with
9 genetics. I bet Luda could give a much better
10 answer than I could. But it might very well be
11 that some interesting interactions give us the best
12 phenotypic predictive power.
13 It might not be just to the case that
14 patients with irritable nociceptors or sensory
15 subtypes or punctate mechanical hyperalgesia
16 respond best to drug X, but it's patients with that
17 sensory phenotype, plus at least moderate sleep
18 disruption, plus low catastrophizing, plus good
19 compliance with treatment.
20 You could keep adding pluses to that, I
21 suspect, endlessly and it may be that studying
22 interactions of those clusters of interrelated

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1 phenotypes winds up giving us our best predictive
2 ability. But we're obviously going to need
3 absolutely enormous studies to tease that out, I
4 think.
5 DR. TURK: Can I interrupt?
6 DR. MARKMAN: Yes.
7 DR. TURK: As I looked at all the
8 psychosocial predictors, they really have one thing
9 in common. They all sort of split people or
10 trichotomize them into levels of emotional
11 distress, whether you want to call it
12 catastrophizing or anxiety or depression.
13 I would wonder if you did a higher order of
14 factor, if you get all those measures together in
15 the same way they did in personality literature
16 where they came out with the Big Five or whatever
17 that they talk about, would you, in fact,
18 find -- if we have a meeting in Bermuda where we
19 could get people around with those different
20 measures and come to agreement on what will be our
21 negative emotional distress measure that everybody
22 would use, we could then resolve having too many of

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1 these psychosocial measures that heavily overlap
2 with each other.
3 DR. EDWARDS: That is spoken like a true
4 lumper.
5 (Laughter.)
6 DR. EDWARDS: I am more toward the other end
7 of the spectrum, although I will say right now on
8 record, whatever it takes to get to a meeting in
9 Bermuda, just let me know.
10 (Laughter.)
11 DR. MARKMAN: Sounds like we need a
12 timeshare.
13 (Laughter.)
14 DR. MARKMAN: Dr. Jensen?
15 DR. EDWARDS: To follow-up on that real
16 quickly, there are a number of predictive
17 studies -- none of them are quite as large or high
18 quality as you'd want -- that do show that
19 pain-specific measures of emotional distress like
20 catastrophizing or fear of pain or that sort of
21 thing can be quite predictive or pain-related
22 outcomes from changes in pain intensity with

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1 treatment to pain-related disability, et cetera,
2 over and above the effects of more general
3 distress-related measures, like the HADS.
4 You can put those things into a regression
5 and they both independently predict some important
6 variants in the outcome.
7 DR. TURK: If you put them in a factor
8 analysis, all of those measures into a factor
9 analysis, would you end up with some higher level
10 factor, because you can't ask all these questions.
11 I mean, the patient burden would be -- I don't
12 know.
13 Would there be an advantage at least to
14 having some common, relatively brief measure of
15 emotional distress and to be very specific on the
16 level of care, but would that help? Because my
17 fear is -- when we wrote in one of the papers that
18 I think you were on, we were looking at all these
19 different factors that are important for people to
20 consider in the AB taxonomy, and I sat there
21 saying no one will do this, because it's requiring
22 too much [inaudible - off microphone]. So we've

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1 got to simplify it. And that would be one way
2 to -- you could use a PROMIS item bank, if you
3 want to go that direction.
4 DR. EDWARDS: I think NIH would appreciate
5 that suggestion.
6 DR. BARON: One word to this correlation you
7 mentioned. In our prediction model, we did a
8 factor analysis. I put this in. If there was a
9 correlation, only the strongest survived to reduce
10 the fact.
11 DR. MARKMAN: Dr. Jensen, and
12 Dr. Silberberg, and Dr. Colloca. And I think
13 that's going to be all the time that we have.
14 DR. JENSEN: I have a question here. Just a
15 brief comment first. We have been doing quite a
16 lot of effort here at this meeting to try to
17 examine profiling, sensory profiling, genetic
18 profiling, psychosocial profiling, et cetera.
19 We may come up with something which is
20 interesting. But I think we are neglecting or
21 forgetting something, and that is the outcome,
22 which is, of course, the pain and the pain

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1 intensity.
2 Now, I think in general, in the pain
3 community, we are doing astonishingly bad when we
4 are trying to measure the outcome. We're just
5 asking on a simple scale from 0-10, how much pain
6 do you have.
7 If we're not going to dissect this further,
8 I don't think this sensory profiling is getting us
9 anywhere, because pain is such that -- it's, as we
10 know, of course, subjective phenomena which is
11 completely different from what people in the cancer
12 world are doing. They're looking at are you
13 surviving or you're not surviving, are you dead or
14 are you not dead, is the tumor gone or not.
15 But when it comes to pain, we don't have any
16 clue about what is behind a reduction of the pain.
17 Is it because of the psychosocial factors that are
18 reduced or is it because you have reduced the
19 allodynia or something else?
20 We need to do better in terms of outcome and
21 that has to be linked to the whole process of
22 profiling.

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1 DR. MARKMAN: Would any of you like to make
2 a comment?
3 DR. WOOLF: Can I just interject something,
4 just to add to that? When we see this in the
5 context of drug development, I think we should be
6 thinking about drugs that are symptom-suppressors
7 and drugs that are potentially curative.
8 DR. JENSEN: I think it's pathetic that we
9 if we look into the human world, we're just looking
10 on this pain intensity. But the basic scientists
11 are using all sorts of measures. They're looking
12 on functional behavior, they're looking on
13 responses to Von Frey hairs, to thermal stimuli,
14 genetic outcomes, et cetera. We're just looking on
15 pain intensity.
16 DR. MARKMAN: Dr. Silberberg?
17 DR. SILBERBERG: I have to apologize, again,
18 because I'm looking at this as someone from the
19 outside and trying to wrap my brain around all the
20 questions and the answers I've heard.
21 I want to go back actually to the very first
22 question, to Clifford's question, which is you come

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1 up with all these tests and if we just think about
2 the physical tests, not the psychophysical tests,
3 and you try to stratify the patients to say who's
4 going to benefit from a particular treatment or
5 not, and then you treat them. If I understood
6 Clifford's question correctly, the question was
7 once they're treated and if they got better, if you
8 go back and do that test, do you see a change.
9 Roy, I understood, you said that you don't
10 see a change. And, Ralf, I didn't understand the
11 response.
12 (Laughter.)
13 DR. SILBERBERG: But I think that's
14 extremely important for the next step, because, A,
15 you could say if it didn't improve, is that a right
16 parameter to use; and, even if it is a right
17 parameter, what is it telling us if you go back to
18 the basic research? What is it telling us the fact
19 that it didn't improve, but yet it's a predictive
20 factor?
21 To try to improve on, going down the road,
22 to improve on the prediction, if you can say, okay,

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1 I see this correlation, but it's not changing after
2 the treatment, it means that it's not really part
3 of the mechanism, it's some kind of side effect and
4 to understand that.
5 I think that kind of also talks about this
6 business all we're doing or you're doing -- I'm
7 certainly not doing that -- measuring pain at the
8 end, asking them, that might help to find or
9 identify what should be done to better define
10 getting better or not getting better.
11 DR. FREEMAN: A couple of things. First of
12 all, to answer for Ralf.
13 (Laughter.)
14 DR. FREEMAN: I don't know if you know the
15 Dutch footballer Johan Cruyff who died this year,
16 but once he was asked in an interview how he did
17 something absolutely remarkable.
18 He answered and then the reporter said to
19 him, "You know, I don't understand." He said, "If
20 I wanted you to understand, I would've answered
21 differently."
22 (Laughter.)

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1 DR. SILBERBERG: I figured as much.
2 DR. FREEMAN: To address your question, I'm
3 not sure. I understand what you're saying, that if
4 it's going to change, then it should be on the
5 pathophysiological or pathological continuum.
6 But I would say not necessarily. For
7 example, I'll just give one -- just say -- and
8 we'll pick on punctate hyperalgesia, because
9 Clifford mentioned it. It may be that that is a
10 phenomenon that takes longer to change, that it may
11 take more than 12 weeks before central
12 sensitization or whatever is driving punctate
13 hyperalgesia changes.
14 It could well be part of the process, part
15 of the continuum, but that -- and nobody, I think,
16 in this room would argue with what Troels said
17 about how hard, rudimentary the measures that we
18 use as our primary efficacy endpoint in pain trials
19 are.
20 Clearly, we need to think of better ways of
21 doing it, and we need to incorporate other aspects,
22 and we need to ask the questions differently and

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1 all of those things.
2 There are a gazillion ways that we showed
3 and could change it, but this is the way it is and
4 this is what we all were attempting to predict at
5 this point in time and merely because the predictor
6 did not change, it doesn't mean that it is not
7 necessarily relevant or it doesn't work.
8 The first thing is it doesn't mean that it's
9 a bad predictor and it doesn't necessarily mean
10 that it's not on the pathophysiological continuum.
11 I tried not to be on Cruyff, but maybe I was.
12 DR. BARON: Perhaps I should mention
13 something, as well. I agree that with the central
14 sensitization, allodynia and pinprick, we would
15 assume that there is an effect.
16 But we look at profiles. Just imagine that
17 a loss of the warm fiber generates the pain and is
18 a predictor for your drug. If you treat the
19 patients with baseline loss of warm fiber, you
20 won't change anything in the warm threshold,
21 because this is a loss.
22 But it's a predictor and you look at

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1 spontaneous pain at the endpoint and this is
2 reduced. A little bit clearer perhaps? So it's
3 not necessarily that the predictor will change as
4 an outcome parameter.
5 DR. MARKMAN: I think Dr. Colloca has a
6 question, as well.
7 DR. COLLOCA: Luana Colloca. Just a
8 comment. We spoke about placebo analgesia as a
9 model to understand endogenous pain modulation.
10 There are some studies currently in
11 patients, patients with low back pain, patients
12 with IBS, and we are learning more about this
13 mechanism as a sort of inner-mechanism or
14 protective mechanism to help patients to cope with
15 their pain or also to respond to different
16 treatments.
17 What I would like to say is that we don't
18 need the placebo to study placebo effects. Indeed
19 the [indiscernible] paradigm and some other
20 mechanisms show that patient expectancy matters a
21 lot.
22 If they expect to respond to a remifentanil,

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1 the front area in the brain shows an activation.
2 If they are receiving remifentanil and we say, now,
3 we stop remifentanil, the same areas stop to work.
4 We need to be careful when we look at
5 outcome and consider the possibility to measure
6 expectancy in patients. This doesn't require fMRI,
7 PET or very expensive and time-consuming methods.
8 But at least the study that we ran in the
9 lab, where we look at different brain imaging,
10 [inaudible - off microphone] covariants, an
11 interaction study, where, for example, it has been
12 shown that endogenous opioids are released and this
13 release in the brain occurs as a measure of
14 neuropathy, plus specific genetic polymorphism and
15 variance for OPRM1 helped to identify the better
16 phenotype for placebo analgesia.
17 This is complex. But still asking merely
18 how much do you expect to improve can predict this
19 path of mechanism in our brain. But why don't we
20 include, also, a very simple, not time-consuming
21 and extremely cheap measure of expectancy in your
22 profiling and phenotyping, QST, CMT, other

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1 measurements [inaudible - off microphone]?
2 DR. MARKMAN: That's a great point. I hate
3 to cut this short. This is an incredibly
4 stimulating discussion. But I think in the
5 interest of time and the larger process, this is
6 going to be our breaking point. I'd like to thank
7 the panel, as well.
8 I think Dr. Dworkin and Dr. Edwards are now
9 going to come and tie this all together and put a
10 bow on it. Thank you, everyone.
11 DR. TURK: If you're interested in this
12 discussion, the next meeting in Bermuda will
13 continue it.
14 MALE SPEAKER: Absolutely.
15 (Laughter.)
16 DR. ROWBOTHAM: I was going to say, at the
17 end of that other point, to put it in as few words
18 as possible, you can have variables that you don't
19 expect to change as factors, but what we're looking
20 for is surrogate outcome measures that are more
21 objective and are going to change, that are more
22 objective than the 0-10 scale.

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1 DR. DWORKIN: Exactly. They are two
2 different groups of measures. In fact, Kushang and
3 I were just whispering that an epidemiology
4 distinction is made between modifiable and
5 non-modifiable risk factors, and Kushang pointed
6 out the genetics are a terrific example of
7 non-modifiable risk factors.
8 But BMI and HbA1c would be examples of
9 modifiable risk factors. And so yes, that will be
10 in the manuscript somewhere.
11 This is the closing session of the meeting.
12 We have a hard stop at 4:00 because of plane
13 reservations and people's schedules and taxi cabs.
14 In the almost-two hours remaining -- and we
15 don't have to use up the full two hours, but we've
16 got two hours -- there's really one objective.
17 We all have to make sure that Rob Edwards
18 leaves here happy. If we can make Rob happy in 15
19 minutes, everybody gets to go home early or make an
20 earlier flight.
21 The kind of operational definition of Rob
22 Edwards' happiness is, is that he has a pretty

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1 clear idea in his head about the manuscript that
2 he's going to draft that you will all be invited to
3 be authors on.
4 At the point at which Rob kind of thinks
5 it's come, this has all come together and that he
6 sees a manuscript to draft, that as Dennis said
7 yesterday morning, you will all have many, many
8 opportunities to comment on, more than you want,
9 because it's at least two or three circulations
10 before we submit.
11 There are typically two rounds of reviews
12 and several iterations to address reviewers'
13 comments. So you're going to see Rob's manuscript
14 over and over again.
15 What we want to do in the next two hours is
16 make sure we're all on, more or less, the same page
17 that Rob can draft a manuscript and to begin that
18 sequence of multiple revisions.
19 Any questions about that? As I said, you're
20 all invited to be authors. If you don't like the
21 way the manuscript looks, you don't have to be an
22 author.

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1 All right. So Rob and I took some time over
2 the lunch break to try and at least come up with
3 some scaffolding of what a manuscript from this
4 IMMPACT-XIX meeting could look like.
5 We ended up with three broad sections. A
6 first section that would be a kind of literature
7 review, highly selective, not systematic of
8 promising models for accelerating the development
9 of precision pain medicine and that these promising
10 models would span the spectrum of preclinical,
11 translational, clinical.
12 I can say more about this, but let me just
13 start off with the three broad sections. So a
14 broad section at the beginning of the paper about
15 promising models, exemplars.
16 The second section where we make general
17 recommendations for what needs to be done to
18 accelerate the development of precision pain
19 medicine. Clearly, we have a consensus already on
20 one of those recommendations, which is a series of
21 many meetings held in Bermuda.
22 I don't know whether Frank Keefe will

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1 publish that in Pain, but we'll do our best. So a
2 section of general recommendations that will be
3 fleshed out in text and summarized in a table.
4 Then we imagined a third section, if we can
5 do this and come to some agreement, of pretty
6 specific recommendations, for example, clinical
7 trials or studies that we think should be done if
8 the money were to become available.
9 It wouldn't be as detailed as an RFA, but we
10 could have a bunch of bullets of studies, that if
11 funding was available, we think should be started
12 next month.
13 That was what we came up with as a kind of
14 broad scaffolding, the promising models for the
15 development of precision pain medicine, general
16 recommendations, very specific recommendations.
17 Did you raise your hand?
18 DR. PATEL: No, I was scratching my head.
19 (Laughter.)
20 DR. DWORKIN: Does that seem reasonable?
21 Any alternatives? Because, of course, this is what
22 the next two hours is to be.

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1 Clifford?
2 DR. WOOLF: I think it'll be critical to
3 define what the goal is in terms of what we see
4 precision pain medicine as being and what is
5 actually achievable in a reasonable timeline,
6 because I think we'd all agree we're a long way
7 from it.
8 And the question is, what is the path that
9 would bring us closer, and what are the elements
10 that are achievable quite soon and the others that
11 we'll be exploring for some time?
12 DR. DWORKIN: I think that's great. When we
13 get to talking about general recommendations and
14 specific recommendations, I think it would make
15 sense to focus on recommendations that could be
16 implemented in the next five years. But there are
17 obviously some longer-term recommendations.
18 Rob and I also discussed that we need
19 definitions and say exactly what we mean by
20 precision pain medicine. And we'll start off
21 asking Dr. Riley, who isn't here today, what the
22 official NIH definitions are, et cetera.

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1 The way I see this paper -- I think the way
2 we thought about this meeting is, what kinds of
3 things should be done in the next 5-10 years that
4 would bring to patients more targeted therapies,
5 therapies where they're either likely to be more
6 robust in their response. Maybe not from this
7 meeting, the other possibility is less likely to
8 have side effects. That's kind of the --
9 Shai?
10 DR. SILBERBERG: I'm going to say one thing
11 and then not say one more word.
12 (Laughter.)
13 DR. SILBERBERG: Listening here for a day
14 and a half as an outsider, my only comment is I
15 wouldn't call it "precision medicine," because I
16 think it's so far off to come to precision
17 medicine.
18 I heard lots of terms which make, to me, a
19 lot more sense, like the last one, which was
20 phenotypic predictive power, to have more accurate
21 prediction, improving clinical practice.
22 There are lots of terms but

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1 "precision" -- it wasn't defined here but in my
2 personal opinion, it's talking about you take a
3 patient, you say I know that this patient should
4 get this or shouldn't get that treatment. That is,
5 I think, so far off that maybe it's doing a
6 disservice to call it that way.
7 DR. DWORKIN: To me, this is very important.
8 I think precision -- I mean, we need to be on the
9 same page about this before proceeding. To me,
10 precision pain medicine would be, let's say, the
11 Danish Demant study of oxcarbazepine replicates
12 with beside QST, whoever's beside QST is used.
13 Then we can determine a 10-minute procedure
14 of beside QST that this patient is relatively
15 likely to respond to oxcarbazepine and this patient
16 is less likely to respond. Is that not precision
17 pain medicine?
18 DR. SILBERBERG: I think it's a matter of
19 degree. So if you have 60 percent/40 percent
20 difference, one has 60 percent probability that
21 they will, the other one has only 40, so you say,
22 I'm not going to favor that one, that, to me, is

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1 not precision medicine, because still 4 out of 10
2 would benefit from this or 4 out of 10 won't
3 benefit from it. It depends, but --
4 DR. DWORKIN: But isn't precision medicine
5 that you know what to use first line? I'm not
6 saying you don't use --
7 DR. SILBERBERG: I think that's good
8 practice. As a novice person, I think that's what
9 you guys are doing all the time. A patient comes
10 in, you evaluate them, you decide on the first line
11 of treatment.
12 But you don't know that it's going to work.
13 You kind of -- based on all kinds of measures.
14 DR. DWORKIN: What would you call what we've
15 been talking about?
16 DR. SILBERBERG: I would say better
17 practice, improved -- "precision" means, in my
18 opinion, that you've got a very high probability
19 that you are right. That's what precision means.
20 DR. DWORKIN: Bob Kerns?
21 DR. KERNS: I couldn't agree more. I don't
22 think we ever heard the phrase specificity and

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1 sensitivity in the conversation in a day and a
2 half.
3 As somebody that had a father who had
4 cancer, when they're talking about choice of drugs,
5 it was really much more approximating what I've
6 come to this meeting understanding the concept of
7 precision medicine and anything that we're talking
8 about here.
9 DR. DWORKIN: Mike?
10 DR. ROWBOTHAM: I think there's a
11 [inaudible - off microphone] biomarker-driven more
12 along the lines of the cancer field, where with
13 this biomarker, that means you definitely get that
14 treatment and then none of the other ones.
15 Then there's precision pain medicine which
16 is [inaudible - off microphone] to that. I think
17 we're talking about here more using profiling and
18 personalizing medicine.
19 When you look at a whole host of factors
20 that allow you to give treatment recommendations
21 that don't exclude the other treatment, they just
22 help you prioritize which ones of the available

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1 ones the patients are most likely to respond to.
2 DR. DWORKIN: Shai, actually, I used to
3 think of it as personalized pain medicine. Does
4 that term make you happier?
5 DR. SILBERBERG: Yes. Personalized. First
6 of all, I think that's kind of what you do anyway.
7 It's just a matter if you have more tools or less
8 tools to make a better decision, and that's kind of
9 the way I took what's going on in this day and a
10 half, is coming up with better tools to provide
11 better personalized medicine.
12 DR. DWORKIN: We were using President
13 Obama's term, but he's on the way out and by the
14 time this paper gets published, there's going to be
15 someone else. So we could use "personalized pain
16 medicine."
17 Roy?
18 DR. FREEMAN: The way I think of all of this
19 as really increasing the probability, increasing
20 the likelihood that an intervention is going to be
21 effective.
22 Now, at what point that increased

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1 probability becomes so strong that we will satisfy
2 Shai that this precise is, I think, a matter of
3 opinion.
4 I think somebody else may find -- I see
5 Luana looking at me. Somebody from Italy may find
6 that, you know, the train arrives 40 minutes late,
7 that's pretty precise.
8 (Laughter.)
9 DR. TURK: After the humor dies down -- and
10 I'm not being humorous. So we're not looking for
11 perfect pain medicine. That's an impossible task
12 to be looking for.
13 Can we improve upon what we have and is that
14 precision, or precise, or whatever you want to call
15 it?
16 DR. DWORKIN: Lots of people have comments
17 on this, but I don't know that we want to spend
18 from now until 4:00 deciding on it.
19 How many people agree with Shai that
20 "precision" is too precise a term for where we are
21 for the next 5-10 years?
22 (Show of hands.)

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1 DR. ANDREWS: You should use a phrase,
2 something like "defined pain medicine," because,
3 for example, with what, say, Alban's presentation,
4 where he was understanding the idea of BCUs,
5 biomarker paired with the analysis, raised BH4
6 levels and a neuropathic patient would respond to
7 an SPRI inhibitor.
8 DR. DWORKIN: Nick, I think if we come up
9 with a new term, we're going to confuse everybody.
10 I'd like to see if we could stick with something
11 that people are somewhat familiar with.
12 How many people are unhappy --
13 DR. FREEMAN: I was lost in my -- I got a
14 little lost in on trains. Can I finish the
15 thought?
16 DR. DWORKIN: I'd rather. And then Luana
17 gets to revise.
18 (Laughter.)
19 DR. FREEMAN: I think that we should think
20 of precision medicine as a goal to strive for and
21 that's how I would present this. Whether how close
22 we are and whether we are there, I think, is --

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1 DR. DWORKIN: Half the room is agreeing with
2 Shai. How many people are unhappy with changing it
3 to "personalized pain medicine"?
4 (Show of Hands.)
5 DR. DWORKIN: Only a couple.
6 MALE SPEAKER: Unhappy with it.
7 DR. DWORKIN: I know. Unhappy with
8 "personalize pain medicine."
9 MALE SPEAKER: Can we separate the issues
10 here? Because there's an existing NIH way of
11 thinking about things and if we come up a totally
12 different way and don't use their way, are we, in
13 fact, going to be missing the way it's being talked
14 at, at a national level?
15 DR. COLLOCA: I think it is a matter of
16 contextualizing, as long as we refer to something
17 that has been proposed at lunch, like
18 President Obama.
19 We are finding this attempt to use
20 phenotypes to target and tailoring the treatment to
21 each single pain patient. That is the goal,
22 tailoring treatment.

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1 DR. JENSEN: Bob, could I?
2 DR. DWORKIN: Sure, Troels.
3 DR. JENSEN: Just a small suggestion or
4 proposal, because, like 20 years ago, we had a
5 paper by Clifford, saying towards a mechanism-based
6 classification. So maybe we could use the word
7 "towards" a precision type of medicine.
8 DR. DWORKIN: We could certainly do that.
9 There was something about accelerating --
10 DR. MARCHAND: It's accelerating the
11 development.
12 DR. DWORKIN: Right.
13 DR. MARCHAND: For me, I mean, I understand
14 what you mean, but we're just heading there. And
15 maybe we will never be there, but at least, we're
16 heading there.
17 FEMALE SPEAKER: Attempting.
18 DR. MARCHAND: I think it's okay like that.
19 DR. DWORKIN: I think we have a sense of the
20 room, which is a somewhat greater comfort with
21 "personalized" than "precision." I could imagine
22 we'll -- the draft paper might have something like

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1 "accelerating the development of personalized,"
2 also known as precision pain medicine.
3 That way, we'll address Dennis' concern that
4 nobody will get an NIH grant if we just use
5 "personalized pain medicine." I think there's a
6 way to have both.
7 But Bob Kerns is still unhappy.
8 DR. KERNS: Is it important to -- as soon as
9 you start talking "personalized," contrast that
10 with another term that people use a lot, which is
11 "patient-centered." I know that's an entirely
12 different kind of context and framing, but does
13 that become important to clarify?
14 DR. DWORKIN: It's a different source of
15 funding. I think that could be something
16 reasonable in the text, yes. All right. Maybe
17 we'll emphasize "personalized," but we'll make it
18 clear that we're in the same ballpark as
19 "precision."
20 Ian?
21 DR. GILRON: I'm just wondering if any of
22 this would be easier if in the title we were to

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1 separate treatment development and clinical care,
2 because psychological therapy, is that medicine? I
3 don't know if it is. That's one issue.
4 Then the other issue is precision methods in
5 preclinical development can be -- absolutely would
6 address Shai's concerns. It'd be very precise in
7 terms of developing treatment.
8 But then if we're talking about
9 implementation in patient care, we could say
10 personalized or tailored patient care.
11 DR. DWORKIN: I'll tell you what I think
12 about that. I think this paper is not about
13 clinical care in the community. It's about
14 therapeutics development.
15 Actually, I really like your point that
16 instead of talking about this is as precision or
17 personalized pain medicine, the title should be
18 changed to pain treatment or pain management so
19 that we can talk about things like catastrophizing
20 and cognitive behavior therapy and hypnosis, for
21 all I know.
22 So, yes, let's lose "medicine," emphasize

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1 "personalized." So some of us can get funding, put
2 "precision" in. I think Bob's point about
3 patient-centered is excellent, how what we're doing
4 is not really the same as what PCORI is focused on
5 right now.
6 Can we now move to the byline of the article
7 since we've spent a half hour on the title?
8 Mike?
9 DR. ROWBOTHAM: I was just going to say the
10 goal is still -- I agree with Troels. We're still
11 trying to move towards precision medicine.
12 Consensus Discussion
13 DR. DWORKIN: So now that we have, more or
14 less, a title, any comments on this kind of
15 structure of three sections, selective review of
16 promising things, general recommendations, specific
17 recommendations? Does that sound reasonable
18 scaffolding?
19 Bob?
20 DR. KERNS: I do think it is important to
21 kind of [inaudible - off microphone]. You said
22 five and then you said 5-10. Especially for that

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1 third section, I think --
2 DR. DWORKIN: When we get to --
3 DR. KERNS: -- it's next steps really.
4 DR. DWORKIN: Right. When we get to
5 sections 2 and 3 and actually start coming up with
6 lists of recommendations, we'll see what it looks
7 like.
8 When Rob and I were doing this over lunch, I
9 think we were kind of implicitly thinking
10 5-10 years, but getting to Bermuda as quickly as
11 possible.
12 Any other comments about this structure?
13 Does that seem like a reasonable structure, three
14 broad sections? Okay.
15 Dan? John?
16 DR. CARR: I like the structure. But are we
17 not actually directing the effort toward something
18 like advancing process of development of pain?
19 We're talking about the process. We're not
20 talking about individual things. Advancing the
21 process, words "personalized" or "precision" pain
22 medicine, because I think the effort overall is

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1 talking about the process, not specific things.
2 DR. DWORKIN: Why don't you hold that and
3 let's see what lists of recommendations we have and
4 what the best way of characterizing our general and
5 our specific recommendations would be?
6 Okay. So for the first section, and here,
7 it's just like Rob and I having a couple of
8 thoughts over lunch. This is really just to get
9 the discussion going.
10 When we thought about kind of promising
11 models, exemplars of precision, -- of kind of
12 what's going on in our field that's sort of a
13 foundation for thinking about the next 5-10 years
14 of advances -- Luda, I haven't said anything yet,
15 but go on.
16 DR. DIATCHENKO: No, no. I'm sorry. I
17 thought you were asking a question.
18 DR. DWORKIN: No, I wasn't asking a
19 question. So what we thought in terms of a
20 preclinical/translational arena of what we heard
21 the last two days, clearly, anti-NGF antibodies are
22 on the horizon and have an interesting and

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1 worthwhile to look at briefly
2 preclinical/translational history.
3 I was thinking of -- Nat gave a presentation
4 last year where he talked about the intense effort
5 that went into the preclinical development of
6 anti-NGF antibodies. Setting aside issues of
7 safety and tolerability, that's a success story.
8 Then a second example, of course, is Nav 1.7
9 and inherited erythromelalgia and genetic loss of
10 function, gain of function situations. The two
11 exemplars, if you will, that we came up with were
12 anti-NGF and kind of sodium channels and what we've
13 learned from rare genetic conditions.
14 If that sounds reasonable to you, we would
15 hope -- we would all very much hope that Nick, and
16 Luda, and Alban, and Clifford, and Andrew -- Andrew
17 still here? Yes -- would help Rob in
18 drafting -- and Nat certainly would help Rob in
19 drafting together a kind of
20 preclinical/translational two or three models and
21 exemplars.
22 We didn't include in that very first bucket

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1 BH4, only because there isn't yet kind of a
2 translational component. You don't have any human
3 data.
4 While the preclinical part is very
5 compelling with kind of sodium channels and
6 anti-NGF antibodies, the story is a little bit
7 better as a model, because you've got that
8 translation into the clinic.
9 But you all who know the preclinical and
10 translational world, let us know if there are other
11 examples in addition to those two.
12 DR. DIATCHENKO: I made my career on CMT.
13 CMT, we just did a full review on all genetic data,
14 just released in Neuroscience. So CMT continues to
15 be the most cited gene in the human pain genetic.
16 CMT has all the components. It has
17 association in an animal model. Actually, I mean
18 unlike GCHI, it does have a clinical trial. It has
19 been done with propranolol, a control for CMT
20 genotype. So it actually went through a whole
21 cycle.
22 A lot of discussion here, it's neuropathic

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1 pain, which CMT is not contributing to. But in the
2 musculoskeletal CMTs, it's a very strong evidence
3 for.
4 DR. DWORKIN: I can't imagine a reason to
5 object to adding that CMT and your propranolol
6 trial to this now three examples of promising
7 avenues of development for personalized pain
8 medicine. We have three examples of kind of in the
9 preclinical/translational arena.
10 Does that sound reasonable to people? These
11 are just examples. So if a reviewer at Pain, where
12 we will submit this, says, "You haven't done a
13 systematic review." We say, "Yes, we haven't done
14 a systematic review. We're not even sure what a
15 systematic review would be of preclinical research
16 that's relevant to precision pain medicine."
17 We will be really unabashed about saying
18 these are just examples of what we think is
19 promising in terms of preclinical research directed
20 towards precision/personalized medicine.
21 Yes?
22 DR. DIATCHENKO: We did a full review and

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1 the CMT is the most cited gene in musculoskeletal
2 and Nav 1.7 is the most cited in neuropathic pain.
3 I mean, that's it. We can focus on them, right?
4 We have a formal reason to focus on these two.
5 DR. DWORKIN: Perfect. You will send us
6 that review, right? Excellent.
7 DR. DIATCHENKO: I can help write this.
8 DR. DWORKIN: This is great. This is the
9 point of the day where everyone is so tired,
10 everyone starts to get agreeable.
11 (Laughter.)
12 MALE SPEAKER: That's a trick you use.
13 DR. DWORKIN: In the same first section of
14 the article, we obviously want to give some
15 clinical examples, kind of promising avenues of
16 clinical development.
17 Some of these seem kind of really
18 noncontroversial, because it's what we've been
19 talking about for the last two days. One is
20 obviously the distinction between irritable and
21 non-irritable nociceptor phenotypes, profiles,
22 whatever we call it, because the best study we have

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1 so far in this domain of personalized pain medicine
2 is the Demant study of oxcarbazepine. That would
3 be one example to describe.
4 Andrew?
5 DR. RICE: The difficulties of doing
6 preclinical systematic reviews, I take. We do
7 them, so I can tell you how difficult they are
8 because of the volume.
9 But I think there's a strong chance of
10 confirmation bias here that we're looking towards
11 the one study, the two studies that really confirm
12 our hypothesis.
13 Actually, the literature isn't that large.
14 I think a systematic review of that area would be
15 more valuable and will enhance the article.
16 DR. DWORKIN: Say more. What do you have in
17 mind by a systematic review, of what?
18 DR. RICE: We say how we've searched and we
19 say --
20 DR. DWORKIN: No, no, no. I know that. But
21 what are you searching for?
22 DR. RICE: Clinical trials that have set out

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1 to look at whether you can relate to response. If
2 we have done the systematic reviews, we don't know,
3 there may be some, in some obscure part of the
4 literature, it doesn't.
5 DR. DWORKIN: We've had over 50 pain
6 specialists in this room for two days. I think if
7 there is a clinical trial published somewhere that
8 pre-specified a kind of stratification hypothesis,
9 like the two Danish studies of lidocaine and of
10 oxcarbazepine and nobody in this room knows about
11 it, I'm comfortable ignoring it.
12 I don't know that we need to spend resources
13 and time doing a systematic review. That's my
14 personal feeling and I've actually argued with
15 Cochrane people about this.
16 I'm not so interested in the study that was
17 published in the Outer Mongolian journal of pain
18 therapeutics if none of us have heard about it. I
19 know that's kind of an outrageous thing to say but
20 I think with the people in this room --
21 DR. FREEMAN: Can I just make a quick
22 comment? I agree with you and I don't think a

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1 systematic review is necessary.
2 But I could not help but notice, with
3 respect to the two Danish studies, that both
4 address a specific hypothesis with a specific class
5 of drug. I would think that the one that was a
6 positive study was quoted probably 10 times more
7 frequently at this meeting than the one that was a
8 negative study, negative in support of the
9 hypothesis.
10 I think we just need to be careful, not so
11 much about publication bias, but about result bias
12 in doing this non-systematic review.
13 DR. DWORKIN: I seemed to recall there was
14 an editorial published along with the lidocaine
15 trial that argued -- was it you, Ralf -- that while
16 technically, it was negative study, boy, if you
17 look at the data, it's what the FDA might even
18 consider very supportive.
19 DR. FREEMAN: No arguments. But I think the
20 point still stands.
21 DR. DWORKIN: But I think we can trust Rob
22 to point out that there was one positive study and

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1 one negative study but that the negative study
2 could be viewed as supportive.
3 Shai?
4 DR. SILBERBERG: Bob, as an honorary
5 Mongolian --
6 (Laughter.)
7 DR. SILBERBERG: -- I want to explain what I
8 think Andrew was saying. For the specific examples
9 that you gave, that you're considering talking
10 about, the anti-NGF, the Nav 1.7 and so on, to have
11 a comprehensive evaluation of the literature, a
12 systematic review, to make sure that you've looked
13 all the data out there, not only cherry-picking the
14 ones that fit kind of the model would, I think,
15 make the paper a lot stronger.
16 we covered all the literature on this
17 specific topic and it all suggests this or there's
18 strong evidence for this or it's not that strong.
19 DR. DWORKIN: I don't want to beat a dead
20 horse. If you all think we need to do systematic
21 reviews of anti-NGF antibody preclinical research,
22 of sodium channel preclinical research, of COMT

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1 preclinical research and then a clinical research
2 on even the things on my piece of paper that I
3 haven't gotten to, I suppose we could devote six
4 months of resources to doing a series of eight
5 systematic reviews.
6 I guess I personally don't see the need for
7 systematic reviews when we are saying upfront that
8 we're just illustrating a process. We're not
9 saying we've done a comprehensive review of the
10 literature. We're not making treatment
11 recommendations. We're illustrating something.
12 Andrew, you started this so what do you
13 think?
14 DR. RICE: As usual, Shai has put it much
15 more eloquently than I can. I think exactly as you
16 put it.
17 DR. DWORKIN: You both think to illustrate
18 something, to say, This is a really nice example of
19 X, that we can't say that until we've done a
20 systematic review?
21 DR. RICE: There might be really good
22 examples of why showing the opposite. We don't

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1 know until the literature says empathically by
2 cherry-picking the one or two papers that support
3 the hypothesis.
4 DR. DWORKIN: But we're not going to
5 conclude that because of some studies that are
6 disappointing, like the topical lidocaine Danish
7 study, that we're going to abandon the development
8 or the hope of precision pain medicine.
9 You all realize the enormous resources to do
10 a series of half a dozen or more systematic reviews
11 that we wouldn't really intend to publish, but are
12 just so that we could put a sentence in that we did
13 a systematic review.
14 (Crosstalk.)
15 DR. FREEMAN: Can I just comment quickly?
16 This is going to save hundreds of hours if -- I
17 totally agree with your point over here. You are
18 using selected and I think it's quite reasonable to
19 say these are cherry-picked pieces from the
20 literature to buttress an argument.
21 It doesn't mean that there is not a
22 counterargument but you are cherry-picking in order

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1 to support an argument to take things in a certain
2 direction.
3 I think a systematic review is a different
4 story and there you would want to give a
5 balanced -- but I think as long as you say
6 explicitly these articles are taken from the
7 literature to support our position, I think that's
8 fine.
9 DR. DWORKIN: I guess, Andrew, to me, you're
10 saying you can do a systematic review and come up
11 with the other conclusion.
12 But I can't imagine that there would be
13 anything in the literature that would lead to a
14 conclusion that we recommend efforts to develop a
15 personalized pain medicine should be abandoned.
16 I personally can't imagine that Rob is going
17 to write an article where that's the conclusion,
18 let's abandon talking about irritable nociceptor
19 phenotypes or sodium channels being relevant to
20 some patients rather than others.
21 If we can't imagine that outcome -- and as
22 Roy said, we're just illustrating some things, why

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1 do we need to check on what was published in Outer
2 Mongolia? I still don't get it.
3 DR. RICE: I'll concede. But I think Roy's
4 point is explicitly pointing out that we haven't
5 done that and we cherry-picked, it should be in the
6 manuscript.
7 DR. DWORKIN: We are now routinely getting
8 the comment when we submit IMPACT manuscripts to
9 Pain, "You haven't done a systematic review." And
10 we always say, "Yes."
11 If we haven't already got the sense in the
12 article, we had a sense saying, "We have not done a
13 systematic review." However, is everyone happy
14 enough with that that we're not going to six or
15 eight systematic reviews?
16 (No audible response.)
17 DR. DWORKIN: Okay, great. Irritable versus
18 non-irritable nociceptor, the positive and the
19 negative, but perhaps supportive study. Another
20 example obviously is kind of the role of abnormal
21 CPM, DNIC as a potential avenue for accelerating
22 the development of precision pain medicine.

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1 We haven't talked about central
2 sensitization, but maybe there's a story to be told
3 about central sensitization and NMDA receptor
4 blockers.
5 Then I think most of us found Dennis'
6 presentation, combined with Rob's presentation this
7 morning very compelling that we don't want to leave
8 out -- along with Ralf's data, don't want to leave
9 out talking about and giving examples of a
10 personalized pain treatment, not medicine,
11 involving psychosocial profiling and presumably
12 psychosocial treatments.
13 That would be a bucket of three or four
14 clinical examples of what we've been talking about.
15 Irritable versus non-irritable, conditioned pain
16 modulation, central sensitization perhaps -- and
17 Alban, we'd need some help from you about this,
18 because you're the expert -- and then also
19 psychosocial.
20 Do those seem reasonable? Did we leave
21 anything out?
22 Ajay?

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1 DR. WASAN: Two quick comments. One is I
2 think we should have at least a sentence or two
3 about why we're not discussing pharmacogenomics,
4 because that'll be -- it's off and on people's
5 concerns. That's the one.
6 DR. DWORKIN: Absolutely. Let the record
7 say that, because we do need to say that and that
8 goes into sentences we have early on in the article
9 about what we consider beyond the scope of the
10 present effort.
11 DR. WASAN: Yes. And the second comment is
12 that on the psychosocial section, you could pull in
13 some of the discussion we've had about placebo,
14 because if you do precision medicine for placebo
15 and you're identifying those likely to respond to
16 placebo, you've inherently identified a group who
17 is better at pain modulation.
18 That gets to the psychosocial profile and
19 psychosocial treatments, in mind, body and
20 treatments, and pain self-management treatments.
21 That's something to think about. You could tie
22 some of the placebo piece into that and it's

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1 another aspect of precision pain medicine.
2 DR. DWORKIN: If you and Luana are willing
3 to help us, I think I kind of -- I guess it's a
4 fifth bucket in this section and we're really only
5 talking about a paragraph or two at most, would be
6 something like profiling to identify robust placebo
7 responders. That would be a very cool, I think,
8 thing to add to the paper.
9 DR. WASAN: My own little editorial for five
10 seconds is that any study that has a placebo arm
11 and is a precision medicine study that has a
12 placebo arm and you do the same kind of analysis in
13 a placebo arm, you actually doubled your search.
14 You've inherently potentially doubled the
15 impact by applying the same techniques to the
16 placebo arm in any study you do. That would be
17 another comment I would put into that section.
18 DR. DWORKIN: Maybe Ralf knows or somebody
19 else. Has anyone ever attempted to use either QST
20 or CPM to identify a robust placebo responder? In
21 other words, what is the sensory profile of a
22 patient who gets a 30 percent or greater pain

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1 reduction with placebo?
2 DR. MARCHAND: I would be happy to hear what
3 Luana has to say about that. But we manipulate the
4 CPM with placebo manipulation and it's working very
5 well, just like other people have manipulated the
6 effect of morphine, for example.
7 DR. DWORKIN: But I think I'm talking about
8 something different, which is kind of sensory
9 profile, identify a healthy placebo responder.
10 DR. BARON: To my knowledge, not with QST or
11 with CPM, but if it comes to Roy's data with the
12 NPSI, we looked at this in the placebo arm and
13 there are differences in NPSI profiles predicting a
14 large placebo -- unpublished, but you can do it.
15 DR. DWORKIN: Nat?
16 DR. KATZ: This is unpublished, too, but
17 we've done -- in our explorations of this whole
18 accurate pain reporting paradigm, we've done now
19 two randomized controlled trials, as well as an
20 intervention study where it turns out that in this
21 thermal -- not just thermal stimulation paradigm
22 where we're measuring how accurately people report

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1 their pain, it turns out that the people who have a
2 high variability in reporting experimental pain,
3 they also have much larger placebo responses than
4 people who have low variability, as well as a
5 larger separation between the drug and placebo.
6 We just finished this interventional study,
7 where we did a randomized controlled trial of
8 training people to report their pain more
9 accurately versus not training them and everybody
10 got pregabalin or placebo.
11 These are patients with painful diabetic
12 neuropathy. It turned out that the people who are
13 trained to report their pain more accurately had a
14 much lower placebo response and a larger
15 separation.
16 This is all going to start rolling out into
17 the literature, but it does seem like there's a
18 very close connection between variability and
19 experimental pain and the propensity to respond to
20 placebo.
21 DR. DWORKIN: This is wonderful. Thank you,
22 Ajay. We will have a couple of paragraphs on sort

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1 of profiling, placebo response and placebo
2 responders with help from Luana and Nat.
3 Ursula?
4 DR. WESSELMANN: Yes. But Nat just related
5 to the difficulty of some pain patients to
6 accurately sense an external stimulus or an
7 external sensation. That might apply actually to a
8 lot of tests that we give, not only to the response
9 to a given drug or a given interaction.
10 DR. DWORKIN: Some of these factors we've
11 talked about at previous IMMPACT meetings and in
12 previous publications. Anything else as possible
13 clinical models of promising avenues for the
14 development of personalized pain treatment?
15 Luda?
16 DR. DIATCHENKO: I thought that maybe in the
17 first section, when we talk about what is known
18 today, especially because it's personalized
19 medicine, biological markers are -- it's a big
20 part. We use psychological and phenotypic markers,
21 but biological markers are important.
22 Maybe it should be two, three paragraphs

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1 talking about what has been done so far with the
2 molecular markers. Maybe you see this in a
3 different part of the manuscript or maybe you see
4 it outside. But I would think this is something
5 which would be to say there is not much that has
6 been done.
7 As I said, we did some systematic review
8 very recently on what has been done at all on
9 genetic of chronic pain condition. And so one
10 surprising thing we found is, okay, so by diseases,
11 who did most of the studies?
12 Well, migraine by far, followed by actually
13 musculoskeletal. From those, surprisingly, TMD is
14 like number one. Neuropathic pain is like almost
15 the last in all the studies, which has surprised me
16 hugely because there is so much basic research in
17 animal study done on the neuropathic pain, but
18 somehow not genetic.
19 Again, I would suggest to put it in -- we
20 can write feasible, about more -- other molecular
21 markers. But in terms of genetic markers, my
22 message will be we didn't do it enough yet. We did

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1 so much so far and there is something which we need
2 to continue to develop.
3 DR. DWORKIN: We actually have to have what
4 you just described because the previous -- well,
5 two of the most recent IMMPACT meetings, and one
6 article is in press and one article is being
7 revised for resubmission, were on biomarkers and on
8 phenotyping.
9 So there's going to have to be some
10 discussion of how the recommendations we've made
11 for biomarkers -- and Shannon has spearheaded that
12 article -- and how the recommendations we've made
13 for phenotyping kind of dovetail or not with what
14 we're now saying about precision medicine and also
15 as you point out, what we haven't included, what's
16 been beyond the scope of all three of those
17 efforts.
18 John?
19 DR. MARKMAN: I know there was a point made
20 earlier that I missed, part of about rehabilitation
21 type testing and outcomes. I'm very interested in
22 symptom-specific functional testing in low back

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1 pain syndromes.
2 For example, matching treatments to patients
3 for problems such all right neurogenic claudication
4 and spinal stenosis for either drug treatment or
5 surgical treatment.
6 To me, if we could think about the ways that
7 symptom-specific activity limitations, specifically
8 pain symptom could be a way to think about
9 optimizing treatment matching as well for
10 precision. I'd be happy to write that sentence or
11 that series --
12 DR. DWORKIN: Yes, that could be in the
13 psychosocial bucket if we define psychosocial as
14 including physical functioning, et cetera.
15 Absolutely.
16 DR. MARKMAN: I appreciate it.
17 DR. DWORKIN: Andrew?
18 DR. RICE: Can I just make one very niche
19 point that you may or may not think merits just a
20 single sentence. It relates to Luda's point about
21 genotyping.
22 The human genotype in a small niche area is

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1 not the only genotype that's interesting for
2 outcomes and that's in the context of neuropathic
3 pain and infectious diseases, which is my area of
4 interest.
5 Particularly for HIV neuropathy, the virus
6 is routinely genotyped and it's a fantastic example
7 of precision medicine actually because the
8 prescribing of antiretrovirals is dependent on that
9 these days.
10 The viral proteins that may cause the
11 neuropathy are dictated by the genotype of the
12 virus. That information is routinely recorded in
13 all HIV patients' files, the genotype of the virus.
14 I think you probably know also that Judy
15 Breuer is very interested in the genotype of
16 Varicella-zoster viruses and whether they might
17 cause neuropathic pain. But the first piece of
18 information for HIV patients, viral genotype is
19 already available in all their case notes.
20 DR. DWORKIN: We clearly have to say
21 something briefly about these questions, because we
22 want to be specific and clear about what we're not

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1 including. So yes, we should add that. So you
2 stay on top of that. If it isn't in the first
3 draft, make sure it gets added.
4 Okay. Let's move on to -- now, it gets to
5 be more fun. These would be recommendations we
6 would make and some of these recommendations are
7 kind of -- at least what Rob and I came up with as
8 possibilities are pretty strong.
9 Maybe on the first one, everybody agrees on.
10 The first one on the list, and there's a lot of
11 discussion about this, is we kind of I think
12 strongly recommend that efforts should be devoted
13 to developing and validating bedside
14 approaches -- bedside meaning something that can be
15 applied in the clinic in phase 3 trials and in
16 clinical practice.
17 Bedside approaches to phenotyping, sensory
18 profiling, developing measures that can be done in
19 the bedside and this is true of QST, of CPM. And
20 we talked about earlier today, translating the hour
21 to hour-and-a-half DFNS protocol into something
22 that ideally your primary care doctor could do in

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1 five minutes.
2 We feel that that really is a kind of top
3 priority to develop such clinically feasible or
4 feasible in the clinic measures of sensory
5 profiling and that -- this gets a little bit kind
6 of provocative -- and that we think that consensus
7 measures should be developed, that we think that if
8 what our goal is to accelerate that the purpose of
9 acceleration is not served by having three
10 different bedside QSTs and six different bedside
11 CPMs.
12 We won't talk about Bermuda in the article
13 but the offer does stand that it seems like this
14 group consensus that getting consensus measures of
15 bedside QST, consensus measures of CPM is really a
16 priority. Otherwise, precision medicine is not
17 going to advance. That would be a first very
18 strong recommendation.
19 Lee, I think we also put in that this should
20 be done according to the drug development tool
21 guidelines, if that --
22 MALE SPEAKER: But this raises the question

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1 that takes me back what you started out talking
2 about, the purpose of the work.
3 Besides highlighting all the stuff that's
4 going on, are we talking about a tool, such as the
5 QST that you'd put together by consensus, that
6 would be used for drug development and drug
7 approval or are you talking about a clinically
8 applicable bedside test for the primary care
9 practitioner to use to perhaps choose different
10 therapies under different circumstances?
11 If you are talking about that, the latter,
12 you don't need to go through the process of doing a
13 DDT program but you cannot use it in the context of
14 getting drugs approved.
15 Under those circumstances, I do think you
16 need to have some clarity. We have this problem in
17 lupus. We have these ridiculous outcome measures
18 in lupus that nobody can understand in the context
19 of the clinic so nobody uses them. And they don't
20 work in clinical trial design to give us new drugs
21 as opposed to a lot of other things that we use in
22 rheumatology.

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1 In the context of this, since we're doing it
2 from scratch now, using what people have created as
3 implementation issues, it should have a clarity
4 about what you want to use it for.
5 Anything you develop for a drug development
6 tool can be used in the clinic if it's easily
7 acceptable. The alternative is not true. The
8 former is going to take resources, a lot of
9 resources.
10 The latter may not be, just opinion. So I
11 think we have to get clarity about what we want. I
12 would opt for a DDT tool to give us both
13 opportunities sooner for newer drugs than later.
14 DR. DWORKIN: I think we have to address
15 that, because I think if we're talking about
16 phase 3 trials, I'm not going to be doing a phase 3
17 trial anytime soon nor is Rob.
18 Then it really is DDT and it has to be that
19 our bedside CPM is something that can be used in a
20 phase 3 trial and end up as part of the drug
21 approval.
22 Mike?

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1 DR. ROWBOTHAM: I would say that going along
2 with some of these things that are being said,
3 especially since we are talking about moving
4 towards precision pain medicine, we really should
5 include a recommendation that blood sample be
6 obtained and biobanked in such a way that you
7 could look at expression profiling more than just
8 regular gene sequencing. You may want to include
9 something that's relatively easy to obtain in a
10 complicated process and analyze [inaudible - off
11 microphone].
12 DR. DWORKIN: Ian?
13 DR. GILRON: Getting back to QST, is there a
14 need to say that we have to do more validation in
15 terms of stability over time or susceptibility to
16 ongoing treatments?
17 DR. DWORKIN: If consensus was achieved on a
18 bedside QST measure, clearly part of the validation
19 of that approach would involve exactly those
20 things.
21 It's not going to get anywhere with drug
22 development tool qualification unless you've got

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1 reliability and boatloads of validity. That would
2 be a critical part of developing, validating,
3 qualifying bedside QST.
4 Now, what starts in Bermuda doesn't stay in
5 Bermuda. It extends for years afterwards.
6 Kristin?
7 DR. SCHREIBER: Kristin Schreiber from
8 Brigham and Women's. Because I want to go to
9 Bermuda, too, I wanted to also just bring up one
10 thing, maybe a little too specific but hasn't been
11 touched on.
12 In terms of QST, so for certain conditions,
13 it makes sense to do testing at the site of most
14 pain which is what I think has been done in a lot
15 of these studies.
16 But other types of pain and even pain
17 prediction, like for example, chronic post-surgical
18 pain which hasn't happened yet, the testing is done
19 in an area that's not currently painful.
20 It would just be nice to address how do
21 those two things relate, the QST that's done at the
22 site of injury and sort of the QST that's done as

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1 an assay of someone's nervous system processing.
2 DR. MARCHAND: Can I comment on that? I
3 think it's really important but it's important also
4 in patients. I think even if you want -- every
5 time you do -- maybe it should be in the report.
6 If you do a test in a patient, you need a
7 side where you have no pain I mean just to be sure
8 that the measuring you're doing -- if you have
9 normal data and everything, then it will apply for
10 both cases.
11 DR. DWORKIN: Is that Gary? I can't see
12 back there.
13 DR. WALCO: It is. Gary Walco, Seattle.
14 Being the token pediatric person at this meeting
15 and given that I need to leave in a couple of
16 minutes to catch a flight, the only thing I would
17 love to include somewhere in this document is that
18 we really need to have a developmental lifespan
19 perspective to see how whatever we do may apply to
20 the younger people and the older people and not
21 just assume that it's all static.
22 DR. DIATCHENKO: Longer, I would say,

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1 because otherwise other people will be upset.
2 DR. DWORKIN: Sorry, Serge.
3 But you're absolutely right. These
4 considerations have to be part -- and Kristin's
5 point have to be part of the development of the
6 bedside QST because you've got patients where you
7 could do a contralateral side --
8 DR. WALCO: Absolutely. Absolutely.
9 DR. DWORKIN: -- other patients where you
10 can't.
11 DR. WALCO: Exactly.
12 DR. DWORKIN: Then your point about are we
13 only testing the affected area or do we want to
14 know if there's widespread augmentation or whatever
15 we call it. It's not going to be a two-hour
16 meeting in Bermuda.
17 Yes, Ralf?
18 DR. BARON: Perhaps we should consider to
19 include one sentence about questionnaires because
20 we -- I have seen some signals with the LANSS with
21 Nat's study and we with PainDETECT.
22 Perhaps many of you know that we developed

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1 or we are in the process of developing a new
2 questionnaire which is called PainPREDICT exactly
3 for this purpose together Pfizer.
4 This is much more extensive than PainDETECT
5 and the others and is capturing nociceptive, as
6 well as neuropathic kind of symptoms, what we think
7 is symptoms. This has been validated due to the
8 standards you would like to see but it's not
9 published yet. That's the only problem. Perhaps
10 you can tell something about this.
11 DR. GOLI: Thank you for that information.
12 This is Veeru from Pfizer. I just wanted to add
13 there's a validation study done on that tool that
14 took us a couple of years to complete. We are
15 actually in the process of having a publication
16 plan that has just been finalized so we are hoping
17 to, with Ralf's help, have that data available
18 soon.
19 DR. DWORKIN: So this would be used for
20 profiling.
21 DR. BARON: Yes. It's profiling based on
22 patient-reported outcomes just from patients. But

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1 we tried to capture some evoked types of things so
2 if you are in contact with heat, what do you feel,
3 without touching the patients, just a
4 questionnaire.
5 DR. DWORKIN: Roy?
6 DR. FREEMAN: This does remind me of an
7 issue which I think is, in a way, quite critical
8 particularly once we are beginning to think of
9 instruments that might be used communally.
10 That is public domain versus non-public
11 domain. I think some comment should be made in
12 this sphere. I realize that this is a sensitive
13 issue but I think it's one that's worthy of -- at
14 least worthy of discussion. The Pfizer involvement
15 did remind me of this.
16 I also want to say there are other islands.
17 Bermuda is not the only other island.
18 (Laughter.)
19 DR. DWORKIN: Okay. It sounds like there's
20 agreement on the need to develop consensus
21 profiling methods.
22 Second, this seems like a low-hanging fruit

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1 to Rob and me as a recommendation: to devote
2 efforts to conducting post-hoc analyses of existing
3 completed clinical trials, to interrogate existing
4 data to see if there's any kind of predictors of
5 treatment effect modification in all the anti-NGF
6 trials which have probably now cost over \$1 billion
7 if you look across the three or four companies that
8 developed anti-NGF antibodies.

9 In NSAID trials, think about all of the
10 rofecoxib, etoricoxib, celecoxib trials that were
11 done in the late '90s and early 2000s and can we go
12 back into those data and look and see in a kind of
13 mining approach that Ralf talked about this morning
14 about, are there profiles of clinical and
15 demographic baseline characteristics that identify
16 kind of robust responders and distinguish them from
17 nonresponders?

18 That seems like a really easy recommendation
19 for us to make that to the greatest extent
20 possible, interrogate existing databases. Does
21 anyone want to add to that, disagree with it? It
22 seems painfully obvious and reasonable.

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1 MALE SPEAKER: I want to point out that if
2 you begin to do that, there are actually a series
3 of studies that were done by officially Searle,
4 then Pharmacia, then Pfizer that looked at
5 the -- they called the APS outcome of acute pain
6 which is that pain in the first seven days
7 versus -- because most of these were longer-term
8 trials.

9 But there is a whole bunch of data that sits
10 there as it relates to the first seven days of
11 responsiveness. And that could also be
12 interrogated to determine differences in that
13 context.

14 DR. DWORKIN: This is sort of like
15 Gary's -- Gary's argument was we shouldn't forget
16 kids. Your point is let's not forget acute pain.
17 We've really focused on chronic pain for the
18 last day-and-a-half but I don't think anything
19 we've said is not also potentially applicable to
20 acute pain. Absolutely.

21 Troels?

22 DR. JENSEN: I'm sorry just to take up a

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1 point that we discussed earlier and that was the
2 issue about systematic review. I know you hate it.
3 (Laughter.)
4 DR. JENSEN: But sorry about it. I don't
5 think you need to necessarily do a systematic
6 review of all sorts of things of phenotyping and et
7 cetera. But in terms of a pharmacological
8 treatment, I think it might be necessary.

9 The reason for that is I'm not sure if we
10 are having all the studies. For example, in
11 post-surgical pain, I think there might be
12 studies -- I can't give you the studies here but I
13 think there might be studies where people have
14 looked into predictors for finding a response to a
15 treatment. Maybe one of Henrik Kehlet's studies
16 could be an issue.

17 I think it would be -- as I said before, I
18 think this paper would be much stronger -- you
19 don't have to do systematic reviews of all other
20 things because the reason why we're having this is
21 that was the studies of irritable nociceptors and
22 we just present that.

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1 Then make the argument that you'd have to do
2 systematic reviews of the other things later on.
3 But I think there might studies here if we are
4 neglecting.

5 DR. DWORKIN: If we're going to add acute
6 pain, obviously acute post-operative pain is a
7 reasonable thing --

8 DR. JENSEN: No, I'm not talking about
9 acute. I'm talking about people with long
10 chronic-standing type of pain. Some of the
11 post-hernia studies, there was a post-hernia study,
12 for example, where they did also topical
13 application of lidocaine.

14 I think they tried to identify patients
15 before and after so --

16 MALE SPEAKER: [Inaudible - off microphone].

17 DR. EDWARDS: I think there are multiple
18 aspects studies --

19 DR. JENSEN: Also, one on QST on hernia.
20 There is an issue there, I think.

21 DR. EDWARDS: Sorry, Troels. I completely
22 agree. Just wanted to clarify one thing, did you

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1 mean a systematic review of studies that predict
2 individual variability in acute and chronic
3 post-operative pain or studies of, let's call them,
4 peri-surgical anesthetic interventions that might
5 be reduce the incidence of chronic post-operative
6 pain or do you mean in an established group of
7 people with persistent pain after surgery?
8 DR. JENSEN: I mean patients that had
9 already some chronic types of pain and where people
10 were identified before an intervention was done.
11 DR. EDWARDS: Okay.
12 DR. JENSEN: A little bit similar to what we
13 did in our oxcarbazepine study.
14 DR. EDWARDS: Got you, yes, I think that
15 would be wise to include.
16 DR. JENSEN: I don't think it will take a
17 lot of effort to do something like that.
18 DR. DWORKIN: We can certainly ask Henrik,
19 if we haven't found something, does he know of
20 anything that we should look at or to look for.
21 Okay. So to move on to something a little
22 bit more controversial as a recommendation, as a

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1 general recommendation.
2 Something like resources permitting, we
3 believe the proof of concept trials should include
4 assessments of patient factors that are
5 hypothesized to modify the treatment effect of
6 whatever is being studied in the phase 2 trial.
7 So a pretty strong recommendation that if
8 you have a treatment and you're doing a proof of
9 concept phase 2 trial of it, we think the
10 investigator should think about, are there any
11 patient factors that he or she would hypothesize
12 modify the treatment effect? And if that
13 investigator can come up with a hypothesis, include
14 the measure in your phase 2 trial.
15 It's a strong recommendation, but we start
16 off with resources permitting and so if you ain't
17 got the resources to do it, you don't have to do
18 it.
19 But if you're a large pharma company and
20 you've got some treatment in phase 2, spend a
21 little bit of time thinking about whether there's a
22 sensory profile, or catastrophizing as a

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1 psychosocial characteristic, or whatever that might
2 modify the treatment effect and put it in your
3 phase 2 trial.
4 Nat?
5 DR. BARON: Put it in, in terms of
6 stratification or post-hoc?
7 DR. DWORKIN: Well, put it in to at least
8 assess it and then whether you stratify or post-hoc
9 is really up to the investigator.
10 Nat?
11 DR. KATZ: I personally agree with that but
12 I have a supplemental question which is, it seems
13 like what we're talking about now are what I might
14 call generic approaches, like do this in every
15 study, and don't think about it too much and use
16 the off-the-shelf thing, and whether it really
17 marries up to the disease you're studying or the
18 drug that you're testing.
19 That's not what we're talking about now. I
20 wonder if we could go beyond that and maybe provide
21 a little bit more direction in the paper about how
22 investigators or companies sponsoring studies could

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1 think in more detail about the actual disease that
2 they're studying.
3 Maybe there are some biomarkers or some ways
4 of fine-tuning diagnostic categories that might
5 give more of a sense of like what disease factors
6 they're studying and do that in concert with their
7 drugs.
8 I'm thinking about Simon's presentation, for
9 example, how they went through this very beautiful
10 elaboration of the biology of their disease. And I
11 thought about how that married up to the class of
12 drug that they were studying. And then that led
13 them to consider certain ways of testing patients
14 and considerations of certain biomarkers.
15 I know that the Biogen did a similar
16 exercise in another recent program and other
17 companies are a little more aggressive about
18 looking for sort of biomarkers.
19 I showed the biomarkers of OA for safety but
20 one could also imagine using biomarkers of not only
21 OA but other disorders for efficacy. It's been
22 done in RA where inflammatory subtypes have been

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1 looked at.
2 I don't think we should just leave this to
3 our paper, but I think we need to go beyond that.
4 DR. DWORKIN: If I'm understanding you
5 correctly, it's a great paragraph or two where we
6 kind of provide a little bit of guidance about what
7 it really means to think about the mechanism of
8 your drug or other kind of treatment, the
9 indication that you want to study it in and how to
10 develop hypotheses about treatment effect
11 modification, and then go from those hypotheses to
12 actually doing some kind of profiling, phenotyping.
13 That's a great discussion, a couple of paragraphs.
14 Nick?
15 DR. ANDREWS: Is there any sort of reason to
16 at least put a little bit of lip service to the
17 FAAH inhibitor that Pfizer talked through which
18 actually flatlined? There was a beautiful example
19 of target engagement and increase in the biomarker,
20 which was the endocannabinoids.
21 It sort of goes against what we've -- it's
22 the negative reason -- I don't know. Is it

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1 something worth considering?
2 MALE SPEAKER: Wasn't the biomarker a sort
3 of -- it wasn't an outcome biomarker. It was
4 whether they was target engagement with the drugs.
5 It's not strictly relevant here, is it?
6 MALE SPEAKER: [Inaudible - off microphone].
7 MALE SPEAKER: It is?
8 MALE SPEAKER: [Inaudible - off microphone].
9 MALE SPEAKER: No, but it's not a biomarker
10 that -- it was looking at variation between
11 individual patients.
12 DR. DWORKIN: Let's investigate this
13 offline, because I remember having some concerns
14 about that trial that made me feel it wasn't
15 definitively negative in a way that I would've
16 wanted it to be definitively negative before
17 abandoning the whole program.
18 Simon?
19 DR. TATE: I just want to comment about
20 incorporation of phenotyping into phase 2 studies,
21 which I agree with the recommendation, by the way,
22 and we are going to start doing this.

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1 But my point relates to standardization in a
2 multisite study, because we actually incorporated
3 the step protocol into our radiculopathy study and
4 it wasn't that easy in terms of making sure that
5 even within a country that you have standardization
6 of the protocol across all the different sites.
7 Actually, what we ended up doing in Denmark
8 in that study was having study nurses travel
9 between sites to carry out the procedure.
10 So I wonder if we can actually put some
11 couple of sentences in towards how this is going to
12 be carried out in a multisite phase 2 study which
13 can be up to 40, 50, 60 sites in 10 to 15
14 countries. That is a realistic concern.
15 DR. DWORKIN: That's closer to phase 3. I
16 think we were thinking phase 2, but --
17 DR. TATE: In these rare pain conditions,
18 then you have to go out to quite a few sites.
19 DR. DWORKIN: I think we all completely
20 agree that we need -- we have to put front and
21 center feasibility. I don't think there's anyone
22 in the room who doesn't think that that's been like

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1 the --
2 DR. TATE: I don't think it's difficult
3 per se. I just think it's just to recognize that
4 we have to pay attention to that standardization.
5 DR. DWORKIN: Yes. Roy and I had a personal
6 experience with this that was compelling.
7 DR. FREEMAN: The videos that I showed were
8 part of that process which --
9 MALE SPEAKER: A quick question. The last
10 recommendation, did you mean something different
11 than the other recommendations in the phenotyping
12 papers, because very similar recommendations are in
13 the phenotyping papers that we put out. Is there
14 something different or am I missing something?
15 DR. DWORKIN: I think the phenotyping paper
16 was about specific measures. This is a strong
17 recommendation to come up with hypotheses and
18 implement phenotyping in a phase 2 trial.
19 MALE SPEAKER: Okay.
20 DR. DWORKIN: I don't know that that was in
21 the phenotyping paper.
22 DR. EDWARDS: Yes, the most recent

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1 phenotyping paper, the one that's in press in Pain
2 did focus pretty heavily on recommendations for
3 specific measures of phenotypes of interest that
4 were identified.
5 For example, we recommended the HADS if
6 people were wanting to measure general emotional
7 distress. And I think we recommended the DFNS
8 protocol when possible as a sensory profiling
9 phenotype, et cetera, et cetera.
10 DR. DWORKIN: We're going to get pushback on
11 a strong recommendation to implement
12 profiling/phenotyping in all phase 2 trials. But
13 let's try and see what we get.
14 Another recommendation that just seems kind
15 of straightforward, we didn't really talk about
16 adaptive clinical trial designs but certainly,
17 there are types of adaptation that could be
18 implemented in phase 2 that would limit the number
19 of subjects, give some early readout on whether the
20 phenotyping is making a difference.
21 I think this is really a two- or three-, at
22 most four-sentence recommendation. And we get some

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1 input from biostatisticians to consider the use of
2 adaptive Bayesian, interim, however we talk about
3 it, analyses as a way of kind of reducing the
4 number of subjects that stratifying, of course,
5 increases.
6 I think several years from now, we'll have
7 an IMMPACT meeting focusing on those kinds of
8 designs we haven't yet.
9 Kristin?
10 DR. SCHRIEBER: Would that include
11 enrichment for a certain population? I mean
12 obviously not all --
13 DR. DWORKIN: We'll get to that at least
14 by -- in terms of how I think of enrichment. And I
15 think the FDA has addressed that a little
16 differently.
17 That was a recommendation for phase 2. For
18 phase 3, how about this? It doesn't seem so
19 controversial. When the evidence base is
20 sufficient -- it's not clear that there are many
21 examples of it being sufficient.
22 But when the evidence base is sufficient in

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1 a phase 3 trial, stratify randomization or at least
2 conduct assessments that allow you after the fact
3 to stratify the analysis to determine whether some
4 patient factor has a modifying effect on treatment
5 outcome.
6 The key phrase there is, in terms of
7 phase 3, is when the evidence base is sufficient.
8 And, boy, Rob and I couldn't come up with very many
9 examples at the present time where there's a
10 sufficient evidence base that you would actually
11 implement stratification either in terms of
12 randomization or analysis in a phase 3 trial.
13 Lee?
14 DR. SIMON: It's really important to
15 recognize that you're saying two different things.
16 One is post-hoc analyses looking in screening for
17 things that might mean that or are you specifically
18 talking about --
19 DR. DWORKIN: Prospective.
20 DR. SIMON: -- a priori defined events.
21 DR. DWORKIN: A priori.
22 DR. SIMON: But then you have to then do

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1 either balanced randomization predicated on that or
2 stratification predicated on that.
3 Because you can just imagine what will
4 happen. People get scared of the stratification
5 because of the 40-percent increase numbers that are
6 necessary and then they won't balance randomize.
7 And then it's uninterpretable.
8 You have to insist that if we're going to do
9 this kind of profiling, they must actually at least
10 do balanced randomization for that. It's the
11 insisting part that puts this as an obligation.
12 DR. DWORKIN: At least to the extent I
13 understand these issues, that gets us into kind of
14 statistical questions about kind of the prevalence
15 in your --
16 DR. SIMON: But you're talking phase 3. If
17 you want it to be interpretable --
18 DR. DWORKIN: Absolutely.
19 DR. SIMON: People will not assume that. If
20 you're talking about profiling, they won't assume
21 that they have to do something unless you tell
22 them.

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1 DR. DWORKIN: No. We will have to -- we
2 will definitely put that in. And this is not a
3 recommendation that's relevant for the next five
4 years. This, I think, is in the bucket of 5-10, at
5 best, years.
6 DR. SIMON: At least.
7 DR. DWORKIN: Right. We're really not
8 talking about anyone doing that kind of phase 3
9 trial now, with only one possible exception that we
10 could think of that we'll get to in a minute.
11 Ian?
12 DR. GILRON: I just wanted to follow up with
13 that, at least that maybe there are a few sentences
14 to follow that to say what if 10 percent of the
15 population have the phenotype that responds and
16 then what's the regulatory response to that.
17 DR. DWORKIN: That's exactly Lee's question,
18 right, how you're going to design the trial. And
19 it goes back to the FDA guidance we circulated.
20 The FDA, not unreasonably, wants to know if
21 you're going to say the treatment works better in
22 this group, does that mean it doesn't work at all

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1 in this group, or the treatment effect is half the
2 size of this group and you can only find that out
3 if you have both groups of subjects. That raises
4 power issues.
5 We really appreciate that Lee has agreed to
6 spearhead the drafting of the phase 3 paragraph.
7 (Laughter.)
8 DR. SIMON: As long as you don't want to do
9 a post-hoc.
10 DR. DWORKIN: I think that was an earlier
11 recommendation that when you've got -- when you've
12 got rofecoxib data lying around and you have
13 nothing to do, do a post-hoc analysis to see if
14 anything predicts rofecoxib response.
15 Mike?
16 DR. ROWBOTHAM: I think there's two things
17 that are being discussed right now. One is
18 differentiating drug versus placebo in an
19 adequately powered trial.
20 But then the other part, though, and
21 especially in patients who are relatively
22 treatment-naïve, is some kind of either sequential

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1 treatment or multiple -- within the same overall
2 trial, looking at multiple treatments that you
3 could say patients with his profile should be
4 treated with this first line rather than that,
5 among available drugs.
6 DR. DWORKIN: Yes. Those studies have been
7 done in psychiatry and they're --
8 DR. ROWBOTHAM: They're there.
9 DR. DWORKIN: -- fabulously expensive and
10 fabulously interesting. I've given up hope that
11 anybody is going to pay for it in pain. But it
12 would make sense to put in something about that.
13 Similarly, the Kwan and Brodie epilepsy
14 study that I think you showed --
15 DR. ROWBOTHAM: I was just going to make a
16 pitch for including something about pragmatic
17 trials, because that's where you do it, because
18 they're all approved treatments and it's just
19 seeing who responds best within a healthcare
20 system.
21 DR. DWORKIN: There are shaking heads. We
22 all agree these studies should be done, but at

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1 least I personally am just like totally despairing
2 that anyone is going to do what NIMH did for
3 antipsychotics and antidepressants. Those are so
4 interesting.
5 This was Ian's point earlier and I think
6 it's a very reasonable general recommendation that
7 doesn't seem controversial. One should consider
8 the potential implications of the personalized
9 phenotyping/profiling on what you expect treatment
10 effectiveness in the community to be.
11 If it's only 5 percent of patients with
12 diabetic neuropathy that respond to lacosamide and
13 95 percent don't and you show that in a compelling
14 way, you really need to discuss -- if I understood
15 you correctly, Ian -- the fact that most of the
16 patients with DPN in clinical practice are not
17 going to respond to this drug.
18 The treating clinician needs to know that
19 and that the investigator needs to help that
20 clinician out by addressing it in a publication.
21 DR. GILRON: I agree. To add to that, we're
22 talking 5, 10, 20 years down the line. Some of

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1 this work with validated measures could help us
2 with currently available treatments as well. And
3 we could actually get precision or personalized
4 care improve with what we have now.
5 DR. DWORKIN: This is the kind of
6 generalizability, kind of external validity
7 relevance to clinical practice paragraph that is
8 critical.
9 We want to add about the importance of back
10 translation. Ralf mentioned that earlier so that's
11 a general recommendation. Mike's point just now
12 about biobanking, and that's obviously kind of
13 important in phase 2 and phase 3, to the extent the
14 patient gives permission, let's collect those
15 samples. That was our list of general
16 recommendations. It's something like eight or nine
17 at this point.
18 Nat?
19 DR. KATZ: Question. It seems like our
20 phenotyping comment, goals so far have been
21 directed towards efficacy. And I just wonder if we
22 should consider safety in some way as well.

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1 DR. DWORKIN: That's a great question. We
2 could consider it briefly in this paper, because we
3 haven't spent any time talking about it or we could
4 put it on the docket for a future IMMPACT
5 meeting or maybe we just do both, consider it
6 briefly in this paper and say it'll be considered
7 much more depth at a future IMMPACT meeting.
8 DR. WASAN: One caveat I would like to
9 raise.
10 DR. DWORKIN: There's too many people
11 talking at once. Ajay first and then --
12 DR. WASAN: One caveat, given all the
13 issues, particularly with opioids and the opioid
14 epidemic we have, where actually safety may
15 actually be a primary outcome that is akin to
16 efficacy, meaning at that bar, just reducing the
17 abuse liability.
18 I think it would be worthwhile in terms of
19 some of the issues that Ian raised with getting to
20 how we can recommend better research to be done now
21 with what we know to actually mention safety that
22 it could actually be a primary outcome. And so all

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1 the same considerations would apply.
2 DR. DWORKIN: There's agreement that we'll
3 mention, not very extensively, kind of personalized
4 precision approaches to safety outcomes in this
5 paper and that we will put on the list for a future
6 IMMPACT meeting accelerating the development of a
7 precision approach to safety outcomes in pain
8 clinical trials.
9 Nat?
10 DR. KATZ: To expand very slightly on that,
11 I mean, ultimately, we're interested in the
12 risk-benefit balance with the drug and so the
13 safety and the efficacy, I think it's worth just
14 framing it in a kind of long-term risk-benefit goal
15 context.
16 DR. DWORKIN: I deeply appreciate you
17 mentioning that, because it gives me an opportunity
18 to say that Kushang is working on an earlier
19 IMMPACT paper on exactly that topic.
20 Is Kushang here? He's hiding.
21 (Laughter.)
22 DR. DWORKIN: We are eagerly looking forward

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1 to Kushang's IMMPACT paper on approaches to
2 evaluating the risk-benefit profile of treatments.
3 Any other general recommendations to add to
4 this list, this table?
5 Lee?
6 DR. SIMON: I have one question to ask you
7 about what you just said. In the context of
8 understanding risk and harm or harm and benefit,
9 are you actually including patients helping to
10 write that since they're the ones that actually
11 help us understand issues associated with the
12 potential harm versus the potential benefit?
13 DR. DWORKIN: I don't remember whether Tina
14 and Penney were at the meeting that Kushang is
15 writing up. But I think it's a great point and we
16 should have patients involved in helping Kushang
17 draft this manuscript.
18 DR. DIATCHENKO: It will please PCORI, too.
19 DR. DWORKIN: Yes, Nat?
20 DR. KATZ: I'm a roll, so I'm going to keep
21 going. We haven't talked about pharmacokinetic
22 phenotypes, whether a patient should be classified

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1 based on whether they actually have some
2 pharmacokinetic subtype that impacts their exposure
3 to the drug.
4 It's kind of shocking how rarely we address
5 that in our clinical trials. We try to make sense
6 out of the data and don't even worry whether the
7 people actually had adequate exposure to the drug
8 in the first place.
9 I wonder since it is directly relevant to a
10 discussion of phenotyping and the context of drug
11 development, whether we're planning on addressing
12 that in any way.
13 DR. DWORKIN: Mike?
14 DR. ROWBOTHAM: To expand on what Nat is
15 saying, what you want to assure is that you've got
16 targeting of data that based on the
17 pharmacokinetics [inaudible - off microphone].
18 DR. KATZ: That's one important implication.
19 Another one is, yes, the ultimate goal is target
20 engagement, but what if 80 percent in group 1 are
21 rapid metabolizers and 20 percent in group 2 are
22 slow, there's some sort of -- there's some

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1 fundamental clinical trial scientific integrity
2 issues that really can't be understood unless you
3 know whether your patients are being exposed to
4 your drug or not.
5 You could just look at PK, but at least to
6 think about whether there might be any major
7 phenotypes that could impact -- metabolic
8 phenotypes that could impact your results. It
9 seems like it's worth at least checking out.
10 MALE SPEAKER: I completely agree. I could
11 make the same -- do want to genotype the people in
12 that regard or phenotype? Phenotyping is probably
13 easier to be honest.
14 DR. KATZ: I don't have an opinion about
15 that question.
16 DR. DWORKIN: But that's going to depend on
17 the drug and any kind of resources but I think we
18 need to -- the same way we're going to put in
19 something about genotyping and how an in-depth
20 discussion is beyond the scope of this paper, we
21 need to do the same thing with pharmacokinetics
22 because we wouldn't be able to deal with it in

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1 depth. But it's obviously critical.
2 Mike?
3 DR. ROWBOTHAM: I just want to get back to
4 the point you just were raising about the NIMH
5 studies where you're looking at multiple treatments
6 and sequence.
7 If we're talking about fairly complicated
8 profiling like for example including QST and
9 psychological variables or catastrophizing, which
10 really study a lot of subjects -- and we're not
11 doing a systematic review.
12 There's one paper, I think, that we should
13 cite in there about it's not truly an N of 1 study
14 but it's Michael Byas-Smith's paper from 1995 with
15 Mitchell Max where they took patients who appeared
16 to respond to transdermal clonidine even though the
17 overall trial was negative and then ran them
18 through a period of crossovers.
19 You could use that as a fairly efficient
20 technique to try and verify that you're seeing
21 something real in patients who may comprise a small
22 proportion of your overall trial group. But it has

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1 a particularly interesting correlation between
2 their drug response and something worth profiling.
3 DR. DWORKIN: We haven't gotten --
4 DR. ROWBOTHAM: I'll send you the reference.
5 DR. DWORKIN: Yes, I know. I have it. I
6 know the study well.
7 We're going to get to clinical trial
8 designs, I think, in a bit. Anything else that's
9 kind of generic, general recommendations for this
10 middle third of the paper?
11 Shai?
12 DR. SILBERBERG: For my understanding, we
13 heard the recommendation [inaudible - off
14 microphone] was measures that you've included in
15 phase 2 --
16 DR. DWORKIN: Yes.
17 DR. SILBERBERG: -- that might affect the
18 outcome. Is that like the list of common data
19 elements that expand [inaudible - off microphone]
20 for all sorts of pain?
21 DR. DWORKIN: No. As I understand the
22 recommendation is we're just telling the

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1 investigator who's designing a phase 2 trial -- and
2 this goes back to what Nat was saying.
3 Think about your drug's mechanism of action,
4 think about the kind of pathophysiologic mechanisms
5 of the patients in whom you want to test it and
6 come up with some hypotheses about which patients
7 you would predict are more likely to be robust
8 responders and put measures of that in your trial.
9 We're not saying anything specific. That's
10 why we talked about it's a very general
11 recommendation that we think investigators should
12 do their very best to come up with hypotheses of
13 treatment effect modifiers.
14 But we're not fleshing it out at all. We're
15 leaving it up to the investigator because, of
16 course, it depends on the pain condition; it
17 depends on the drug.
18 DR. SILBERBERG: [Inaudible - off
19 microphone]. All diseases that you might want to
20 include like in a table saying, regardless of what
21 area of pain we're looking at, these thing you
22 should look at.

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1 DR. DWORKIN: Yes. Rob had a slide of many,
2 many potential characteristics that could go into a
3 lengthy profile, and that would be a
4 reasonable -- I think it would be a reasonable
5 table to have in the article, which would be as
6 comprehensive a list as we can come up with of
7 potential patient factors. So age, sex, weight,
8 height and extending for another 30 or 40 bullets.
9 DR. MARCHAND: You can say that you know
10 that it's not everything, but it's mainly what we
11 see --
12 DR. DWORKIN: But we can try to make it
13 pretty comprehensive like what are all the
14 potential things that one could consider. Great
15 idea.
16 Nat?
17 DR. MARCHAND: At the risk of leaving
18 it -- you know, think about it. People will say,
19 yes, I thought about it and I didn't find anything
20 that --
21 DR. DWORKIN: It's really a checklist. It's
22 a checklist to help the investigator make sure

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1 they've considered all the possible things to
2 include in the profile, what a wonderful idea.
3 Nat?
4 DR. KATZ: Yes, another question. We do
5 know something about meaningful phenotypes of
6 certain common painful disorders that are commonly
7 the subject of clinical trials.
8 For example, there's a small literature on
9 phenotyping in osteoarthritis, which, by the way,
10 Lars has another great paper on that that I just
11 emailed to you.
12 We know something about phenotyping and back
13 pain. There's some biomarkers that have been
14 studied in back pain, for example, something about
15 phenotyping a postherpetic neuralgia that's been
16 discussed today, et cetera, et cetera.
17 In this paper, are we going to have any kind
18 of disease-specific sections where we describe
19 what's known about the phenotypes in specific
20 disorders that are commonly studied in clinical
21 trials?
22 DR. DWORKIN: We could. This is a nice

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1 segue into the third part of the part of the paper,
2 where the two of us came up with some examples of
3 specific recommendations that were really talked
4 about earlier today and yesterday.
5 But it's different than what you're
6 suggesting. I don't know whether one or the other
7 or both. We were thinking would it make sense to
8 have a list of specific recommendations that would
9 be kind of if all of a sudden The Gates Foundation
10 took a serious interest in pain, what clinical
11 trials and other studies do we recommend be
12 undertaken?
13 We kind of said in such a list of what we
14 think should be done, if there was money available,
15 a study of CPM in patients with OA in a separate
16 study and some neuropathic pain condition and
17 duloxetine.
18 A placebo-controlled trial of CPM and as a
19 treatment effect modifier for duloxetine. It could
20 be a tricyclic just as easily in patients with OA
21 and in patients with some neuropathic pain
22 condition.

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1 Now, that's very different than what you
2 were suggesting. You're suggesting a section of an
3 article where we actually talk about why one might
4 think CPM would be interesting to look at in OA?
5 DR. KATZ: Maybe, but I was actually
6 thinking of something much less ambitious than
7 that, which is simply postherpetic neuralgia.
8 You're considering doing a study on postherpetic
9 neuralgia. Here's what the literature has to say
10 about phenotyping patients with PHN.
11 I mean, go back to Mike's paper and Ralf's
12 work, et cetera, you're considering doing a study
13 in fibromyalgia. Here's what you know about
14 phenotypes in fibromyalgia, epidermal nerve fiber
15 biopsies, whatever. You're considering doing a
16 study -- in other words, summarize the literature
17 on what's known about phenotypes and disorders of
18 interest to the people reading the paper.
19 DR. DWORKIN: I just want to say for the
20 record, because Andrew is staring at me, what you
21 just said requires a systematic review.
22 (Laughter.)

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1 DR. DWORKIN: This is an example of where
2 Bob does agree with Andrew. Up until this moment,
3 we totally disagreed but now, we're in agreement.
4 It looks like Ralf's on board, also.
5 Nat came up with an example of where we do
6 need systematic reviews. Now, the issue is there's
7 a whole boatload of acute and chronic pain
8 conditions.
9 This, Nat's suggestion, if we pursue it
10 expands the paper, because we have much more to
11 discuss and we do have to do some systematic
12 reviews before we say to a PHN investigator these
13 are the phenotypes that you should consider.
14 John?
15 DR. FARRAR: I think it's a separate paper.
16 I think we risk diluting the effectiveness of this
17 paper if we include all of that. And if we're
18 going to be thorough about it, one could argue that
19 for the major pain syndromes, you might actually
20 want separate short papers of the systematic
21 review.
22 I mean, it depends on how complete you want

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1 to be. I would strongly argue that it's a separate
2 paper.
3 DR. DWORKIN: All right. How about this?
4 ACTTION has resources. If any of you like Nat's
5 idea and have a fellow, a resident, a graduate
6 student, a junior faculty member or yourself want
7 to do a series of systematic reviews and kind of do
8 the paper that Nat and John just described, we
9 would be happy to support it.
10 DR. MARCHAND: Are we talking about a
11 systematic review, for example, for CPM and another
12 one for something else or altogether?
13 DR. DWORKIN: We'd have to think about that,
14 Serge. Nat was talking about it in terms of pain
15 condition.
16 DR. MARCHAND: Okay.
17 DR. DWORKIN: Are there studies of CPM and
18 PHN? I don't think so, but there could be.
19 (Crosstalk.)
20 DR. DWORKIN: They might be from Outer
21 Mongolia, so we'd have to think about -- you'd
22 probably want to do both at the same time in a

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1 systematic review, look at conditions, look at CPM,
2 QST, catastrophizing, et cetera.
3 So this involves a bunch of good questions
4 and if anyone of you is interested or know someone
5 who's interested, we need to do this offline and
6 think of it as a kind of ACTTION project or a
7 series of projects.
8 DR. EDWARDS: Just one very quick addition
9 to that, I love that idea. I think it's really
10 neat. Nat, as I'm sure you already know, the
11 universe of phenotyping papers for a given
12 condition is much larger than what we've been
13 talking about at this meeting, which is phenotypes
14 that predict treatment response.
15 If you wanted to do, say, a systematic
16 review of phenotyping in fibromyalgia, you would
17 come up with huge numbers of papers that would
18 identify characteristics on which fibromyalgia
19 patients differ for which you could form subgroups.
20 But there might not be any data or very
21 little data anyway on whether those phenotypic
22 profiles predicted treatment response. You'd find

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1 papers on fibromyalgia phenotypes associated with
2 greater or less physical disability or a cognitive
3 dysfunction or that sort of thing.
4 So we just want to specify, I think, in
5 advance, how broad we wanted to be in our
6 systematic review of the "phenotyping" literature
7 for a given condition.
8 MALE SPEAKER: I would suggest you don't
9 base it on the condition, but on the method.
10 DR. EDWARDS: Okay. That would --
11 MALE SPEAKER: The one on CPM, for example.
12 DR. EDWARDS: Yes.
13 DR. DWORKIN: We don't have to think about
14 this further, because we don't know whether anyone
15 is going to volunteer to do it. But if someone
16 volunteers to do it or volunteers a fellow or a
17 spouse to do it --
18 (Laughter.)
19 DR. MARCHAND: She's on the phone right now.
20 She would like to talk with you.
21 MALE SPEAKER: You mean ex-spouse.
22 (Laughter.)

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1 DR. DWORKIN: Shai, I think there are some
2 ex-spouses in the room kind of floating.
3 (Laughter.)
4 DR. DWORKIN: We will convene a little
5 working group to kind of flesh out these details of
6 whether the systematic review is by condition, by
7 profiling. But first, we need a volunteer.
8 What do you all think -- because we're
9 certainly coming to the end of the list of what Rob
10 and I came up with -- about recommending some
11 specific trials, like CPM as a treatment effect
12 modifier in a trial of duloxetine, in OA, maybe
13 axial low back pain, maybe neuropathic pain.
14 Another example, kind of replicating the
15 oxcarbazepine trial with pregabalin, like do
16 irritable nociceptors modify the treatment effect
17 of pregabalin? It's a different mechanism of
18 action than oxcarbazepine. It would be kind of
19 interesting if you got the same pretty figure for
20 pregabalin.
21 Another example, capsaicin, the capsaicin
22 response test that was used in the trial of topical

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1 clonidine. Let's look at that as a potential
2 treatment effect modifier for oxcarbazepine, for
3 topical lidocaine.
4 We can continue this but would it make sense
5 in this article -- because we can fill it out
6 offline -- to list 6-10 phase 2 clinical trials
7 that we think Bill and Melinda should fund when
8 they decide they've done enough with malaria or is
9 that going too far out on a limb?
10 DR. MARCHAND: I think going with a
11 recommendation is okay. I mean, especially, the
12 example you're giving are making so much sense. I
13 mean, we want that. For sure, people will come
14 with other ideas after that.
15 But the idea is just to go and say, what
16 will help in the short term, as you said, and in
17 the next five years?
18 DR. DWORKIN: Shai?
19 DR. SILBERBERG: As an NIH person, I would
20 recommend not do it, because inevitably bias creeps
21 into the [inaudible - off microphone], the people
22 on the paper, the groups that are here, the

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1 [inaudible - off microphone].
2 I think that could detract from the paper as
3 opposed to being kind of a more consensus paper for
4 the whole community not to make recommendations
5 about specific things, but, in general, what needs
6 to be done.
7 DR. DWORKIN: John?
8 DR. FARRAR: As a slight modification to
9 that, I agree that if we recommend specific
10 diseases and specific drugs that there's going to
11 be a perception of bias.
12 But I liked your concept of basically
13 looking at things that have been done in specific
14 disease -- and we could express it as on taking
15 successful efforts to look at this in specific
16 diseases with specific drugs and expanding that to
17 look at other diseases and other drugs.
18 So that in a more general way, I think you
19 could express a need to move forward with some very
20 low-hanging fruit without necessarily identifying
21 the drug and the disease entity.
22 We could quote that there's the

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1 oxcarbazepine study and that this study ought to be
2 reproduced with different drugs and different
3 diseases. You just say that.
4 DR. DWORKIN: That's easy enough to do.
5 John?
6 DR. MARKMAN: I thought when you asked the
7 question yesterday, Bob, it kind of crystallized
8 the discussion and sharpened it a bit when you
9 posed these hypothetical trials of duloxetine
10 [inaudible - off microphone].
11 I think to address Shai's concern, it might
12 be useful though, I think, for the reader to have a
13 table, which talked about sort of what bucket these
14 models fell into and an example of an illustrative
15 study and what it would look like.
16 I think it's a way to sort of define the
17 issue of all of these special interests, but also
18 to give an example, to crystallize the readers, in
19 their mind, what is an illustrative example of a
20 trial where we do a pharmacologic challenge or a
21 psychophysical challenge? So they have something
22 specific to latch on to and maybe list four or five

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1 different types of these.
2 DR. DWORKIN: If there's some value, one way
3 of addressing Shai's concern, which I personally
4 hadn't thought of and I think is really very
5 important for ACTTION to be concerned about, is
6 instead of saying duloxetine or oxcarbazepine, say
7 kind of either SNRIs or tricyclics as treatment,
8 with CPM as treatment effect modifiers, so the
9 broad class of dual reuptake of inhibition, or
10 sodium channel blockers instead of saying
11 oxcarbazepine, or topical anesthetics instead of
12 saying topical lidocaine.
13 Maybe there's a way to address your concern,
14 but also what John is saying. We'll try and
15 do -- and it'll be very brief, because this does
16 sound controversial -- this kind of midrange
17 recommendation, not highly specific, but more
18 specific than the general recommendations we just
19 listed and see what you all think.
20 Luana?
21 DR. COLLOCA: Probably instead of
22 suggesting in detail kind of study, it makes sense

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1 to identify gaps and try to reconcile the first
2 part where you propose promising models with the
3 second part of the recommendation.
4 Based on the first two paragraphs, the 31
5 can reconcile and in a sort of concise way suggest
6 a concept or a methodological issue that needed to
7 be disentangled, because today, we don't know how
8 we can accelerate this development of personalized
9 pain management, pain medicine.
10 I would suggest studies, but concept, area,
11 gaps where we need to do more. And for Robert, who
12 introduced the idea of interaction and explore
13 together instead of continue to have this dualism
14 psychology versus neurobiology.
15 It's time to frame everything in terms
16 of psychoneurobiology, because there is this
17 distinction. We distinguish because we are
18 physicians, psychologists, but patient come to the
19 lab or to the clinics, it's their pain, their
20 effective component, their genes.
21 It's a time where we should sit together
22 and try to work together to reconcile this domain

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1 that we separate, but in our patients are not
2 separate.
3 DR. DWORKIN: We only have about less or
4 more than 10 minutes. First, I'm going to call on
5 Troels, and then I'll tell you what we'll do with
6 the remaining nine minutes.
7 DR. JENSEN: I just want to ask, is there
8 going to be a section or a paragraph about outcome
9 parameters?
10 The reason I ask is, for example, if you
11 go -- I'm taking up the point, which has been many
12 times by Henrik Kehlet, if you're looking into
13 post-surgical pain, you have to have outcome
14 parameters, which is related to the particular
15 condition you are talking about.
16 If it's a patient who has a mastectomy, you
17 don't want to ask about, for example, walking. You
18 want to ask something about which has to do with
19 breathing, et cetera.
20 If you're having a patient with hernia, you
21 want to ask whether you have pain, for example,
22 during sexual activity, et cetera. If you're

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1 having a patient with a knee, you want to ask
2 something about walking.
3 This is important. It's also important, for
4 example, for postherpetic neuralgia, where is your
5 postherpetic neuralgia, et cetera.
6 DR. DWORKIN: Yes. We need to include that
7 when you're doing phenotyping, you need to consider
8 what the measure that's assessing efficacy.
9 Absolutely, Troels.
10 DR. EDWARDS: I think we also need to
11 include -- Andrew's about to talk and I just cut
12 him off.
13 But I was going to mention that he did a
14 really nice job in his presentation identifying
15 some of the limitations of what are used as outcome
16 measures in the preclinical literature. I think we
17 should certainly address that in the manuscript as
18 well.
19 DR. DWORKIN: Andrew?
20 DR. RICE: Thank you, Robert. It was just
21 to support Troels' point, but I think it goes a bit
22 further with the comment I made yesterday. I think

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1 in fact, Troels, I think, was one of the first
2 people who suggested it.
3 Within the German databases, we now have
4 actually quite a lot of information about specific
5 conditions for sensory profiling. And some of them
6 are very, very homogenous.
7 So it might be worth raising the concept of
8 condition or hypothesis-specific sensory profiling.
9 There's no point in doing certain profiling
10 measures in some conditions where it's not
11 relevant.
12 DR. DWORKIN: Luda?
13 DR. DIATCHENKO: If we're talking about
14 something which -- if we would have money, so there
15 is a very good point Michael brought that we should
16 recommend collect biological samples. But what for
17 are we going to recommend?
18 If I may, what I would suggest is -- and I
19 don't know if we can do this within
20 practice -- actually, if we can collect all samples
21 on treatment of neuropathic pain and do javas [ph]
22 on them and make publicly available, then everyone

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1 will benefit from this.
2 It's not that much money. I mean really you
3 can do javas for \$50 right now. We're really
4 talking about \$100,000, which is small in
5 comparison with clinical trial itself, right?
6 What we heard from NIH, from the yesterday
7 person --
8 MALE SPEAKER: Will.
9 DR. DIATCHENKO: Will, right. So he said,
10 well, we will collect samples, and then you guys
11 can look at this. And then you can contact them
12 and can phenotype them. I mean, this all will
13 happen in 10 years like the earliest.
14 On the other hand, if we will all collect
15 all samples and we'll do javas, then everyone can
16 come back to your own cohort and see the specifics,
17 which you did for this cohort, but in the realm of
18 genome-wide significance.
19 This is what I would envision as will be
20 kind of best to do. I don't know the structure
21 which allows to do this, but maybe in practice, the
22 structure.

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1 DR. DWORKIN: My only concern about that is
2 to kind of really talk about that and provide the
3 rationalization in, say, something about mechanisms
4 is more than a -- I worry -- is more than a few
5 sentences. We need to really see if it's something
6 that can be incorporated in a paper.
7 DR. DIATCHENKO: Five sentences. I can do
8 it in five sentences.
9 (Laughter.)
10 DR. DWORKIN: Rob, I know -- I'm confident I
11 can speak for Rob in saying he would love to have
12 you send him the five sentences.
13 Shai?
14 DR. SILBERBERG: One has to consider here
15 you need to consent the patients to give the
16 samples which adds complexity, because it depends
17 on what the form says, how it's written, et cetera.
18 Then you've got to biobank them. And where
19 are you going to biobank them? And you have to
20 have them well phenotyped, which all takes time.
21 So it's not as -- from an NIH --
22 DR. DWORKIN: Slight modification, Luda is

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1 going to draft five sentences. Before you send
2 them to Rob, send them to Shai. If Shai approves
3 them, Shai can send them to Rob. Okay? So we got
4 a plan.

5 So we've only got 5 or 10 minutes left. So
6 you've all had your say. What I would like to do
7 is to see if Rob has any questions. Because
8 remember -- remember the objective. I've done all
9 the talking. You guys have done all the talking.

10 The objective of the last two hours was to
11 make Rob happy. And if he's not happy, we're all
12 staying here. So, Rob, are you happy? Do you have
13 any questions?

14 DR. EDWARDS: So just as a general comment
15 and for future reference, tropical drinks with
16 little umbrellas in them on the beaches of Bermuda
17 tend to make me happy.

18 (Laughter.)

19 DR. EDWARDS: This has been a delightful
20 meeting. You guys have been great. I have many
21 pages of notes. I think if I were to go through my
22 notes right now and estimate length of this

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1 manuscript, it would be probably longer than is
2 feasible to write. So some sections we'll wind up
3 having to condense a little bit, I'm sure.

4 But we don't need to do any work on that
5 now, I don't think. That'll happen organically as
6 this gets produced.

7 I don't think I have any questions, but I
8 will extend a hearty thank you in advance to Luda,
9 and Clifford, and to all of the other people whose
10 help I will draft in writing various sections of
11 the manuscript. I suspect this will be a good read
12 for a lot of people and hopefully quite useful for
13 the field.

14 DR. DWORKIN: Thank you all very, very much
15 for your participation. And you will be hearing
16 from us. Have safe flights home.

17 If Valorie and Andrea are back there, thank
18 you, Valorie and Andrea, for another flawless
19 meeting.

20 (Applause.)

21 (Whereupon, at 3:50 p.m., the meeting was
22 adjourned.)

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