

*ACTION - CONCEPT/DNC MEETING ON  
DIABETIC PERIPHERAL NEUROPATHIES*

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*December 12, 2017*

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*A Matter of Record  
(301) 890-4188*



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1 DR. GIBBONS: Chris Gibbons, neurologist  
2 from Boston.  
3 DR. SINGLETON: I'm Rob Singleton. I'm a  
4 neurologist at the University of Utah.  
5 DR. HARATI: Yadollah Harati, neuromuscular  
6 specialist from Baylor College of Medicine, Texas.  
7 DR. DYCK: Jim Dyck, neurologist, Mayo  
8 Clinic, Rochester, Minnesota.  
9 DR. SMITH: Gordon Smith, neurologist in  
10 Utah.  
11 DR. MALIK: Rayaz Malik, endocrinologist,  
12 Cornell, Doha, New York.  
13 DR. POP-BUSUI: Rodica Pop-Busui,  
14 endocrinologist, University of Michigan.  
15 DR. RUSSELL: James Russell, neurologist,  
16 University of Maryland.  
17 DR. JARPE: Matt Jarpe. I'm a biochemist at  
18 Regenacy Pharmaceuticals in Boston.  
19 DR. HOKE: Ahmet Hoke, neurology at Johns  
20 Hopkins.  
21 DR. BENNETT: Dave Bennett, I'm a  
22 neurologist at the University of Oxford.

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1 DR. BRIL: Vera Bril, a neurologist from the  
2 University of Toronto.  
3 DR. BRUEHL: Dave Bruehl, psychologist and  
4 pain researcher at Vanderbilt University.  
5 DR. HERRMANN: David Herrmann, neurologist  
6 at University of Rochester in New York.  
7 DR. GEWANDTER: Jen Gewandter, University of  
8 Rochester, clinical trialist in pain.  
9 DR. KOLB: I'm Noah Kolb, a neurologist at  
10 the University of Vermont.  
11 DR. CALLAGHAN: Brian Callaghan,  
12 neurologist, University of Michigan.  
13 DR. FEDLMAN: Eva Feldman, neurologist,  
14 University of Michigan.  
15 DR. ZOCHODNE: Doug Zochodne, neurology,  
16 University of Alberta.  
17 DR. FREEMAN: And Amanda?  
18 DR. PELTIER: You already introduced me.  
19 Amanda Peltier at Vanderbilt University, neurology.  
20 DR. FREEMAN: Why don't we get going? As  
21 you see, this is a unique meeting. It's a  
22 combination of CONCEPPT, which I'll talk a little

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1 bit about, and the International Diabetic  
2 Neuropathy Consortium, which my colleague Chris  
3 Gibbons will talk about in just a second.  
4 There are some housekeeping matters, which I  
5 can let you read through quickly on your own.  
6 Restrooms, I guess, located outside to the left.  
7 The rest is somewhat self-explanatory. Checkout is  
8 12:00 noon. Feel free to refer to these at any  
9 time.  
10 What I'd like to do now is give a brief  
11 introduction, overview, and set the stage for the  
12 proceedings that will follow. This meeting is, I  
13 think, a somewhat unique one, and you'll see why in  
14 just a few moments.  
15 Now, typically at this point, I would  
16 introduce Bob Dworkin, who some of you met  
17 yesterday. He is the director of ACTTION, and he  
18 would give this talk. I'm going to talk through  
19 his slides, not do it nearly as well, nor with as  
20 much authority as he would have done, so bear that  
21 in mind.  
22 Personally, I think ACTTION has really been

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1 a remarkable achievement. You see the mission  
2 statement over there: "to identify, prioritize,  
3 sponsor, coordinate, and promote innovative  
4 activities with a special interest in optimizing  
5 clinical trials that will expedite the discovery  
6 and development of improved analgesic, anesthetic,  
7 addiction, and peripheral neuropathy treatments for  
8 the benefit of public health."  
9 The achievement of ACTTION and IMMPACT,  
10 which preceded and now is under the rubric of  
11 ACTTION, has been quite remarkable. Since the  
12 existence of ACTTION over -- I'm not quite sure how  
13 many years. Since 2010 and IMMPACT just before  
14 that, I think around 100 publications, all of which  
15 have been really important publications in major  
16 medical journals have occurred, and really it's  
17 made an enormous and I use the word impact with  
18 respect to those features that relate to  
19 neuropathic pain, pain in general, addiction,  
20 anesthesia, and many other aspects of the related  
21 disciplines.  
22 ACTTION was born initially out of a

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1 collaboration with the FDA, who felt that there  
2 were deficiencies, that there were deficits in the  
3 neuropathic pain trial. The organization has grown  
4 since that initial time, and as you see, a number  
5 of partners, FDA, Department of Defense, Department  
6 of Veterans Affairs, NIH, American Chronic Pain  
7 Association, Chronic Pain Research Alliance,  
8 professional societies, you can read the list,  
9 industry, again, read the list. And industry has  
10 provided support for meetings such as this.  
11 Now, there have been a number of activities.  
12 These are all organizations that fall under the  
13 rubric of ACTTION. IMMPACT was one of the first  
14 and, in fact, preceded ACTTION.  
15 Bob has a number of strengths, innumerable  
16 strengths, but one of his major weaknesses is this  
17 addiction to acronyms.  
18 (Laughter.)  
19 DR. FREEMAN: And they are all misspelled  
20 acronyms, and in fact, somebody once looking at  
21 this said, "What's wrong with this guy? Does he  
22 have a sticky key on his computer?"

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1 Here you see IMMPACT, and I think many of  
2 you in the audience are familiar with the role  
3 IMMPACT has played in the clinical trial  
4 methodology for pain in very spheres. You see some  
5 of the more recent publications.  
6 One the points, I think this is a good  
7 opportunity to make, is from meetings such as this  
8 there are always one or more publications. They  
9 are spearheaded by individuals who are in  
10 attendance. All of the members of the audience,  
11 all of the participants are contributors and will  
12 be authors, but only all of the members of the  
13 group. So this means nobody outside of this  
14 meeting with the possible exception on this  
15 occasion of somebody who made an attempt but could  
16 not make it because of inclement weather.  
17 These are two of the more recent  
18 publications. "Evidence Based Diagnostic Criteria  
19 for Major Acute and Chronic Pain Conditions," and  
20 this meeting was really borne out of the initiative  
21 as far as acute and chronic pain is concerned.  
22 Here, you see two of the publications from those

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1 meetings and initiatives. "Addiction, Anesthesia,  
2 Sedation in Peripheral Neuropathy," and "Peripheral  
3 Neuropathy," which I'll talk about in just a while.  
4 CONCEPPT, double P of course, is one of  
5 those initiatives, another one on sedation, and  
6 another obviously really important these days on  
7 addiction.  
8 Outcome measures are a major initiative, and  
9 this will, I think, be part of the process that we  
10 will embark on in future meetings, but more about  
11 that briefly later. Here you see, QUALITE, PAACT,  
12 development of validation of a novel patient-  
13 reported outcome measure for pain. Lots to talk  
14 about, but not now. Validation of an  
15 accelerometry-based outcome measure, and all of  
16 these are done in conjunction with the FDA.  
17 Then there is an ongoing process on the  
18 analysis of clinical trial data that has been  
19 submitted to the FDA; again, a really important and  
20 interesting initiative, no time to talk about that  
21 now.  
22 Then finally, number 6, education and

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1 dissemination, and there are number of ongoing  
2 educational initiatives focusing on pain, pain  
3 treatment, and clinical trials.  
4 I now want to move on to talk a little about  
5 CONCEPPT, which is the axonal peripheral neuropathy  
6 initiative. Now, a couple of years ago, the  
7 previous division director of the FDA, Bob  
8 Rappaport, made the observation, the obvious  
9 observation, that there is no drug approved for  
10 axonal peripheral neuropathy, despite the  
11 prevalence and thought that we should begin to  
12 address this in similar ways to the neuropathic  
13 pain, chronic pain, acute pain initiatives within  
14 the rubric of ACTTION.  
15 That was really how CONCEPPT was born. It  
16 is the Consortium for Clinical Endpoints and  
17 Procedures for Peripheral Neuropathy Trials, but  
18 much bigger than that. And I think that title just  
19 allowed the CONCEPPT acronym to emerge.  
20 So far, we've had a couple of meetings, the  
21 first of which took place in 2015, and you see one  
22 manuscript from that meeting, lead author you'll

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1 see at the back, Jennifer Gewandter, published this  
2 year, another manuscript in preparation, and Chris  
3 will be talking a little bit about that.  
4 A second meeting took place earlier this  
5 year on chemotherapy-induced peripheral neuropathy,  
6 and one manuscript from that so far and another  
7 manuscript, which is circulating among the members  
8 of that meeting.  
9 We have also a meeting planned for later  
10 this year on small fiber peripheral neuropathy, and  
11 there is a systematic review that is currently in  
12 progress.  
13 That brings us to this meeting. Now, as you  
14 see or may have noted, the initial activities, the  
15 primary initiatives were in chemotherapy-induced  
16 peripheral neuropathy and small fiber neuropathy,  
17 and these are ongoing processes.  
18 I had decided that diabetic peripheral  
19 neuropathy would be third in line for a number of  
20 reasons, which I'll begin to talk about in just a  
21 while.  
22 The background to that is really as follows:

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1 I think all of us have in our collection -- I think  
2 the last time I saw one of these slides was just a  
3 couple of weeks ago in a presentation by Rayaz  
4 Malik. We have the slide, which lists in very  
5 small print in five columns the number of failed  
6 clinical trials in diabetic peripheral neuropathy.  
7 The list has actually, unfortunately or  
8 perhaps fortunately, stopped growing just because  
9 there's so little interest now in diabetic  
10 peripheral neuropathy, and I speak not neuropathic  
11 pain in diabetic. I speak about disease  
12 modification.  
13 These failed clinical trials have been of  
14 multiple drug classes, multiple targets, and  
15 multiple mechanisms of action. I ask myself, as  
16 I'm sure you all have asked yourselves, is this  
17 because the disease is just too complicated, or is  
18 it because the drugs are just not good enough, or  
19 perhaps we need combinations of drugs? Or is it  
20 because there is something wrong with our clinical  
21 trial methodology?  
22 Is it that the architecture of our clinical trials

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1 is not adequate for the disease.  
2 Now, 1 and 2 is not in our power, perhaps  
3 with one exception, to change. We can't change the  
4 disease. We can't change the drugs. But what we  
5 can do is examine intensely the clinical trial  
6 methodology, and that is what I hope we are going  
7 to be able to do over the next year or two, and  
8 this just the start.  
9 I had put this third in line, but following  
10 the meeting of the International Diabetic  
11 Consortium at Sitges, there was such a degree of  
12 enthusiasm for looking at ways to develop the  
13 field, expand the field, grow the field, and  
14 enhance the clinical trial methodology that I  
15 thought that I would harness that enthusiasm,  
16 enthusiasm on the part of so many members of the  
17 audience, and move it up on the agenda. We were  
18 fortunately able to have this meeting very quickly  
19 after that meeting earlier this year in Sitges.  
20 There is this quote that I think is  
21 apocryphally attributed to Einstein that "insanity  
22 is repeating the same thing over and over again,

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1 making the same mistakes over and over again, and  
2 expecting different results." My view is that is  
3 where we are with clinical trials in diabetic  
4 peripheral neuropathy.  
5 On a personal note, I think I prefer the  
6 Tallulah Bankhead quote, "If I had to live my life  
7 again, I'd make the same mistakes only sooner," but  
8 I think scientifically, probably that's not  
9 appropriate. I think what we do need to do is  
10 deconstruct the diabetic peripheral neuropathy  
11 clinical trial and rebuild it from the ground up.  
12 That's really what I want to talk about a little,  
13 the deconstruction of the diabetic peripheral  
14 neuropathy clinical trial.  
15 What that means is looking at the inclusion  
16 and exclusion criteria; the assessments; the  
17 instruments; the scales; the outcome; and bring it  
18 into the modern era; looking at assay sensitivity;  
19 looking at scalings; looking at reproducibility and  
20 validity; and trying to assess the placebo  
21 response, which has become a really important issue  
22 in disease modification trials in diabetic

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1 peripheral neuropathy, as important as it is pain.  
2 But we haven't adopted the same scientific rigor  
3 with looking at the placebo response in these  
4 trials.  
5 Now, this is all work in the future. What  
6 we are going to do is start today and at this  
7 meeting at the basement, begin to look at the  
8 clinical trial and its taxonomy. What I want to  
9 talk about now briefly is taxonomy and why taxonomy  
10 matters.  
11 I understand that perhaps with the possible  
12 exception of a few neurologists, it's hard to get  
13 too excited about taxonomy, but it is absolutely  
14 critical. What the aim is, to have a widely  
15 accepted, consistently applied evidence based, and  
16 I emphasize evidence based, taxonomy using  
17 standardized, reproducible evidence based criteria.  
18 The aim is really to standardize so that  
19 when we are talking about the same disease, we are  
20 talking about the same disease, so commonality of  
21 terminology and language. What we want to do is to  
22 build a taxonomy that is suitable not just for

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1 randomized clinical trials for interventions, but  
2 also for cohort studies, case control studies, and  
3 even case reports, observational studies,  
4 interventional studies, and prevention strategies  
5 so that we have something that is evidence based;  
6 where it can't be evidence based, consensus, expert  
7 opinion, and that in the long run, the hope is that  
8 this will facilitate research, education, clinical  
9 practice, and allow, for example, meta-analyses to  
10 take place. When we are looking at different  
11 clinical trials, we understand that we are speaking  
12 about the same disease with the same criteria. The  
13 long-term goal, of course, is to develop treatments  
14 for this devastating disease.  
15 This is really prompted by the success that  
16 this endeavor has had in psychiatry and in  
17 headache, and I'll talk a little bit about those.  
18 Psychiatry, the DSM-III has transformed, possibly  
19 even revolutionized, psychiatry and has resulted in  
20 a number of evidence based treatments for  
21 psychiatry. In the same way, the classification of  
22 the International Headache Society has done that

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1 and even more.  
2 These are two different approaches to  
3 taxonomy. The DSM-III is more syndromal. It has  
4 its axes or as we are going to use over here, its  
5 dimensions, whereas the International Headache  
6 Society has a hierarchicalist approach in their  
7 classification, and I'll elaborate on that. What  
8 I'm hoping that we will do is have some merger,  
9 some fusion of both of these approaches.  
10 Why I think that we should use the  
11 dimensional approach is that I think our disease,  
12 diabetic peripheral neuropathy, is more of a  
13 mosaic, and that allows us to, for example,  
14 integrate the neurobiology, the biopsychosocial,  
15 and it allows us to encompass a precision medicine  
16 based approach where we can look at genetic  
17 factors, environmental factors, lifestyle factors  
18 within that set of dimensions.  
19 What I think of is a major taxonomic success  
20 is the headache classification, and let me talk a  
21 little bit about this. This is the International  
22 Classification of Headache Disorders, and I'm going

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1 to show you, if you'll bear with me, their approach  
2 to a couple of headaches. And I'd like as we move  
3 forward to use this as a model within our  
4 dimensions because this, as you, I'm sure, are  
5 aware, has probably revolutionized but perhaps  
6 transformed the way headaches are approached and  
7 headaches are treated.  
8 They classified primary headache, secondary  
9 headache, and painful cranial neuropathies and  
10 other facial pains. Primary headaches, migraines,  
11 tension headache, trigeminal autonomic cephalgias,  
12 and other primary headache disorders. Migraine,  
13 migraine with, migraine without aura, chronic  
14 migraine, complications from migraine and so on.  
15 Pay a little attention to this because this  
16 is the kind of approach that I think we should have  
17 when we speak about our individual diabetic  
18 peripheral neuropathies. This forms the basis of  
19 every clinical trial in headache so that they are  
20 talking about the same disease in the same way.  
21 For example, at least five attacks  
22 fulfilling criteria B to D. What are B to D?

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1 Headaches lasting 4 to 72 hours, untreated or  
2 unsuccessfully treated. Headache is two of the  
3 following characteristics: unilateral location,  
4 pulsating quality, moderate or severe pain  
5 intensity, aggravation by or causing avoidance of  
6 routine physical activity, two of those five.  
7 During headache greater than one of the following,  
8 and then not better accounted for by another IHD-3  
9 diagnosis.

10 A couple of notes, clarification notes,  
11 which I won't go through in detail, and then the  
12 last criterion for every headache disorder:  
13 consideration of the possible diagnosis. Here  
14 you'll see, we'll talk about the differential  
15 diagnosis of diabetic peripheral neuropathy.

16 Migraine with aura, typical aura, brainstem  
17 aura, hemiplegic migraine, retinal migraine, and  
18 the hierarchical structure you see, 1.2.2.1, 1.2.2,  
19 1.2.3, 1.2.4. Migraine with aura, very similar  
20 approach, but greater than one of the following  
21 fully reversible aura symptoms, 1, 2, 3, 4, 5, or  
22 6. Greater than two of the following four

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1 characteristics, and you see the four. Aura  
2 spreads gradually over to 5 minutes, each  
3 individual aura symptom last 5 to 16 minutes,  
4 greater than one aura symptom is unilateral, aura  
5 accompanied or followed in greater than 60 minutes  
6 by headache.

7 Migraine with typical aura, and here you see  
8 it. Typical aura with headache, so fulfills  
9 criteria 1.2.1, migraine with typical aura.

10 Headache with or without migraine characteristics  
11 accompanies or follows the aura, and typical aura  
12 without headache, so aura occurring without the  
13 headache. A migraine is migraine.

14 Then it brings us to our approach, and that  
15 is a model that obviously has been very successful,  
16 very successful from a clinical trial approach and  
17 very successful in terms of understanding the  
18 phenomenology of the disease and the basic science  
19 of the disease. It has been incorporated in a  
20 widespread fashion.

21 As I mentioned, I chose a dimensional  
22 approach because I wanted to in a way mirror what

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1 had been done with acute and chronic pain, but I  
2 thought it was really ideally suited for diabetic  
3 peripheral neuropathy because of this mosaic. It  
4 doesn't really fit the hierarchy that the headache  
5 classification incorporates, but within what we are  
6 looking at, I think there's a lot of room for that  
7 hierarchical approach.

8 What are the dimensions? I know I sent  
9 stuff around, and I know also when you send stuff  
10 around, nobody looks at it. So I want to go  
11 through this very briefly just to give you the  
12 overview.

13 There was this series. Somebody proposed  
14 that you never send more than three articles to  
15 read because the people you send them to then read  
16 none, and I know I sent more than three. So let me  
17 go through this.

18 (Laughter.)

19 DR. FREEMAN: First, the core diagnostic  
20 criteria, and this really is the hierarchical  
21 classification of migraine. These are the  
22 inclusion criteria, the exclusion criteria,

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1 perhaps. This is the disease. The basis for the  
2 diagnosis, the symptoms, the signs, the  
3 investigations and test results. And if applied in  
4 consistent manner, provide the standardized  
5 decisions -- "standardized" is the operative  
6 word -- for determining whether an individual fills  
7 criteria for that specific neuropathy.

8 As part of this in the manuscript, at least  
9 in the pain manuscripts, the major differential  
10 diagnoses under consideration, I actually  
11 feel -- and I want to make this point right  
12 now -- I in many ways with some exceptions mirrored  
13 what was done with acute and chronic pain. But I  
14 actually think we could restructure this, and I  
15 want you to be mindful of the possibilities that  
16 these dimensions are somewhat fluid.

17 I, for example, think the differential  
18 diagnosis is actually best positioned under two,  
19 common features. This provides additional  
20 information regarding the disorder helpful in  
21 describing the disorder.

22 These features may or may not be present in

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1 all cases, but this provides the full dimension of  
2 the picture. Variations common and uncommon not  
3 used as part of the core diagnostic criteria.  
4 Epidemiology is part of this, and life span  
5 considerations are part of this. Pediatric and  
6 geriatric issues; common medical comorbidities,  
7 very obvious.  
8 Dimension 4, and this is where I think this  
9 differs a little from what has happened in the past  
10 because here we want to begin to look at the  
11 neurobiology, the underlying mechanisms, genetic,  
12 environmental, lifestyle, other potential  
13 etiological factors, the risk factors, the  
14 protective factors, and psychosocial factors;  
15 stress, allostatic load, mood, affect, anxiety,  
16 mood, coping and so on.  
17 Then finally, Dimension 5, functional  
18 consequences, and going back, personally, I wonder  
19 whether psychosocial might be best positioned under  
20 this: functional consequences, falls, physical  
21 functioning, interference with activities of daily  
22 life.

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1 That's the structure. Bear those all in  
2 mind as people give their talks, as you sit on  
3 panels, think about how you can fill in the gaps.  
4 I want to now make some acknowledgements,  
5 first of all to Andrea, who I don't think is in the  
6 room any longer, and Jill and Valorie, who is not  
7 here, who played a major role in the logistics,  
8 organizing this, making all of this happen so  
9 smoothly. I want to thank them at the outset and  
10 thank them at the end.  
11 I also want to thank my co-director of  
12 CONCEPPT, Jennifer Gewandter, who did a lot of  
13 behind-the-scenes work for the meeting and has been  
14 and will continue to be enormously helpful.  
15 I also want to make it clear that this is  
16 not designed to replace the ADA guidances initially  
17 in the 1990s most recently that Rodica put  
18 together, which are major contributions to the  
19 field but do not address this issue specifically;  
20 does not replace the NEURODIAB consensus statement  
21 that Solomon put together so well.  
22 I would view this as in parallel and in the

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1 same way that those are not overlapping with one  
2 another, they all address diabetic peripheral  
3 neuropathy from specific and different vantage  
4 points. So will this do.  
5 I also want to say that this is iterative,  
6 that this is the foundation. As the evidence  
7 changes, this will change, and I view this as being  
8 a working document and a document that will  
9 hopefully endure with modifications as the evidence  
10 changes.  
11 I mentioned the manuscripts. Typically  
12 from -- and we can discuss this in a little bit  
13 more detail, but I want to introduce the notion  
14 now. Typically from these meetings, there is at  
15 least one manuscript. Everybody contributes.  
16 My vision for this is that there will be one  
17 primary manuscript which will address only the core  
18 diagnostic criteria and that I together with Chris  
19 and Jen will take the lead on putting that  
20 together. And then there will be multiple  
21 individual manuscripts that will be the individual  
22 talks that take place. Whether we combine them or

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1 separate them, we can discuss. I think personally,  
2 they could easily be stand-alone manuscripts.  
3 I'm hoping that all of these will go into  
4 high level journals, whether it be Annals of  
5 Neurology, Neurology, the diabetes journals, Muscle  
6 and Nerve, General Peripheral Nerve Society, all of  
7 those are options.  
8 I'm sure there's something else I wanted to  
9 say, but I do not remember.  
10 (Laughter.)  
11 DR. FREEMAN: I want to finish with this  
12 conclusion, which is taken from the cephalalgia  
13 paper on the International Classification for  
14 Headache. Every patient entered into a clinical.  
15 This was the hope, their ambition, their plan. And  
16 I'd like this to be our plan following this  
17 meeting. "Every patient entered into a research  
18 project, be it a drug trial or a study of  
19 pathophysiology or biochemistry must fulfill a set  
20 of diagnostic criteria." I would add common  
21 diagnostic criteria.  
22 I now hand over I think to, I think, Chris,

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1 who will give the International Diabetic Neuropathy  
2 Consortium perspective on this.  
3 Presentation – Christopher Gibbons  
4 DR. GIBBONS: We'll move to the next set of  
5 slides.  
6 It's already been a morning of revelations,  
7 so I discovered that the IDNC has already been  
8 taken by Troels Jensen, so we are going to have to  
9 as a society come up with a new idea for our title.  
10 But outside of that, we'll move on.  
11 In any case, put on your thinking caps. I'm  
12 going to give you an introduction today of some of  
13 the discussion we've had that's gotten us to this  
14 point, hopefully where to go forward, and what this  
15 essentially means.  
16 As you heard earlier from Roy and for most  
17 of the people in the room when we met in Spain this  
18 summer at the Peripheral Nerve Society, we had a  
19 dedicated session, and it was, I think, really  
20 impressive that, first of all, we had our first  
21 essentially session dedicated to this through the  
22 PNS, which has really been important because we

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1 haven't had a foundation or a place at the table.  
2 These were the topics that were covered.  
3 The bottom one here, the Diabetic Neuropathy  
4 Consortium, is now the time? This was what I think  
5 the main point that was raised at the meeting, and  
6 thanks to Eva for really making that happen. I  
7 think Eva put forward a great idea and got a lot of  
8 us very enthusiastic about this and started the  
9 process moving.  
10 It is now the time, and I think based on  
11 that enthusiasm and work with Roy and getting  
12 things going here, obviously we're now six months  
13 later all at a meeting here in Washington, DC, and  
14 I think it's a really remarkable time frame to  
15 think about how much has actually happened so  
16 quickly. This is fantastic, and really want to  
17 thank Eva for getting the ball rolling on this.  
18 Conceptually, where are we going to stand?  
19 The Peripheral Nerve Society, again an umbrella  
20 organization, and it exists already with two other  
21 consortiums, the Inflammatory Neuropathy Consortium  
22 and then the CMT and related neuropathies. I

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1 really see that this potential has -- again, we  
2 will fit as the third major consortium as part of  
3 the Peripheral Nerve Society.  
4 I think there's an enormous potential here,  
5 but there are a couple of steps we need to take in  
6 order to actually make this a reality. That's a  
7 little bit what I wanted to introduce today, which  
8 will be followed up by this afternoon, but these  
9 are the steps that are required.  
10 So in discussion with the Peripheral Nerve  
11 Society, there are a couple of details they would  
12 like us as a group to address. First of all, they  
13 would like us to have a constitution, including  
14 things like missions, aims, goals.  
15 Get some board members. We need to have  
16 chairs, vice chairs, ultimately past chairs, but  
17 secretary, treasurers, the executive committee, and  
18 then board members. So these are things that we  
19 need to have in place before the Peripheral Nerve  
20 Society will recognize us as an independent group  
21 within their purview.  
22 I drafted a couple of things which I want to

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1 introduce, and for those of us you interested,  
2 we'll discuss this in more detail later. But  
3 here's a draft of a mission statement that I hoped  
4 we could work on during this meeting to actually  
5 get us really step forward to nearly completing all  
6 the tasks assigned to us in preparation for the  
7 next upcoming Peripheral Nerve Society meeting.  
8 As a draft concept, the mission is to  
9 improve the life of patients of diabetic  
10 neuropathies by promoting clinical and basic  
11 science research, educating clinicians, basic  
12 scientists, and other health professionals with the  
13 goal of improving clinical care. It's really going  
14 to be focusing on three areas, and this will be  
15 research, education, and clinical care.  
16 These are going to be the sub-goals, and we  
17 kind of go through these targets, I think these are  
18 broad and some of this is important to be fairly  
19 broad and encompassing, again, not knowing how long  
20 and how far off in the future this will really be  
21 targeted.  
22 The research is going to be both promoting

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1 both clinical and basic science with a goal of  
2 understanding that both the pathophysiology of the  
3 diabetic peripheral neuropathies at a mechanistic  
4 level and advancing human subjects research with an  
5 aim to prevent or reverse the complications of  
6 neuropathy in the setting of diabetes.  
7 Education will be again training both the  
8 basic scientists, the clinicians, and other health  
9 professionals in the related neuropathies. Again,  
10 we're not talking about diabetic peripheral  
11 neuropathy. It's really the neuropathies. And  
12 then really to provide a continuing discussion and  
13 education between these groups so that we can  
14 facilitate progress.  
15 So basic science and clinical researchers in  
16 isolation, we're not going to make a lot of  
17 progress. We really need to integrate this  
18 information, so as much as we can, provide a bridge  
19 between these groups.  
20 Then finally, care, to promote standards of  
21 care and quality of care internationally,  
22 developing guidelines, outcome measures. Again,

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1 we've heard a lot about the taxonomy of this  
2 process and how it will really form a foundation.  
3 Again, this is not really meant to supplement or  
4 alter existing guidelines but really to build on  
5 the knowledge that we have so that we can continue  
6 to move forward.  
7 Conceptually from a board membership  
8 standpoint, this is all idea generation stage. I  
9 imagine six board members, four executive board  
10 members, and these would be the rough outline. We  
11 could certainly alter that number based on people's  
12 input here, but this would be a concept to start  
13 with.  
14 This is going to move us to this afternoon's  
15 discussion. The interest group, for anyone who's  
16 interested and hopefully if not all, almost all of  
17 you will be in this group today from 4:30 to 5:30.  
18 I really want everybody to participate. We're  
19 hoping to generate a lot of information and ideas  
20 on this. Certainly consider yourself for board  
21 membership, if you're interested, enthusiastic, we  
22 want you, and self-nomination is encouraged.

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1 One of the key tasks I'd like to really  
2 address this afternoon is that we've been able to  
3 secure two afternoon sessions at the Peripheral  
4 Nerve Society meeting, and I want to really  
5 establish an outstanding series of lectures based  
6 on what we can generate from an idea and outline  
7 this to the board, so the Peripheral Nerve Society  
8 will really see that we're successful, we're  
9 serious about this, and that we can really make  
10 some progress very rapidly. So I'd like just to  
11 have that as one of our major discussion points  
12 this afternoon.  
13 These are all points to think about between  
14 now and this afternoon. We'll continue to discuss  
15 throughout the meeting, but please, feel free to  
16 generate ideas, approach me offline, online. We'll  
17 have lots of discussion, but this is really again  
18 the foundation of hopefully what will be a very  
19 successful consortium.  
20 That's essentially all I want -- Doug, did  
21 you have a question?  
22 DR. ZOCHODNE: I didn't know if you wanted

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1 us to interrupt you at all.  
2 DR. GIBBONS: Please, feel free.  
3 DR. ZOCHODNE: Two or three slides back when  
4 you had the aims, we've been their advocacy. Other  
5 than Lyrica research, still really under the radar  
6 with the public, I wonder if that shouldn't be a  
7 goal.  
8 DR. GIBBONS: Yes, I think raising awareness  
9 of this would be critical. We're certainly a  
10 massively underrepresented physician group of  
11 interests. Considering the magnitude of the  
12 disease and the numbers that we're dealing with,  
13 the interest in this by physicians is woefully  
14 underrepresented, and in part, it relates to  
15 advocacy and recognition more broadly.  
16 So I think that's an outstanding idea, and  
17 we'll have potential time for reiteration and  
18 modification this afternoon of these statements.  
19 So keep these ideas coming, so this will hopefully  
20 be something else.  
21 Vera?  
22 DR. BRIL: To follow up, I would say

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1 peripheral neuropathy in general is very poorly  
2 recognized and that the PNS has really not moved  
3 forward recognition of this disorder in the public  
4 the way MS is recognized or Parkinson's or  
5 Alzheimer's.  
6       So it's not just this subgroup, but the  
7 entire organization should be much more dedicated  
8 to raising public awareness, so you don't have to  
9 explain what the disease is every single time you  
10 have a patient with it.  
11       DR. PELTIER: I think that goes back to not  
12 having a real dedicated patient advocacy group. So  
13 a lot of the major diseases that have done a lot of  
14 work as far as getting research funding and pushing  
15 through Congress like attention have had a lot of  
16 patient groups. We've not done a very good job of  
17 organizing our patients, either, and getting them  
18 to or inspiring them to work with us, either.  
19       DR. GIBBONS: So that was my final slide.  
20 This was just a taste of what's to come, so again,  
21 we'll have further discussion this afternoon and  
22 hopefully really get some juicy details organized.

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1 Thank you.  
2       DR. FREEMAN: The next speaker is Stephen  
3 Bruehl, who many of you may not know. He's a  
4 professor of anesthesiology at Vanderbilt  
5 University. His scientific work is multivariate,  
6 but I think if there's one encompassing aspect to  
7 it, it's the psychophysiological aspects of pain.  
8       With respect to this meeting itself, he was  
9 one of those -- he was the spearhead, I think,  
10 behind the Budapest classification of complex  
11 regional pain syndrome, sometimes called, in fact,  
12 the Bruehl criteria. He's going to talk to us  
13 about the development of a taxonomy for a  
14 condition, and he does this in a very beautiful and  
15 stimulating way.  
16       Stephen.  
17       Presentation -- Stephen Bruehl  
18       DR. BRUEHL: No pressure to make taxonomy  
19 beautiful and stimulating.  
20       (Laughter.)  
21       DR. BRUEHL: I do apologize in advance. It  
22 is difficult to make this very exciting, but I will

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1 do my best. I think that the reason I'm here is  
2 because I was brought into the parallel development  
3 of chronic pain diagnostic criteria in a systematic  
4 way that is an effort ongoing still, and also more  
5 recently, trying to do the same thing for acute  
6 pain conditions.  
7       The idea is that we would end up with a  
8 consistent taxonomy for each of these general  
9 classes of conditions where within each of those,  
10 every individual condition is worded in the same  
11 style, the same kind of format, the same  
12 dimensions. The idea is make some consistency.  
13 The whole point of taxonomy is to make order out of  
14 chaos. That's what our task is here today.  
15       Diagnostic criteria should help you lead to  
16 a dichotomous diagnostic decision. That's the  
17 whole point, and you will notice something -- or  
18 after I point it out, you'll notice something  
19 subtle about this.  
20       So implied in this is when you create  
21 diagnostic criteria, you are defining the  
22 condition. In everything you do in trying to come

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1 up with a taxonomy, remember 20 years from now,  
2 what you come up with is going to be the de facto  
3 definition of what that disorder is. This is why  
4 my suggestion is you put some thought into this and  
5 come up with a systematic way to make sure you're  
6 doing it right.  
7       The idea is that if you've got a set of  
8 disorders that are potentially confusable and  
9 they're overlapping criteria, but you indeed  
10 believe they are different things, you want to have  
11 diagnostic criteria that will force you to pick one  
12 of those so that one person cannot have two similar  
13 disorders.  
14       It is very important that you use the right  
15 wording in these because otherwise, you'll get a  
16 person -- take an example person, if you can take  
17 those diagnostic criteria and apply three different  
18 diagnoses to the same individual within the same  
19 class of disorders, that is not a very useful  
20 taxonomy. So they do need to be mutually  
21 exclusive.  
22       The whole point of putting effort into the

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1 wording of the actual criteria is that when you  
2 take a person who's not familiar with them and you  
3 hand them a sheet of paper that says here's the  
4 diagnostic criteria, go see your patient, and I  
5 want you to try to make a diagnosis using these  
6 criteria, you want to make sure if you give that to  
7 10 different people, that they will all come up  
8 with a similar diagnosis. That really is  
9 contingent on how well you have created the wording  
10 and the decision rules implied in there.  
11 I will say that one thing that I found  
12 surprising when I worked on the AAPT criteria, this  
13 is the chronic pain effort, I assumed that  
14 everybody in the room was thinking about things the  
15 same way that I was. I was trained as a clinical  
16 psychologist, and from literally the first year in  
17 graduate school, we started learning how to apply  
18 diagnostic criteria in the DSM for psychiatric  
19 disorders. Back then, it was DSM-I think III-R,  
20 but it's still the same thing.  
21 I assumed everybody thought about diagnosis  
22 this way. What I discovered in talking with a lot

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1 of the physicians -- and this is across a wide  
2 range of conditions and specialties -- a lot of  
3 them had no clue about this. They had never really  
4 thought about it before. They didn't  
5 systematically apply criteria.  
6 This parallels what Roy showed in his talk,  
7 and this is for major depressive disorder. But  
8 just as an example, think about this like a Chinese  
9 menu. You get two from here, you get three from  
10 here, and that's how you come up with the  
11 diagnosis.  
12 So in the DSM-V, you have to have five or  
13 more of the following symptoms during the same two-  
14 week period, and it has to be a change from  
15 previous functioning. At least one of them has to  
16 be depressed mood or loss of interest. Then you go  
17 through, and you've got a list of nine very  
18 specific symptoms that are each worded in a very  
19 concrete way to where it minimizes the amount of  
20 judgment required to decide whether the person  
21 meets it.  
22 Some of these, I've done a better job than

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1 others, but significant weight loss when not  
2 dieting or weight gain, that's fairly objective.  
3 The person could report that, or you could observe  
4 it.  
5 In DSM-V, one thing they add is symptoms  
6 cause clinically significant distress or  
7 impairment, and the episode is not attributable to  
8 physiological effects of a substance or another  
9 medical condition.  
10 You'll see headache and in DSM-V and in most  
11 of the conditions, I think, in the AAPT chronic  
12 pain criteria, that last thing is always like you  
13 don't get this diagnosis if something else better  
14 accounts for the symptoms. That probably is  
15 something you would want to do as well. I just  
16 throw that out there to think about.  
17 Just to show you that this kind of effort  
18 like you're embarking on here will produce  
19 something tangible, this is an example of one of  
20 the papers that came out which proposed diagnostic  
21 criteria for chronic central neuropathic pain  
22 associated with spinal cord injury.

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1 I have to say when I came out of that first  
2 AAPT meeting, I had serious doubts that it was ever  
3 going to produce anything at all because it seemed  
4 like too much work, people weren't being paid to do  
5 this, nobody was talking responsibility. It seemed  
6 like nothing could happen, but surprise, surprise,  
7 it has actually produced a whole set of criteria,  
8 some are still in the works, but this is one of  
9 them.  
10 You can see they've got very specific  
11 criteria including things like pain duration of at  
12 least three months. The pain has to be in the area  
13 affected by the SCI. It's got sensory changes in  
14 the same neuroanatomically plausible distribution  
15 indicated by the presence of at least one positive  
16 or one negative sign.  
17 Those are very concrete and easy to follow  
18 for any clinician, and if you're doing a clinical  
19 trial and you want inclusion criteria, that's the  
20 kind of thing you want where it's easy to follow  
21 that. No other diagnosis better explains the pain.  
22 If you were trying to come up with

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1 diagnostic criteria, you really have to let the  
2 wording of those criteria be driven by two issues.  
3 One is validity, one is reliability, and I want to  
4 talk a little bit about what I mean by both of  
5 those and in practice what that actually plays out  
6 as, how do you make sure the criteria are reliable  
7 or valid?  
8 I'm going to use the example of complex  
9 regional pain syndrome to do this because that is  
10 what my first experience with this was, was there a  
11 mass diagnostic criteria that everybody could meet  
12 that had an unexplained pain and they weren't  
13 specific enough. We embarked on an effort to  
14 systematically and empirically change those  
15 criteria to improve them and make it a little more  
16 narrow and harder to get the diagnosis.  
17 Reliability and validity are both related.  
18 You have to have reliability, but simply making  
19 them reliable doesn't mean that they're valid. You  
20 could have criteria that everybody agrees on that  
21 are totally meaningless. So you really have to get  
22 both of these.

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1 The types of reliability, one is inter-rater  
2 reliability, and this is the idea that if you take  
3 two different clinicians who see the same patient,  
4 you would hope that they would agree on the  
5 presence or absence of the conditions. This can  
6 apply to both the individual components like the  
7 individual symptom items that are in the criteria,  
8 and it can also apply to the full diagnosis that  
9 you get when you apply the full set of criteria.  
10 There's also test-retest reliability, and  
11 these are those criteria stable over time? So  
12 sometimes we call it intra-rater reliability if we  
13 have the same clinician see a patient over time and  
14 try to apply them and see do they meet the criteria  
15 each time. More frequently, we're talking about  
16 are these across multiple clinicians getting  
17 consistent diagnoses over time. Both of these are  
18 equally important.  
19 If we're looking at the reliability of these  
20 individual bullet points within the criteria, so  
21 criterion 1, criterion 2, we want to figure out are  
22 they operationalized well. As an example from the

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1 old 1994 IASP criteria for CRPS, it said -- the  
2 wording was literally, "Evidence of changes in skin  
3 blood flow."  
4 That sounds good when you first put it on  
5 paper, but when you talk about how somebody's going  
6 to apply that in practice, what does that mean?  
7 Does that mean I need to do thermography, Doppler  
8 measurements of blood flow? Is simply sticking my  
9 hand on there and saying yes, it feels cool, and  
10 that implies blood flow changes. There are a lot  
11 of ways to interpret that, and you don't want to  
12 have things in there that are too generic that  
13 can't be applied consistently.  
14 A hypothetical example -- and this came up  
15 during the development of the AAPT criteria -- was  
16 if you say progressive distal sensory  
17 abnormalities. Well, what do you mean by that?  
18 You probably know what you mean, but you want to  
19 put that on paper if you have a specific idea there  
20 because does positive or negative apply? Does it  
21 have to be positive? You want to say things like  
22 that that are going to alter the outcome.

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1 We've got these bullet points. Here are the  
2 criteria. There's also an implied or not -- it's  
3 not even implied. It's an explicit decision rule  
4 for combining those. Let's say you've got five  
5 criteria. Do you have to meet all five of those?  
6 If you've got five criteria, maybe having three of  
7 those or three or more is really what you're  
8 talking about.  
9 That is a decision rule. It's what the  
10 person is going to use. They tick through the  
11 list. See the person has these things. How do I  
12 combine that to make a decision as to whether the  
13 person has the diagnosis?  
14 The wording of the decision rule can make a  
15 difference. So something that's really  
16 straightforward is you've got five things and you  
17 have to have three or more. Anybody can follow  
18 that. That's very easy. But if you look around at  
19 some of the criteria that have been developed, you  
20 will see very complicated decision rules like that  
21 you've got them broken out in the A, B, and C, and  
22 you have to have 2 of 5 symptoms for criterion B

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1 but you only have to meet criterion C if you've got  
2 less than four on this other one.  
3 You start getting into things like that,  
4 it's hard to follow that. If somebody is busy and  
5 not paying attention, that could easily lead to a  
6 diagnostic error.  
7 We talked about test-retest reliability.  
8 This is stability over time. Now, obviously, this  
9 makes no sense if it's a condition that you would  
10 expect to vary a lot from day to day, and there are  
11 conditions like that where the symptoms -- CRPS is  
12 even one of those where you can actually have  
13 changes in things on a fairly short-term basis.  
14 But let's assume that we have a condition that  
15 should be pretty stable because the underlying  
16 pathophysiology is stable. That makes it really  
17 easy, and you do want to see stability over time,  
18 especially shorter periods of time.  
19 So if you have a set of criteria you've  
20 developed and you have, let's say, two different  
21 clinicians diagnose that patient and then a month  
22 later apply the same criteria, they should come up

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1 with exactly the same diagnosis between them and  
2 across time periods if you've got good criteria  
3 because things should not have changed in a month  
4 unless you've implemented some new super effective  
5 treatment.  
6 How do you know if criteria are reliable?  
7 Well, you can focus on, again, the individual  
8 components of the criteria or the overall  
9 diagnostic decisions. And if you want a very cheap  
10 way to initially look at the wording of criteria,  
11 you can do what's called a vignette study. You  
12 have a hypothetical patient description, and you  
13 include in there things that would give you  
14 information about whether they meet the criteria.  
15 You throw in some red herrings, things that are  
16 irrelevant. And then you identify 100 clinicians,  
17 and then you mail it out to them or email it out to  
18 them, and you just say take a look at this, we're  
19 interested in whether you can take these criteria  
20 we're going to give you here and apply them to the  
21 patient described in this scenario and tell us does  
22 the patient have this diagnosis.

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1 If you can get in this kind of system, a lot  
2 of people coming back with the same diagnosis, you  
3 know you've probably done a decent job of coming up  
4 with the wording for those criteria. It doesn't  
5 say that it's going to work in practice, but at  
6 least gives you an initial hint about the  
7 reliability of the criteria.  
8 Now, if you send this to 100 people and you  
9 get half the people saying they do meet the  
10 criteria and half saying they don't, clearly, you  
11 have to go back to the drawing board because  
12 there's something not right about the wording of  
13 the criteria that's making it hard to apply.  
14 You can do field trials, also. This is  
15 something that DSM has always done is you actually  
16 have clinicians that are participating in multisite  
17 research projects where they're doing diagnosis of  
18 patients and then looking at some of these  
19 reliability issues in a real-world setting.  
20 Statistically to bore you even further,  
21 there are ways to numerically capture whether you  
22 are doing a good job in getting reliable criteria.

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1 So kappa is a common one, and this is used for like  
2 dichotomous diagnoses. This is to say if you've  
3 got two raters, are they agreeing more than chance,  
4 and that's how kappa differs from a correlation  
5 coefficient.  
6 Correlation coefficients you see in the  
7 literature in this context. They're wrong because  
8 they don't factor in whether you are going to have  
9 chance agreement. So kappa is correcting for  
10 chance. That's what you'd want to use.  
11 There's another option called an intra-class  
12 correlation coefficient, and this is a little more  
13 flexible. You can look at ordinal variables,  
14 interval variables like a scale from zero to 10.  
15 You can also look at ratio variables.  
16 Both of these are in the same zero to 1  
17 scaling just like you see with the traditional  
18 correlation coefficient. In the literature,  
19 there's a number 0.60 that is pretty much accepted  
20 as this is adequately reliable. So if you do your  
21 criteria and you do a vignette study or a field  
22 study and you look at agreement and you calculate

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1 kappa or intra-class correlation, if you're below  
2 0.60, it probably means you need to go back and  
3 revise that before you start getting that out to  
4 the literature and say you should be using this.  
5 Do the criteria reflect what they are  
6 supposed to reflect? That is a very fundamental  
7 question, and that is validity. If a patient gets  
8 a diagnosis, does it really mean that they have  
9 this condition? It's a straightforward question,  
10 brings up a difficult issue, which is surprisingly  
11 difficult. What is X syndrome? What is peripheral  
12 neuropathy?  
13 Give me an example of any diagnosis you can  
14 think of in this area, and you'll have to answer  
15 this question. What is it? Then you have to think  
16 about who's defined that, where did you learn that,  
17 is this something you've gotten from clinical  
18 experience, was this the way you were trained and  
19 somebody else told you this? Is this based on  
20 research in the literature? How do you assess it  
21 if you want to do that?  
22 There are many people who say, well, I can't

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1 really put it into words, but I know it when I see  
2 it. That's great, but if you can't put it into  
3 words, you're not going to be able to come up with  
4 criteria to diagnose it.  
5 The question is you may think that this set  
6 of things defines the diagnosis, but would  
7 everybody in this room agree on that? Do each of  
8 you have your own variants and things you may more  
9 or less attention to? So those are the things you  
10 want to think about with the question of validity.  
11 For pain, it was a little different because  
12 these are all pain disorders. Pain is subjective.  
13 You can't go do a test that will tell you whether  
14 somebody is having pain and how intense that pain  
15 is, not really.  
16 Definitive pathophysiology, in most cases,  
17 we don't really know. We know things that  
18 contribute, but we don't know the full picture.  
19 Because of those, that meant there was no real gold  
20 standard to use to say these paper and pencil  
21 criteria we've got here are an indicator of this  
22 underlying mechanism, so we know they're good.

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1 We didn't have that luxury. Now, I don't  
2 know in the case you're talking about, you can do  
3 peripheral nerve testing and biopsies and maybe see  
4 things that you would consider more of a gold  
5 standard, and if that's the case, your job is much  
6 easier.  
7 You want to be able to have clinical  
8 criteria that don't require that elaborate testing,  
9 hopefully, that can do a good job of approximating  
10 that gold standard mechanism you can assess. That  
11 would probably be the task for you guys in  
12 determining the validity of the criteria.  
13 There's also the issue of fuzzy boundaries,  
14 that you have a set of mechanisms that may be all  
15 in combination, you've got a set of clinical  
16 features, and where is the dividing line between  
17 conditions within that? Is it a continuum, and  
18 you'd say people down here, this is a different  
19 disorder than this group? Or are there particular  
20 features that would define a subgroup that's  
21 distinct?  
22 There's no clear answer to how to make those

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1 decisions, but there are some ways to statistically  
2 test those and determine whether you're right when  
3 you come up with a guess. It's an iterative  
4 process of guessing and then looking at the data to  
5 see whether they support it, and if not, you modify  
6 it and then do the same thing again.  
7 Construct validity is what we talk about.  
8 This is like are we measuring what we really think  
9 we're measuring. In pain, these are indirectly  
10 measurable, so we have a lot of problems, and all  
11 we're able to show statistically is relative  
12 validity because we can't really assess a gold  
13 standard. This is like the worst case scenario for  
14 what you might be trying to do, but I'm going to go  
15 ahead and walk through a little bit here.  
16 Content validity simply means would a person  
17 who's an expert in the area and would a patient  
18 look at your criteria and say yes, this pretty much  
19 captures what I think are the most important  
20 aspects of this disorder. Internal validity, the  
21 way I use it, I'm talking about if you've got  
22 criteria that have subgroups under it of signs and

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1 symptoms, do those hang together in a way that  
2 matches the way they actually exist in the real  
3 world?  
4       Concurrent validity is looking at your  
5 criteria relative to some gold standard, maybe a  
6 test of some kind. Convergent validity, I love the  
7 term "nomological net." I learned that in graduate  
8 school. It's basically saying if you have  
9 something that is inherently unmeasurable, you have  
10 all these other things around it that are related  
11 that should be related in certain directions. You  
12 want to make sure all of those interrelationships  
13 fit the construct that you're interested in.  
14       Then you've got discriminate validity, and  
15 this is can we use these criteria to distinguish  
16 between groups that we think are distinct.  
17       What gold standard do we use? So in the  
18 context of pain, we may have a current consensus  
19 based standard. So this would be something that a  
20 roomful of people like you would come up with, and  
21 at the end of the meeting, you say this is what we  
22 think the criteria should be. Now, that could be a

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1 gold standard.  
2       It could be -- and this is based on actual  
3 literature -- usual method of diagnosis. This was  
4 used to develop the fibromyalgia criteria in 1990.  
5 DSM has used expert clinician diagnosis.  
6       You also have and something that's a little  
7 bit easier, previously published diagnostic  
8 criteria that you can use as a reference point.  
9 That's talking about really relative validity or  
10 what we have coming up with better than the  
11 existing criteria.  
12       Empirical validation, how do we actually  
13 test validity? It's nice that there are these  
14 statistical techniques that if you can get a large  
15 enough data set of patients and get systematically  
16 collected data on test results, signs, and  
17 symptoms, you can apply these techniques and  
18 actually get some good and meaningful information  
19 to help guide you in developing diagnostic  
20 criteria.  
21       These would be things like principal  
22 component analysis, cluster analysis, got other

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1 options, but they're all basically doing the same  
2 thing. It's saying I'm going to give this data set  
3 to the computer and say tell me how many different  
4 subtypes of patients are in this group of patients,  
5 and it will come up with subgroups of patients.  
6 And then you can look at the profile of signs and  
7 symptoms associated with each of those empirically  
8 defined patient groups to say do I recognize any of  
9 these.  
10       You go yes, this one right here clearly  
11 looks like X condition, and this one, the pattern  
12 of signs and symptoms clearly looks like this other  
13 condition. And if you've done that, you've done  
14 something really nice, which is you had kept your  
15 judgment out of this initially and let the computer  
16 based on the actual data identify the subgroups.  
17 Now, that's kind of the ideal situation if you were  
18 to try to figure out how many different conditions  
19 you should parse your data set into. And I'll show  
20 you some examples of these in a moment here.  
21       So you want to identify groups of  
22 statistically similar patients that are based in

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1 the patterns of clinical features. So what you're  
2 doing is essentially defining empirically what the  
3 prototypic presentation of a condition is.  
4       You also may want to identify at a lower  
5 level here, groups of signs and symptoms that may  
6 cluster together within a patient population. So  
7 if you remember those diagnostic criteria for the  
8 DSM-V or the ones that Roy showed for headache, you  
9 might want to decide are those specific signs and  
10 symptoms grouped together in a way that actually  
11 reflects the real world.  
12       You also may want to show whether two  
13 conditions are distinct. Now, migraine versus  
14 tension type headache, I did this right after  
15 graduate school, but we happened to have a data set  
16 of really careful diagnoses of patients that met  
17 the IHS criteria at the time for migraine headache  
18 and tension-type headache, and we asked a simple  
19 question: Are these two different disorders, or  
20 are they basically the same thing? Are they really  
21 distinct?  
22       We took the diagnostic information, and we

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1 did a cluster analysis. The computer said there  
2 are two different groups of patients in here, and  
3 we said well, show us what they look like. It gave  
4 the clinical features for each of the two groups  
5 the computer came up with, and that matched up with  
6 the IHS diagnoses.

7 It turns out it matched up quite well. The  
8 computer identified migraine headache and tension-  
9 type headache, and that supported the idea that  
10 they were really two different conditions that even  
11 a computer who doesn't know anything could  
12 distinguish. So that's the kind of thing you can  
13 do with this approach as well.

14 We frequently will ask, do proposed criteria  
15 have concurrent validity relative to whatever our  
16 current reference standard is, whether it's a test  
17 or some existing set of criteria. If we're  
18 revising criteria, do they improve on existing  
19 criteria in terms of being able to discriminate  
20 between known groups of patients?

21 If we're going to do this, we have to start  
22 looking at how you would be able to justify saying

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1 these criteria are valid. You would look at  
2 sensitivity and specificity, so that's true  
3 positive and true negative rate.

4 Probably more important conceptually is  
5 positive predictor power and negative predictive  
6 power, and that is how probable is it that a  
7 positive or negative diagnosis you make is  
8 accurate? That's your diagnostic accuracy. The  
9 problem with that particular statistic is that you  
10 have to know the base rate in the population to  
11 calculate it. Most of the time we don't know that.  
12 So another alternative is positive and negative  
13 likelihood ratio. So there's a statistic. You can  
14 get a number that will tell you how accurate you're  
15 likely to be if you apply the criteria in the real  
16 world.

17 We've got a diagnostic threshold that we  
18 have to set. So if you've got five criteria, how  
19 many of those do you have to meet to get the  
20 diagnosis? This will affect both sensitivity and  
21 specificity, and it affects them on opposite  
22 directions.

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1 So if you reduce the threshold, so instead  
2 of three, you say you only need two of these, what  
3 you're going to get is an increase in sensitivity.  
4 You're going to capture more people, but  
5 specificity is going to go down. You're going to  
6 over diagnose.

7 These are going to move proportionally, and  
8 your goal is to find the threshold for diagnosis  
9 that optimizes the balance between those two. You  
10 do this by using a receiver operating  
11 characteristics curve. This is plotting  
12 sensitivity versus -- it's actually one minus  
13 specificity, I think. But you do this, and you'll  
14 see this nice line. And you can see by the shape  
15 of the line where you get the optimal balance of  
16 sensitivity and specificity.

17 That's the theoretical basis for doing this.  
18 Now I want to walk through what we actually did  
19 with CRPS just as an example to show you an  
20 approach you might use.

21 In 1994, there was a room full of people in  
22 Orlando, Florida. These are all clinicians and

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1 research experts in complex regional pain syndrome.  
2 You may know it as reflex sympathetic dystrophy.  
3 But they all got in this room, and they as a group  
4 came up with a set of diagnostic criteria that they  
5 ended up getting reified by putting it into the  
6 International Association for the Study of Pain  
7 Taxonomy.

8 They defined it, published it. In theory,  
9 people were supposed to use this. It didn't get  
10 used, and you'll see why, basically because  
11 everybody could get the diagnosis or it was way too  
12 easy.

13 You had to have an initiating noxious event  
14 or cause of immobilization, right, but then if you  
15 read the fine print, it said you don't have to have  
16 this. Now, what use is it to include something  
17 like this in diagnostic criteria? It makes no  
18 sense to me.

19 Number 2, continuing pain, allodynia, or  
20 hyperalgesia that's disproportionate to the  
21 inciting event. Probably no way around the  
22 judgment involved in disproportionate, but it could

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1 be that you could have no allodynia or hyperalgesia  
2 and have only pain and still potentially meet this  
3 criterion.  
4       Number 3, evidence at some time for edema,  
5 changes in skin blood flow, or abnormal sudomotor  
6 activity in the region of pain. Then you've got  
7 number 4, the exclusion criteria, if something else  
8 can explain the symptoms, you don't get the  
9 diagnosis. So just made the points I did.  
10       Do the criteria adequately capture the core  
11 defining signs and symptoms of CRPS? This is a  
12 little more of the judgment call, but that's one  
13 issue we wanted to address.  
14       Is the structure of the criteria optimal?  
15 So the 1, 2, 3, and 4, does that make sense what's  
16 included in each of those to break it down the way  
17 they're broken it down? Is the decision rule, you  
18 had to have all four of these, does that make  
19 sense?  
20       Then this is going to determine our  
21 sensitivity and specificity. So sensitivity is how  
22 well do we identify CRPS positive cases.

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1 Specificity is if a person doesn't have CRPS, do we  
2 weed them out appropriately?  
3       If we're going to look at the first issue of  
4 content validity, we had to go back to the  
5 literature. So you read the literature, there was  
6 this condition called reflex sympathetic dystrophy,  
7 algodystrophy, neurovascular dystrophy, a variety  
8 of names, but people were all talking about the  
9 same thing.  
10       If you looked at the set of symptoms and  
11 signs that had been described in the literature to  
12 be associated with the condition, those criteria I  
13 just showed you did reflect four of those:  
14 allodynia, hyperalgesia, skin temperature and  
15 color, sweating changes, the sudomotor, and then  
16 you've got edema.  
17       However, in the literature, you also very  
18 frequently saw trophic changes to hair, nail, and  
19 skin; tremors; dystonia; range of motion  
20 impairments; hemi-body hypoesthesia; you go on and  
21 on, a bunch of these things that were pretty odd  
22 features that were reported frequently that are

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1 totally ignored in the diagnostic criteria.  
2       We decided to empirically look at some of  
3 these questions, and this is a really simple way to  
4 do it is we created a standardized form with  
5 instructions that go along with this for assessing  
6 all the clinical signs and symptoms that we felt  
7 the literature described were associated with the  
8 condition.  
9       For the symptoms, this was self-report by  
10 the patient, and we also had objective signs seen  
11 by the examiner when they actually saw the patient.  
12 Then there were definitions for how you assessed  
13 each of these particular issues that were designed  
14 to be clinically useable, so it didn't require  
15 elaborate testing.  
16       We had this form, and we did a multisite  
17 study. Ended up being international, so we had  
18 about 10 sites in the end who participated in this.  
19 Everybody used the same form, and what we were able  
20 to address was -- we ended up with about 123  
21 patients. It took a year and a half, two years to  
22 get the data, but we ended up with 123 that met

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1 those diagnostic criteria I showed you. They all  
2 had the same evaluation.  
3       The questions we asked was does it make  
4 sense to include objective signs and subjective  
5 symptoms in the same criteria. The criteria I  
6 showed you, you could meet it solely based on the  
7 patient telling you something. You didn't have to  
8 see anything at all in the clinic. And the  
9 question we asked was, is that appropriate, or do  
10 we need to require that people see objective signs  
11 as well?  
12       What we ended up seeing -- and this is just  
13 looking at the frequencies -- is for those features  
14 that were both assessed in the clinic and the  
15 patient reported, if you look at the pattern of  
16 signs and symptoms, what you will see is that the  
17 features that were more common like color changes  
18 were common in both the symptoms and the signs.  
19       Now, the numbers differ because the numbers  
20 are always higher for symptoms because the patient  
21 is going to have more opportunity to see it than  
22 you will in the clinic. But roughly, the

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1 proportions vary in a similar pattern across signs  
2 and symptoms. So the things that are very uncommon  
3 like fingernail changes are uncommon in both of  
4 those categories.  
5       What this told us was that they're both  
6 probably providing meaningful information, but that  
7 maybe we should be assessing both and not just  
8 symptoms alone because clearly, you don't get  
9 exactly the same number in both cases.  
10       Internal validity of the groupings of signs  
11 and symptoms supported by the data; this is the  
12 critical one, number 3, evidence at some time,  
13 meaning not even in the clinic, just by patient  
14 report, for edema; changes in skin blood flow, how  
15 defined, I don't know; or abnormal sudomotor  
16 activity in the region of pain. Any one of those  
17 three could meet this criterion. Maybe this is too  
18 low a threshold.  
19       What we did is something called principal  
20 components analysis to look at the  
21 interrelationships between the signs and symptoms  
22 in that large data set that we got. And what we

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1 found was that they tended to cluster into  
2 subgroups of symptoms that were relatively  
3 distinct. So we had what we called a sensory group  
4 that was hyperalgesia and allodynia. Vasomotor  
5 group, this is the skin temperature and color  
6 changes tended to group together.  
7       Oddly enough, the sweating and the edema  
8 grouped into the same cluster, we weren't exactly  
9 sure why that was, and then motor and trophic  
10 changes like range of motion, strength, tremor,  
11 dystonia, that all kind of clustered into the same  
12 thing.  
13       You'll notice the motor and trophic factors  
14 are not reflected anywhere in those diagnostic  
15 criteria that the consensus group came up with.  
16 And then you've got overlap here for vasomotor and  
17 sudomotor. The computer says they're different  
18 things. The consensus criteria lump them together.  
19       What we concluded from this was that the  
20 IASP criteria are really not internally valid and  
21 that probably is not justified to combine  
22 vasomotor, sudomotor, and edema all into one

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1 criterion because this could lead to poor  
2 specificity or over-diagnosis, which was the  
3 clinical problem we were having. It suggested a  
4 revision.  
5       So how do we revise this? What do we do  
6 with this information? So we ended up with a  
7 sample of 117 patients meeting CRPS criteria. We  
8 had another group of patients that had pain that  
9 were clearly not CRPS. This was like diabetic  
10 neuropathy patients and a variety of other groups.  
11       The idea is that we had a group that by  
12 diagnosis had CRPS and another group that we knew  
13 had pain from other causes, and they all underwent  
14 the same evaluation using this form that I showed  
15 you up there. What we found when we tried to  
16 distinguish between the CRPS group and the non-CRPS  
17 group was that those criteria we came up with were  
18 very sensitive. It picked up everybody that had  
19 CRPS, but it wasn't very specific at all.  
20       Frequently, people with these other pain  
21 conditions would get misdiagnosed as CRPS using the  
22 criteria as worded, and it basically says that if

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1 you just base it on appearance, the non-CRPS  
2 patients, by this definition we had, looked very  
3 similar to CRPS patients.  
4       That is going to lead to over-diagnosis if  
5 you're doing it in a clinical setting, and in a  
6 clinical trial, that's a problem because you're  
7 going to get a lot of people that don't even really  
8 have the condition you're interested in that are  
9 going to meet entry criteria.  
10       I would say that all of those methods I just  
11 described there, you could easily apply to a study  
12 of any condition you wanted to pick in your area.  
13 You just have to be thoughtful and systematic about  
14 it, but it is something that is easy research to do  
15 because it can be done as part of clinical  
16 practice. It's a matter of coordinating and  
17 collecting the same data at all the sites using the  
18 same methods.  
19       How are we going to improve diagnosis?  
20 Well, we thought that including objective signs was  
21 important so that you don't have a diagnosis that  
22 is solely based on the patient saying they have

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1 something because there are a lot of ulterior  
2 motives for saying you have features, especially in  
3 the chronic pain context.  
4 Motor and trophic changes need to be  
5 included because they're clearly something distinct  
6 and they aren't reflected in the criteria. Also,  
7 splitting out vasomotor features from the edema and  
8 sudomotor features, that's clearly what that  
9 principal components analysis said is that they're  
10 two different things.  
11 Then in Budapest, Hungary, we had some  
12 revised changes, a proposed revision of the  
13 diagnostic criteria that we looked at, so it was  
14 kind of expert opinion at to what needed to be  
15 further changed based on these empirically-derived  
16 criteria. We came up with this set, which is  
17 continuing pain disproportionate to any inciting  
18 event.  
19 Now, based on the data, we've got four  
20 categories of symptoms, and the threshold for  
21 diagnosis, at least in terms of symptoms, is you  
22 have to have at least one symptom in three or more

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1 of the following categories. So you've got four  
2 categories; three of those have to be positive.  
3 We also require signs. You've got the same  
4 four categories. Patient has to show at least two  
5 features out of these four. If they have that and  
6 there's no other diagnosis that can explain the  
7 symptoms, they get the diagnosis of CRPS.  
8 This now is what CRPS is. We have defined  
9 what CRPS is. Not everybody agrees with it. You  
10 can't please everyone because they all have their  
11 reasons. The clinical criteria, we did something a  
12 little bit odd. I wouldn't necessarily recommend  
13 it, but we also had a different threshold for  
14 diagnosis for research settings. The idea was if  
15 we want to absolutely make sure we rule out people  
16 that don't really have the condition, if you apply  
17 this different criterion, you'll maximize  
18 specificity but still capture a lot of the CRPS  
19 patients.  
20 We empirically tested it. So if you look at  
21 sensitivity and specificity, the old  
22 criteria -- this is in a totally different sample,

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1 by the way, from what I talked to you about  
2 earlier. So the old criteria, perfectly sensitive,  
3 but they're not very specific. Lot of  
4 misdiagnosis.  
5 We used the Budapest clinical criteria we  
6 came up with. They're still very sensitive. You  
7 capture the people with CRPS, but now specificity  
8 has gone up by 27 points on this scale here.  
9 Budapest research, as intended, improves  
10 specificity a little more.  
11 This is the justification for saying these  
12 new criteria are better than the old criteria. We  
13 can't answer the question of whether in the big  
14 scheme of things our criteria reflect reality, the  
15 underlying mechanisms, because we don't know the  
16 mechanisms. But it works better than the old  
17 criteria empirically.  
18 We ended up going through a process with  
19 this then where these criteria, we published a  
20 couple of studies on this. We proposed it to the  
21 IASP taxonomy committee. They eventually voted on  
22 it. The IASP board voted on it, and now it is part

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1 of the official taxonomy.  
2 The things out of all of this that I hope  
3 you take home are wording matters. The individual  
4 features, the wording matters. The decision rules  
5 you come up with, the wording matters. You want to  
6 make sure it's all operationalized, so it's worded  
7 in a way that somebody knows exactly what you mean  
8 by it. They know how to assess it.  
9 Little changes can affect things a lot,  
10 especially if you're changing a decision rule from  
11 saying three of these to four of these are required  
12 to meet the diagnosis. That has an impact. Thank  
13 you.  
14 (Applause.)  
15 DR. FREEMAN: We will have plenty of time  
16 for questions during the moderated session. I want  
17 to emphasize that this is highly interactive, so  
18 feel comfortable interrupting the speaker, but  
19 don't do it too frequently.  
20 (Laughter.)  
21 DR. FREEMAN: But definitely during the  
22 moderated session -- the way the meeting will be

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1 structured is after each set of talks, there's a  
2 moderated session with panelists. Panelists will  
3 speak for a few minutes of their either impressions  
4 of the talk, their impressions of the topic, but it  
5 is a free-for-all. This must be highly  
6 interactive.

7 What I didn't mention, which perhaps I  
8 shouldn't mention, but there is a stenographer who  
9 you see at the back who is taking down all of your  
10 interruptions. So interrupt politely because this  
11 is part of the permanent record and could be viewed  
12 by anybody, so just so you know that. That will,  
13 of course, help us collate everything that happens  
14 at the meeting and will allow us to put together  
15 the work product.

16 Now, I think everybody knows Chris Gibbons,  
17 who is an associate professor of neurology at  
18 Harvard Medical School, who will talk about one of  
19 the projects that is ongoing with CONCEPPT, which  
20 is looking at the instruments for assessing the  
21 neurological features of disease, the signs that we  
22 use in diabetic peripheral neuropathy and other

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1 peripheral neuropathies.

2 Chris, why don't you go.

3 Presentation – Christopher Gibbons

4 DR. GIBBONS: Excellent. Moving on a little  
5 bit, so this is going to be, I think, an equal  
6 opportunity offender talk. I'm going to try and  
7 insult every single person in the audience before  
8 we're done, so hopefully, you'll really enjoy this  
9 and get something out of it.

10 But the point of this is I'll go through a  
11 couple of details as we're getting into this and  
12 how we just really heard a very insightful talk on  
13 how to think about taxonomy. Some of the things we  
14 need to think about, really review how we got to  
15 where we are. What is some of the background to  
16 the information of when we're doing an examination  
17 and we jot this down or think about research  
18 criteria, how do we get there? What are the  
19 current criteria? How do these exams fit and  
20 across spectrums?

21 Review some of the relationships between  
22 these examinations and the current criteria for

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1 complications of diabetes. What are the different  
2 neurological complications and how they fit the  
3 examination criteria.

4 Then I want to conduct a little bit of an  
5 exercise, going through why we want to think about  
6 this, why it's so important, then really again  
7 feeding forward to this what we're going to be  
8 doing for the rest of these sessions, hopefully  
9 pretty dynamically.

10 Historically, again, the neurological  
11 examination has been around for quite a bit of  
12 time. There's been a lot of development actually  
13 over hundreds of years now at this point. Thinking  
14 about how people grade reflexes, sensation, muscle  
15 strength has really developed over time, a lot of  
16 contributions from different groups.

17 Ordinal grading is one of the big steps  
18 forward. How do we ordinarily grade in a numeric  
19 fashion muscle strength? That's something that was  
20 really done -- and Lovett introduced this, who was  
21 a Boston orthopedist, on a 6-point scale, which  
22 then really was converted to the current MRC scale.

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1 The numbers are reversed, but the concept of the  
2 MRC scale really came into prominence during World  
3 War II with the concept that war injuries and nerve  
4 injuries specifically, how do we predict if  
5 somebody's going to have any chance of recovery?  
6 Is there no strength? Are they completely  
7 paralyzed? Is there a flicker of strength?

8 This is where a lot of the data started to  
9 generate and come from when we're thinking about  
10 this scoring system. If you're interested  
11 historically, Peter Dyck actually had a really nice  
12 paper outlining some of the history of this in JPNS  
13 back in 2005, and it goes through a lot of the  
14 evolution of the examination and how we've come to  
15 where we are.

16 Historically, these are some of the things  
17 to think about, how we got to these systems, but  
18 the concept of the exam was frequently based on war  
19 injuries or major traumatic injuries and how we  
20 quantify that. I think moving forward to the  
21 concept of what we're talking about here with the  
22 diabetic peripheral neuropathies, we have to think

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1 a little bit about how that might fit.  
2       Where are we now? If you peruse the  
3 literature and you're interested in finding your  
4 exam du jour for diabetic peripheral neuropathy,  
5 you have at this point at least 16 different  
6 examination criteria to choose from. There are  
7 more out there. I'm sure we didn't get everything,  
8 but again, these scales are really pretty widely  
9 different in scope, what they're trying to  
10 accomplish, weighting of the different systems.  
11       Predominantly, they're based on the MRC  
12 criteria where you're looking at an ordinal system  
13 of grading from paralysis to full strength, not  
14 everything, but a lot of them are based on that.  
15 Again, looking at this as a pattern recognition  
16 approach to diagnosis, so that's a lot of the  
17 background to this concept.  
18       These are some of the scales you can choose  
19 from, if you're interested, and Jen over there has  
20 done a remarkable job putting some of this  
21 together, and we've been working on this for a  
22 while. But if you're looking at these, here you

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1 vibration, touch, joint position, pinprick. What  
2 you're seeing are these bars across. A full bar  
3 means more global assessment proximally and  
4 distally. If you're seeing here, it's more distal  
5 to slightly proximal, and this is just distal.  
6       If you're looking at that, you can start to  
7 see a distribution both of territory and of  
8 magnitude of what you're checking. You can see  
9 some check everything. Some are much more distally  
10 focused so that UENS is really again distally  
11 focused, but some of these are really checking  
12 every single muscle group or sensory group that you  
13 can possibly imagine across.  
14       When you're looking at this, again, it gives  
15 you a very different perspective on what  
16 examination might be chosen for what particular  
17 scenario. But it's important to consider not just  
18 what the examination is measuring but what are the  
19 scoring assessments? So how relative is the  
20 weighting?  
21       If we're looking at motor reflex, large  
22 fiber or small fiber sensation, it's important to

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1 pick your scale du jour. Some of the different  
2 systems that you can consider looking at here,  
3 whether it's vibration, reflex, pinprick, muscle  
4 strength, touch, joints, temp, allodynia, two-point  
5 discrimination where there's associated physician-  
6 recognized or patient- or clinician-recognized  
7 symptoms, nerve conductions.  
8       You can really see that there are a lot of  
9 different options on this menu, and again, we heard  
10 about the menu selection criteria, how would you do  
11 this. Well, there are a lot of different options.  
12 You can see they're pretty widely distributed.  
13       This only gives you one particular picture  
14 on the challenge that you're seeing. This is just  
15 whether this is included globally or not. If we  
16 dig into some of the details, this is going to look  
17 a little painful, and I apologize, but we'll walk  
18 through this. But this is a really important slide  
19 conceptually.  
20       Again, you're looking at your scales here,  
21 and you're looking at different groupings, so  
22 muscle strength, reflex, and then sensory,

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1 recognize that if you're measuring a scale one way  
2 shifted or another, you can see some have no motor  
3 examination. This is INCAT's. This isn't really  
4 one we're going to be using for diabetic  
5 neuropathies, but some of these have no motor  
6 assessment where some are 90 percent motor  
7 weighted.  
8       This range of weighting of motor from 0 to  
9 90 percent and this similarly for the large fiber,  
10 small fiber, and reflex testing, really gives you  
11 an enormous difference in terms of an outcome of a  
12 particular study, depending on which scale you  
13 choose. So if we're thinking about this broadly,  
14 it's pretty critical to consider all of these  
15 options as we start to go through this process of  
16 taxonomy across these different specific systems  
17 that we're thinking about.  
18       This, I think, creates a challenge, and this  
19 is one of the things we're faced with because all  
20 of these scales, with the exception of maybe INCAT,  
21 have been published in just the length-dependent  
22 diabetic peripheral neuropathy. You're going to

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1 get very different discussions depending on the  
2 result, and of course, if we can't have the same  
3 language or use of conversation, we're going to get  
4 into a lot of trouble. This may be some of the  
5 challenges we're facing.

6 The real question is why is this relevant.  
7 If we have a drug -- and maybe it's just because we  
8 haven't had a drug. Maybe we just haven't had a  
9 drug that's worked. But if we had a drug that  
10 worked, halted neuropathy progression or even  
11 reversed diabetic neuropathy in some way, shape, or  
12 form, does it really matter? Could we just pick  
13 any one and it doesn't make any difference  
14 whatsoever?

15 It's an important concept. Does this make a  
16 difference? Is this worth the effort?

17 Pulling to a side a little bit, some of our  
18 own data -- and this is again more recent data on a  
19 longitudinal study of diabetic neuropathy, trying  
20 to get at some of the questions, well, does it  
21 matter? What changes? What's going on?

22 This was just a natural history study

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1 looking at a little over 60 individuals with  
2 relatively stable hemoglobin A1Cs who were followed  
3 for three years with basically just every exam,  
4 every test. Lots of things done repeatedly just to  
5 understand what changed and when.

6 We really selected a group that was quite  
7 well controlled in terms of risk factors. They  
8 didn't smoke. Their blood pressure was controlled.  
9 Their hyperlipidemia was controlled. Triglycerides  
10 were under good control. Again, from a numbers  
11 perspective, this was a reasonably well controlled  
12 group of individuals with diabetes.

13 This is publishing one or reporting one  
14 scoring system. There was no change in examination  
15 over three years. Looking at this exam, this was a  
16 fairly balanced exam looking across motor, reflex,  
17 large fiber, small fiber symptoms. No change at  
18 all over three years, none. There were no change  
19 in symptom scores over three years either, none.

20 Then we looked at lots of other things as  
21 well. We looked at quantitative sensory testing.  
22 We looked at nerve conduction velocities and

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1 amplitudes. We looked at autonomic function, and a  
2 lot of figures here, some with type 1 diabetes,  
3 some with type 2 diabetes, repeated measures,  
4 basically, the result is over time, nothing changed  
5 at all of any sort. Again, from a three-year  
6 period, we were stuck with nothing changed in any  
7 measurable way.

8 But why bother? Nothing is going to change.  
9 Why bother measuring it? Are we just wasting our  
10 time? What's the point of all of this? Are we  
11 ultimately going to get somewhere from here to  
12 there if what we're doing isn't making any  
13 difference?

14 Well, this comes into an important concept  
15 as we move into this meeting, no pun intended here,  
16 but looking at this different topics that we're  
17 going to address today, diabetic neuropathy,  
18 neuropathy of the pre-diabetic state, treatment-  
19 induced neuropathy, lumbosacral radiculoplexus  
20 neuropathies, and then focal entrapment  
21 neuropathies. These are pretty different disorders  
22 if we really think about it, and we'll hear more

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1 about the details.

2 Maybe we need to consider these individually  
3 as we're trying to do today. Maybe these aren't  
4 the same problem even they all fall under the same  
5 heading of diabetes-related complications.

6 Ahmet, jump in.

7 DR. HOKE: Chris, you said nothing changed,  
8 but did you guys look at the skin biopsy?

9 DR. GIBBONS: We don't have data on skin  
10 biopsies on that particular study, no. So that's a  
11 good question, and you're getting at hints and  
12 details, yes, that I'm trying to throw out and hide  
13 for later. But yes, absolutely, but that's exactly  
14 the point.

15 Maybe there are ways we can get into that,  
16 and that's hopefully what we are going to do is  
17 generate what are the specific things we need to  
18 look at to get to that data.

19 Again, for these different diseases, they're  
20 not the same, and I don't think we should consider  
21 them as such. One size is clearly not going to fit  
22 all. If we have different exams, we have different

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1 ways of scoring, are they going to fit across all  
2 these different disorders we're talking about in  
3 the next two days? The answer clearly is no, and  
4 if we select the same answer, we're going to have a  
5 problem.  
6 If I'm just looking globally at some  
7 criteria, whether it's motor, reflex, large fiber  
8 sensory, or small fiber sensory, what are the  
9 different disorders that we're talking about today  
10 and tomorrow, and how might we think about these?  
11 So you'll forgive my scatter plot efforts at  
12 drawing on a moving airplane with a mouse trackpad,  
13 but if I splat something across the top here --  
14 (Laughter.)  
15 DR. GIBBONS: -- and I call this diabetic  
16 peripheral neuropathy, this is maybe what some of  
17 us would think about.  
18 Most of us almost never see motor neuropathy  
19 anymore. Is there some? Absolutely. Do we see it  
20 regularly? I would say not really. Again, not  
21 except in really advanced cases.  
22 Is there reflex involvement? Of course, we

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1 see absent reflexes quite frequently. But large  
2 fiber, small fiber, absolutely, we see both. So if  
3 I was going to throw a splat on the screen, that's  
4 probably what I would imagine, and maybe that's one  
5 way of thinking about the conversation, our  
6 weighting systems.  
7 What about neuropathy of the pre-diabetic  
8 state? Again, that's going to be a much smaller  
9 involvement. Would we see motor? I would say if  
10 we did, we probably wouldn't be calling this in  
11 this category. There'd be something else going on.  
12 But reflexes, maybe. Maybe we'll talk about that,  
13 but small fiber, certainly, and maybe a little of  
14 the large fiber touch in there.  
15 These are the things we'd want to think  
16 about, and maybe this has a different perspective  
17 on this discussion for later that we want to think  
18 about.  
19 Treatment-induced neuropathy, if I'm drawing  
20 another splat here, I'm thinking this is  
21 predominantly small fiber, maybe touching on large  
22 fiber, maybe some reflex. Really a hint of motor,

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1 but I would argue that that's a debatable issue.  
2 But that's a very different, again, overlap than  
3 these other conditions.  
4 What about the lumbosacral radiculoplexus  
5 neuropathies? Well, again, we'd be looking at  
6 different conditions there, and yes, there'd be  
7 some sensory involvement, reflex involvement, no  
8 question. Again, it depends on which group or  
9 targeted nerve we're thinking about. Motor, that's  
10 where we're thinking most commonly. I think again,  
11 we may see some discussion about how much weighting  
12 that would do and where it would go, but just  
13 conceptually, these are different problems.  
14 The entrapment neuropathies, of course, it  
15 depends on what's entrapped and where and whether  
16 they get to it, whether there's sensory, motor. I  
17 would argue you're really not going to see much of  
18 that unless you're having a major problem. But  
19 again, very different diseases, so something to  
20 think about as we're having this discussion moving  
21 forward.  
22 DR. HOKE: Chris, why don't you have

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1 autonomic evaluation or autonomic fibers in that?  
2 DR. GIBBONS: I do think about that. This  
3 was really thinking predominantly about the  
4 examination, which I think most of us would  
5 struggle a little bit more on the autonomic, which  
6 would be more physiology and symptom based. So if  
7 I'm just looking at exam, maybe I could get to  
8 autonomic with some measures, particularly  
9 orthostatic for bedside, but for the most part, I'd  
10 say that's going to be one that we have to think  
11 about, and particularly for the treatment-induced  
12 neuropathy, I'm going to highlight that later.  
13 Hopefully, we'll discuss that amongst the other  
14 neuropathies as well.  
15 That's a little bit trickier to get at in  
16 terms of bedside testing, though. So that's where  
17 if we're focusing just on the exam, that's I think  
18 a little bit more of a challenge.  
19 I wanted to do a little bit of an example in  
20 thinking about why this might matter. Many of you  
21 are familiar with this particular trial publication  
22 down here, but this is looking at the tafamidis

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1 trial on familial amyloid polyneuropathy.  
2 As most of you are aware, this is a  
3 randomized controlled trial of tafamidis. It was  
4 an 18-month duration trial, and the primary outcome  
5 was a 2-point change in the NIS-LL. We'll talk  
6 about that a little bit more later, but the NIS-LL  
7 is a pretty comprehensive lower extremity  
8 examination looking at sensory, motor, reflex.  
9 This was the primary outcome.  
10 Just showing a figure from the actual trial  
11 here at 6 months, 12 months, and 18 months, really  
12 what you're looking at is the decline or in this  
13 case, as the number went up, this is getting worse.  
14 The treated group was lower than the placebo group,  
15 so there was less of a decline, if you will, in the  
16 treated group. This was the primary endpoint  
17 looking at that.  
18 Now, if we think about this, why this exam?  
19 Would it have mattered if we chose a different  
20 examination? If we look at the raw data  
21 and -- it's not always the easiest to get raw data  
22 when you're looking at change from a baseline score

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1 when you have to go to the various subtexts to find  
2 raw values, but the tafamidis group essentially  
3 changed from 8.3 to 11.1. The placebo group went  
4 from 11.4 to 17.2.  
5 Their NIS-LL scores worsened, but again,  
6 there was a difference in baseline score, which  
7 always creates some challenge. But what you really  
8 found was that the worsening in the placebo group  
9 was predominantly motor based. So that's what  
10 we're seeing here. The placebo group got worse  
11 because of a motor decline.  
12 Thinking about the NIS-LL score, this  
13 strength in lower extremities is rated based on a 0  
14 to 4 scale. There are subdivisions for fractional  
15 in the 3 to 4 range, but the total score is 0 to 64  
16 for motor strength. Reflexes, which are generally  
17 0, 1, or 2 with some age adjustment, which wasn't  
18 really relevant in this population. They were  
19 generally younger individuals, so I don't know how  
20 many fell into an age-adjusted reflex scoring. But  
21 the score ranged generally then is 0 to 8 for  
22 reflexes.

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1 Sensory in the lower extremities was a 0, 1,  
2 or 2 at both great toes, and so that gives you a  
3 score of 0 to 16, looking at a variety of sensory  
4 measures. So this is your proportionate assessment  
5 in the NIS-LL.  
6 If we went back in time and we selected a  
7 different examination, and we decided not to go  
8 with the NIS-LL, what might have happened? Back to  
9 our handy slide of all these details, if we look at  
10 their percent scores in the different scoring  
11 systems, again, we know that in this particular  
12 case, the study demonstrated that the individuals  
13 who got worse got worse from a motor perspective.  
14 So if we looked at who got worse, these are all the  
15 scales that would have detected no change.  
16 If we selected any of the ones in yellow  
17 here, we would actually have had a failed clinical  
18 trial without any hint of a positive, potentially  
19 not moved forward. There wouldn't have been a hint  
20 of a change. We might have detected that in  
21 conversations that people were worse clinically,  
22 but if we're looking at a sensory exam and we saw

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1 no change, that might have killed the advent of  
2 that movement into a further study.  
3 Those that did have more motor weighting are  
4 really all modifications of the neuropathy  
5 impairment score and the plus/minus. There are a  
6 variety of iterations of this, but those are more  
7 motor heavy scales. Those are ones that might have  
8 detected the change. These others would not.  
9 This is one thing that says well, perhaps  
10 the selection of the proper examination is quite  
11 critical to this decision-making process. If we  
12 had those 18 potential exams, 14 would have had no  
13 clinical effect and really would have killed the  
14 trial or any future development. Four potential  
15 effective scales again were all variations on the  
16 neuropathy impairment score, and this again, I  
17 think there's really clinically relevant  
18 implications for what we're trying to do in  
19 selection moving forward. What is going to be  
20 appropriate, what is going to have a dynamic range  
21 of change, and how do we think about that.  
22 Again, if we go through our criteria here,

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1 what we're selecting, what we're interested in,  
2 these different scales, we need to think carefully  
3 about our selection process because they are not  
4 the same thing, and we need to be very careful  
5 about how we're choosing.  
6 I wanted to throw a little bit of a teaser  
7 for one of the other talks coming up on treatment-  
8 induced neuropathy of diabetes. So that's  
9 predominantly a painful small fiber neuropathy.  
10 You see pain here in red. Some people have it in  
11 gray, but progresses, this is the more severe  
12 looking case. But this is a distribution of severe  
13 neuropathic pain. Visibly, when we look at this,  
14 it's not complicated to see that this hurts, this  
15 is bad, and this is horrendous. Visually, this is  
16 quite simple to see.  
17 If we chose the NIS-LL for this examination,  
18 what would we see?  
19 DR. HOKE: No change.  
20 DR. PELTIER: It wouldn't be any different.  
21 DR. GIBBONS: No change. NIS-LL would be 4  
22 in every single one of these cases, but something

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1 is different, but we're not measuring it with that  
2 particular scale.  
3 DR. DYCK: I think your example is very  
4 good. In TTR amyloid, they made a modified NIS  
5 precisely for this reason because they thought it  
6 was overly representing motor. So they put in a  
7 lot more emphasis on sensory exam and a smart  
8 somatotopic so you could show changes throughout  
9 the entire body. They modified it precisely  
10 because of the disease exactly per the discussion  
11 we're having here.  
12 DR. GIBBONS: I think that's a perfect  
13 example, I think, of how you can evolve general  
14 data and move on in terms of examination hopefully  
15 to fit what we're all thinking here.  
16 It's interesting, I think was thinking  
17 back -- actually, I was having a discussion with  
18 Roy the other day. I remember learning in medical  
19 school amyloid neuropathy was a painful small fiber  
20 neuropathy. And if you go back in the old  
21 textbooks, you don't see much about the motor  
22 involvement. It was one of those that it was a

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1 painful small fiber neuropathy. If it's really  
2 painful, it's amyloid. Think about that. That was  
3 just the thing going on in the back of my head.  
4 So as you're really thinking about this, the  
5 historical perspectives on some of these don't  
6 always fit. So that's where again the evolution  
7 and the motor data that we're really seeing in the  
8 amyloid story is particularly intriguing.  
9 Again, for this one, if we don't have loss  
10 of reflexes or strength or other large fiber  
11 perception, again, you're not going to see any  
12 difference. Again, it's quite critical to select  
13 the appropriate scale for the appropriate process.  
14 Clearly, choices of outcomes measures  
15 matter, and that's hopefully what we're going to  
16 accomplish moving forward is really having a pretty  
17 dynamic discussion about what is appropriate for  
18 each of these disease states.  
19 Thank you very much, and I think we are on  
20 schedule.  
21 (Applause.)  
22 DR. FREEMAN: I think probably now is a good

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1 time to have the first break, and then we'll meet  
2 again afterwards to discuss the various talks that  
3 you've had.  
4 I just want to clarify one of the reasons  
5 for having Chris give this talk was to provide a  
6 perspective of what CONCEPPT is actually doing,  
7 long-term goals, variability in the various  
8 diagnostic assessments. But I want to be quite  
9 clear, this is not a meeting about outcomes. I'm  
10 hoping we will be having that soon. This is a  
11 meeting about diagnostic criteria, taxonomy,  
12 inclusion criteria, exclusion criteria.  
13 We are right at the very foundation of a  
14 clinical trial, and moving forward, as you see,  
15 there's a lot to think about and a lot to discuss  
16 as far as ultimate clinical trials go. So it's  
17 relevant as far as the exams themselves, the  
18 validity, reliability, reproducibility because  
19 these are part of our diagnostic criteria, but we  
20 still are at ground level. In the afternoon,  
21 perhaps tomorrow, we will talk more about next  
22 steps. Enjoy your tea.

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1 (Whereupon at 9:48 a.m., a recess was  
2 taken.)  
3 Q & A  
4 DR. FREEMAN: I view this session as more  
5 conceptual. Perhaps a heading for it, an alternate  
6 heading, is what are we talking about when we talk  
7 about diabetic peripheral neuropathy? I think the  
8 subtext of this session, which is going to be a  
9 moderated panel discussion initially and then with  
10 interruptions, interjections, comments from  
11 everybody -- the subtext is, as somebody said to me  
12 when I invited them, "Is this meeting really  
13 necessary? Hasn't it all been done before?" And I  
14 gave my views as to why it absolutely was necessary  
15 and that it has never been done quite this way  
16 before.  
17 So topics that I think are worthy of  
18 discussion are going to be how reliable, how  
19 reproducible are the criteria that we use for  
20 diagnosing peripheral neuropathy in the various  
21 peripheral neuropathies that we're going to  
22 discuss.

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1 I think Stephen highlighted very clearly the  
2 continuum from subjective symptoms, to more  
3 objective signs, to more objective special  
4 investigations. I think we're all aware of the  
5 flaws in all of those and the challenges of  
6 incorporating all of those in a taxonomy where, for  
7 example, if someone wants to do an epidemiological  
8 study, they will not be doing, Ahmet's point, skin  
9 biopsies, nerve conduction studies, whereas they  
10 may choose to do signs and how valid, how  
11 reproducible are the signs.  
12 Do we, for example, need to do the kind of  
13 study that Stephen did with complex regional pain  
14 syndrome, looking at the alternatives, various  
15 causes of foot pain, various causes of numbness, or  
16 are we pretty much where we want to be and it's  
17 just a matter of implement it?  
18 Having said all that, why don't I start with  
19 Chris and any additional comments that you'd like  
20 to make.  
21 DR. GIBBONS: I think having actually breaks  
22 in between provides some great opportunity for some

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1 offline conversations. So I'm going to pull Vera  
2 back into a conversation over here because  
3 actually, one of the points she made, which is  
4 really critical, was again as we think about  
5 diabetic peripheral neuropathies and examinations  
6 and why would we choose one versus another,  
7 particularly if we're looking at early scoring,  
8 it's pretty important to think about that concept  
9 and why we might choose one or the other.  
10 If you just want to throw in your two cents  
11 on that, I think that was right on target.  
12 DR. BRIL: The question really is what are  
13 you trying to identify. If you're identifying a  
14 person with diabetic peripheral neuropathy, for  
15 what purpose, and that helps determine what you  
16 need to measure a little bit. Because if you want  
17 early neuropathy, for example, in diabetes -- and  
18 this is the distal symmetrical sensory neuropathy,  
19 or sensory motor -- you actually don't want much  
20 motor involvement because that's a little advanced  
21 if you're enrolling patients for a clinical trial.  
22 So you focus elsewhere.

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1 This may be why the NIS-LL when it was used  
2 in diabetic peripheral neuropathy studies was not  
3 that helpful or the drugs failed. At the bottom of  
4 all of this, it could just be that all the drugs  
5 failed so far.  
6 But you need to tailor what you use to  
7 identify the range of patients you want. It may  
8 not identify all the patients with that disease, so  
9 the sensitivity is different, but at least you will  
10 go to the earlier spectrum in some diseases. That  
11 was what we were talking about at the break, plus  
12 the fact that the TCNS does have reflexes.  
13 (Laughter.)  
14 DR. BRIL: And that was an error on the  
15 second slide, but I didn't want to bring it up in  
16 the talk. But I'll say it now.  
17 DR. FREEMAN: Rodica, and then Solomon.  
18 DR. POP-BUSUI: First of all, I'd like to  
19 thank you, Roy and Chris, for all your efforts in  
20 putting this meeting together. It is really great  
21 to be here. And I'd like to make just some initial  
22 comments; we'll talk some more.

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1 The first talk that you gave, Chris,  
2 regarding the mission and the aims of the  
3 consortium or whatever the name will be, I think  
4 that's also very important to identify because at  
5 some point, I feel that's saying we need to educate  
6 clinicians and we need to educate patients.  
7 Perhaps this is a little bit of a problem  
8 because if we aim to educate all physicians,  
9 clearly the type of tools will have to very  
10 different than the tools that we are going to use  
11 to identify outcomes for clinical trials. If you  
12 want to establish diagnostic criteria that are  
13 going to be used by practicing clinicians, again,  
14 if we make them very complicated, they are not  
15 going to be used.  
16 I think that as an endocrinologist, I am  
17 seeing patients with diabetes every day in my  
18 practice, and even us endocrinologists are  
19 outnumbered by the diabetes epidemic. It's even  
20 more so for neurologists because not all of you are  
21 interested in diabetic neuropathy to start with.  
22 So I think that we have to have very clear messages

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1 that we want to convey out of this meeting.  
2 In addition, Amanda mentioned there are no  
3 patient support groups. I think that that's a  
4 little not quite true. Maybe there is not a very  
5 strong patient support group for diabetic  
6 neuropathy right now, but however, the American  
7 Diabetes Association and also the Juvenile Diabetes  
8 Research Foundation are very, very strong  
9 proponents of patients with diabetes and partnering  
10 with them. It's also going to be very helpful for  
11 us to succeed.  
12 Again, I think that maybe one way to start  
13 this, we'll try to identify diagnostic criteria,  
14 and measures, taxonomy associated with that that  
15 can then be used to identify personalized type of  
16 diabetic patients or pre-diabetic neuropathy  
17 patients that we want to target in this  
18 intervention in a typical precision or personalized  
19 care.  
20 Those are my initial comments.  
21 DR. FREEMAN: Solomon?  
22 DR. TESFAYE: Again, I'd like to thank the

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1 organizers, Roy and Chris, principally of this  
2 meeting.  
3 I think also when we are thinking about an  
4 endpoint, we need to think about the mechanism of  
5 action of that particular drug and how it's going  
6 to work. Therefore, then we target the population  
7 that we're studying, depending on the proposed  
8 mechanism of action -- so one size doesn't fit all  
9 or one endpoint, so it depends on that.  
10 The other thing, I hope this meeting will  
11 address is that we have incredible under-diagnosis  
12 of diabetic neuropathy in clinical care at the  
13 moment, certainly in the U.K. We tend to use a 10  
14 gram monofilament, which diagnoses the condition,  
15 in around 14 percent of patients coming in to an  
16 unselected eye screening program, whereas if you  
17 even used a handheld device, a neurometric device,  
18 you'd diagnose the condition in 51 percent. It's a  
19 massive discrepancy.  
20 I hope this meeting will address that we  
21 really need to do better, and actually, these  
22 patients have an incredibly false sense of

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1 security. They think they're doing okay. They're  
2 told your feet are fine, you don't have any  
3 problems until they present to clinic with a foot  
4 ulcer and they have an incredibly terrible outcome  
5 at that point with very high mortality rate.  
6 DR. FREEMAN: Can I just pick up on a couple  
7 of these points and maybe reframe or frame the  
8 situation?  
9 I think all three of the commenters raised  
10 the issues with respect to the differing phenotypes  
11 of diabetic peripheral neuropathy, and I think  
12 that's the challenge that is going to be in Gordon  
13 and Rob's hands, where I think they are going to  
14 need to incorporate the different phenotypes, mild,  
15 moderate, and severe, early, late, sensory, motor,  
16 autonomic.  
17 I think these are all different phenotypes,  
18 and I think there is room in this kind of a  
19 taxonomic approach to the generalized peripheral  
20 neuropathies to include all of those. It may be  
21 that -- and my focus, the focus of this meeting and  
22 of CONCEPPT, is really the clinical trial. I think

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1 Rodica's consensus -- and I say Rodica, all of the  
2 people who contributed to that, her consensus  
3 statement guideline focused on the clinician, but I  
4 think there should be room for the clinical  
5 diagnosis as well.  
6 The way I would view this as being  
7 successful is that if this is an enduring  
8 manuscript that provides criteria for somebody  
9 doing an interventional clinical trial but also a  
10 cohort study, also a case study, and even the  
11 clinician in practice, I think it is possible to do  
12 all things for all of those, and clearly there's  
13 going to be a difference in the level of  
14 investigation that goes into those criteria.  
15 I think Stephen gave us an example of that  
16 when he spoke about the clinical criteria for  
17 reflex sympathetic dystrophy, CRPS, and research  
18 criteria. That possibly is one way that Gordon and  
19 Rob can do that in their approach. I think it's a  
20 little less relevant for the talks given by James  
21 and Chris, but it's probably very relevant for the  
22 talk that Vera is going to be giving on entrapment

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1 neuropathies.  
2 Who was next? Yes, Stephen?  
3 DR. BRUEHL: I just want to make a follow-up  
4 point with that. So what I didn't show up there is  
5 on the CRPS criteria, you've got the core set of  
6 criteria that are the same across all the patients  
7 that we consider to have CRPS, but there are two  
8 subtypes. There's a type 1 and type 2, and the  
9 difference is that type 2 is associated with  
10 evidence of a peripheral nerve injury and type 1 is  
11 not, and that's based on this historic clinical  
12 distinction.  
13 The reason I mention that is because what  
14 Roy was just talking about is differing phenotypes.  
15 The question you're going to come up with is you  
16 have a basic set of diagnostic criteria for  
17 whatever condition and you think all the patients  
18 should have this, but that there are differences in  
19 severity or there are differences in particular  
20 subfeatures, what you could do is have one set of  
21 diagnostic criteria with a definition of what  
22 operationalizes the difference subtypes.

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1 If it is so different, the phenotype is so  
2 different that you would really consider it two  
3 separate conditions, then you need to have mutually  
4 exclusive separate sets of diagnostic criteria for  
5 the two things. So you have some flexibility based  
6 on what we've done before, and we have done this  
7 with some of the other chronic pain diagnoses in  
8 the AAPT effort.  
9 DR. PELTIER: Well, like a perfect example  
10 is would you consider type 1 distal symmetric  
11 polyneuropathy different from type 2 distal  
12 symmetric polyneuropathy? I would posit that there  
13 is a difference in the phenotype, time that they  
14 present. Then do you have more negative or more  
15 positive symptoms in each one?  
16 Also going back to Rodica's point, is that  
17 you also have to make whatever we do accessible to  
18 not just endocrinologists but also family  
19 practitioners and to make it relevant to them.  
20 Because one of the things that drives me nuts is  
21 when I hear diabetics say, "Oh, no one's ever taken  
22 my shoes off before," which you would argue that's

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1 all part of the practice guidelines, but yet, then  
2 why do people come in and say that's never happened  
3 to them?  
4 Giving them a reason, talking about the  
5 mortality risks, the five-year mortality risk is  
6 higher with neuropathy, period.  
7 DR. RUSSELL: Can we just perhaps  
8 conceptually understand what we're going to try to  
9 achieve here? In other words, are we going to come  
10 up with consensus criteria, which is what has been  
11 done before, or are we going to do what Stephen  
12 suggested, which is actually take those criteria  
13 and systematically test them in a rigorous fashion  
14 to determine whether they're reproducible,  
15 sensitive, specific, et cetera?  
16 DR. FREEMAN: That was the question that I  
17 raised at the initial. Where are we at this point,  
18 and where are we with signs? Where are we with  
19 symptoms? Where are we with special  
20 investigations? Do we need to systematically, as  
21 Stephen did, compare the equivalent of complex  
22 regional pain syndrome, in terms of classical

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1 criteria, versus other causes of foot pain, plantar  
2 fasciitis, metatarsalgia, calcaneal spurs, or are  
3 we happy enough? And that's really to me is  
4 exactly is the focus of this discussion. And if we  
5 need to go in that direction, how do we go about  
6 doing that?

7 Or are we okay? We can just say okay, we  
8 are prepared to live with pain, dysesthesia,  
9 sensory distortion as symptoms when patients say as  
10 they do then, and Gordon can say one of five  
11 criteria in his talks, either this or that or the  
12 other.

13 I don't really know the answer to this, and  
14 of course, it depends on effort and resources and  
15 who's willing to commit their time to doing such a  
16 study. But I think that's a critical question,  
17 where are we now with those criteria?

18 DR. HERRMANN: One complexity that I was  
19 thinking about during the talks, it also gets to  
20 the changing criteria for diabetes, right? When we  
21 talk about the peripheral neuropathy and the  
22 neuropathy aspect, if you just look at symptoms and

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1 signs, we could investigate that and see how you  
2 differentiate symptoms and signs in, say, diabetic  
3 peripheral neuropathy and maybe subtypes from, say,  
4 those in HIV neuropathy or idiopathic neuropathy.

5 There may be considerable overlap there, but  
6 everything rests on the diagnosis of diabetes. As  
7 that changes over time and maybe others in the  
8 audience will say they won't change in the next  
9 10 years, but if they do and as you make the  
10 definition of diabetes more inclusive, that will  
11 affect the specificity and the characteristics of  
12 the criteria and how we deal with that. Do we  
13 develop a continuum of glucose dysmetabolism? I  
14 just throw that out.

15 DR. FREEMAN: That I think will come up in  
16 the next sessions where Rob talks about impaired  
17 glucose tolerance.

18 I think Jen had her hand up. No, no yet.  
19 Chris?

20 DR. GIBBONS: Just to get to a couple of  
21 these points and maybe step back a little bit from  
22 an overall perspective, so the focus of this

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1 meeting will be fairly tight. Again, we're working  
2 on taxonomy, defining things fairly specifically.

3 What we're also trying to generate here is  
4 this consortium where many of these other related  
5 activities are going to occur, whether it's  
6 clinical, whether it's research, whether  
7 establishing concepts. I think the consortium will  
8 be a much larger target of things to approach, and  
9 maybe many people here will be having different  
10 foci within this. But the current meeting will  
11 just be a small portion, I think, of globally what  
12 we're trying to accomplish overall.

13 DR. FREEMAN: Can I just before -- Vera,  
14 I'll come to you in just a second, and then to  
15 Stephen.

16 Just as a show of hands, I'd like to get a  
17 sense of who actually thinks -- let me ask this in  
18 three specific ways. Who thinks that with respect  
19 to signs, signs of diabetic peripheral neuropathy,  
20 we need to do a study like Stephen did, or we're  
21 okay? Who thinks we're okay? We don't need to do  
22 anything more as far as signs go.

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1 (Show of hands.)

2 DR. FREEMAN: Who thinks we're not okay,  
3 that we should actually look at this more  
4 carefully?

5 Okay. Slight majority.

6 DR. POP-BUSUI: I'd like to make a comment.  
7 So I think that we should not ignore the data that  
8 we have acquired, and in fact, we know we have so  
9 much wealth of information in the DCCT EDIC. We  
10 have acquired signs and symptoms now for 30 years,  
11 and we have also acquired the entire spectrum of  
12 information regarding diabetes history, control,  
13 risk factors, biomarkers.

14 There is no other study, and it's  
15 continuously -- it hasn't even mentioned. We do  
16 have a lot of data, and we do have these signs that  
17 have been, in fact, acquired through your help  
18 because every single site had a board certified  
19 neurologist who had acquired those signs.

20 So I think that we have a lot of information  
21 on signs already that we should include in our  
22 consideration.

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1 DR. FREEMAN: I absolutely agree. The  
2 problem is unless -- I agree with that, and I think  
3 we should look at that. I also think -- I don't  
4 know if you saw earlier, but as part of the ACTTION  
5 initiative, they are looking at all of the studies  
6 that were submitted for neuropathic pain to the  
7 FDA. I think we should do the same with disease  
8 modification for diabetic peripheral neuropathy.  
9 However, until you do it in an objective way  
10 like Stephen did it, looking at -- and this  
11 requires a hypothesis-driven study, the equivalence  
12 of PHN, the equivalence -- I forget what the other  
13 neuropathic condition that you looked at -- and  
14 comparing those to CRPS, I don't think we are quite  
15 there yet.  
16 Stephen and then --  
17 DR. BRUEHL: Can I make a couple points?  
18 DR. FREEMAN: Yes.  
19 DR. BRUEHL: I think you're pointing out  
20 exactly what the issues are in mapping out how to  
21 do something like this. I was thinking it might be  
22 useful to have a visual here to conceptually think

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1 about this.  
2 In Chris' talk, he had the four different  
3 areas, which in some ways, I might consider might  
4 be different mechanisms. Physiologically, we're  
5 talking about something different for each of  
6 those. When we define the diagnostic criteria, we  
7 are defining some variety of overlap across  
8 different mechanisms. In all likelihood, every one  
9 of these conditions may have different mechanisms  
10 going on.  
11 It would be helpful, if you feel like the  
12 literature is strong enough, to keep in mind what  
13 the mechanisms you want to capture are. You have a  
14 list of those. Then you go for a given condition,  
15 where should that just -- based on what you already  
16 know, where should that blob go? How much should  
17 it cover? Should it leave out the motor or  
18 whatever it may be?  
19 Then if you have mechanisms in mind, what  
20 you think is you got a mechanism, and then in some  
21 cases, you have an existing objective test that you  
22 know is a marker for that mechanism, a reasonably

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1 good marker. That's theoretically meaningful. So  
2 that's really nice.  
3 Now, the point about clinical use, nobody is  
4 going to do these really elaborate expensive tests  
5 out in Dubuque or I don't know, randomly picking a  
6 name, but some small town somewhere, Bucksnot,  
7 Tennessee.  
8 (Laughter.)  
9 DR. BRUEHL: It's an actual place. They're  
10 not going to use this, right? So they need  
11 clinical criteria.  
12 So you've got this theoretically meaningful  
13 objective test, and if you can demonstrate that any  
14 given sign or symptom or combination thereof is a  
15 valid and reliable marker of that objective test,  
16 that's what you want in your ultimate clinical  
17 criteria, because if you tie it backwards, it goes  
18 right to this issue. So kind of keep that in mind  
19 as you're doing this.  
20 I think the other question that was brought  
21 up had to do with should we start from scratch or  
22 not, and you have to start somewhere. Now, you

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1 could be totally atheoretical. I don't recommend  
2 it, but if you've got an existing data set that has  
3 the right data elements, you could inquire and see  
4 what comes out using the pattern recognition  
5 approaches I was talking about and do it all based  
6 on empirical things.  
7 It's nice, though, because we're not totally  
8 stupid people, and if you've seen a lot of these  
9 patients, you have an idea in mind theoretically of  
10 what a given condition is. So you can look at it  
11 in this incremental validity manner where you've  
12 got a starting point that may be consensus based,  
13 and what you're trying to do is then optimize that  
14 using the empirical approaches, which could be  
15 collecting a new data set across a variety of sites  
16 as in a consortium, as long as you can all agree on  
17 what the key elements of that need to be. And it  
18 doesn't take a ridiculously long time. If you see  
19 a fair number of patients and are willing to commit  
20 to this, it can be done pretty quickly, within a  
21 year, a year and a half, something like that.  
22 Just keep all of this in mind. I'm not

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1 trying to steer the direction one way or the other  
2 as to whether you start from scratch or not. You  
3 could do either one of these, but I don't think you  
4 can totally ignore what you already know.  
5 The other issue is do you feel like for any  
6 of these particular conditions, there is already a  
7 published set of diagnostic criteria that have been  
8 validated or represent a clinical standard that is  
9 pretty much widely accepted, and if it is, then you  
10 can use that kind of thing as a starting point.  
11 DR. FREEMAN: I will come to the question,  
12 and somebody should make notes of this. Two  
13 things, first thing is that we are going to end  
14 this meeting with criteria. We're not going to end  
15 this meeting by saying, well, we just don't know  
16 enough at this point, we need to do a study.  
17 That's the one thing.  
18 But the other thing is I think it'd be  
19 really good to have a research agenda, and Rodica  
20 has offered to look at the DCCT and the EDIC  
21 databases, perhaps do a cluster-type analysis on  
22 those, other databases that exist. I think we can

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1 then in a way make this iterative, make this  
2 flexible, and begin to then use data to modify this  
3 as time goes on. I think that will be a very  
4 useful research agenda.  
5 There were some questions. I think Vera was  
6 next.  
7 DR. BRIL: We're happy with our scale.  
8 We've validated it in a single center and trained  
9 the people, but the study that Peter did at the  
10 Mayo with many people in this room should really  
11 give us all pause because they did the signs. They  
12 were neuromuscular physicians mostly. They did the  
13 signs, and they made the diagnoses, and there was  
14 not good concordance.  
15 We're talking now about reliability. That's  
16 like a specter that's hanging up there in the  
17 corner of the room that depending on how widespread  
18 we want this work to be, we have to realize the  
19 limitations. Even in the EDIC, it was neurologists  
20 in each center. Well, most diabetes patients are  
21 never going to see a neurologist, right? They're  
22 going to be out there in the community.

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1 There's many elements, but even if they do  
2 see a neurologist, that neurologist may examine  
3 differently than the next neurologist. There was  
4 standardized training in this particular study.  
5 It's a data set that is quite pure, and there was  
6 standardized training in our set. So what we  
7 published had to do with a small group of examiners  
8 and standardized training, but when we get out  
9 there and don't do it, you get this variability  
10 even in things like signs, which should be really  
11 easy to assess.  
12 In our own minds, I think, we all think we  
13 can do it, and yet there was this variation that  
14 reminds us a little bit -- pain, when you describe  
15 pain and you describe a symptom, you can then more  
16 or less categorize what the patient says, but when  
17 you're looking, I wonder what the variation was  
18 really, and that weakness, and that limited range  
19 of motion, and how much variation there was in that  
20 particular category of your chronic regional pain  
21 syndrome because it's surprising.  
22 DR. FREEMAN: I couldn't agree more.

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1 Eva, Doug, then Dan, then Rayaz.  
2 DR. FELDMAN: I just want to make one point  
3 early on that Amanda made that I'd like to  
4 reiterate, and that is, while I am a big advocate,  
5 for example, of the DCCT EDIC database and work  
6 closely with Rodica on it, it is a type 1 database.  
7 I really do think that many of us who see hundreds  
8 and hundreds of these patients believe that the  
9 neuropathy in type 1 and type 2 may be quite  
10 different.  
11 So I think we need to keep that in mind as  
12 we're doing our taxonomy.  
13 DR. FREEMAN: You want for EDIC as well?  
14 DR. POP-BUSUI: No. What I want to say is  
15 do we know for sure that the actual disease, it's  
16 different or the risk factors that contribute to  
17 the disease? And I think that's another question  
18 that we can answer.  
19 DR. FELDMAN: I think it's something that we  
20 need to ask and answer.  
21 DR. FREEMAN: Gordon is nodding. Gordon  
22 will address this. Doug?

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1 DR. ZOCHODNE: I'm going to say, Roy, that  
2 in terms of this meeting, I actually like these  
3 microphones with the lights that come on. It's  
4 sort of like optogenetically activated neurons that  
5 pop up and down. I think it's quite neat.  
6 (Laughter.)  
7 DR. ZOCHODNE: My relevant point was that  
8 Stephen mentioned mechanisms and Amanda brought up  
9 type 1 and type 2 and Eva did as well. I think  
10 we've moved on. This was Anders Sima's idea, that  
11 there were differences, and we pushed that aside.  
12 No, no, we're not going to think about differences,  
13 but it's emerging. The insulin resistance of  
14 neurons, the insulin sensitivity in type 1.  
15 I think it might be a good strategy to keep  
16 them separate at this stage.  
17 DR. FREEMAN: Rayaz, Dan, Teresa.  
18 DR. MALIK: The reason we're all here is  
19 because things aren't working. So if we just say,  
20 you know what, we don't really need to look at this  
21 objectively, as Stephen has said, and we just carry  
22 on as we're doing, then I think we're going to come

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1 back in 10 years' time, and we're going to say same  
2 old problems.  
3 I honestly advocate an objective approach.  
4 Just do it properly, look at the symptoms, look at  
5 the signs, look at whatever tests you want to use,  
6 and address them objectively as opposed to opinion.  
7 Chris, your data, I think, highlights the  
8 fact that probably when you did this study, you  
9 wanted to show that there's going to be a change.  
10 You didn't see any change. Three years. Okay.  
11 They were well controlled or whatever, but that  
12 data speaks for itself.  
13 I disagree with anybody who says we just  
14 need to carry on doing what we've been doing for  
15 the last 40 years.  
16 DR. FREEMAN: The insanity advocate.  
17 Stephen and then --  
18 DR. BRUEHL: I'll make an response to what's  
19 been said just a second ago. The type 1 versus  
20 type 2 example is the perfect prototype of exactly  
21 how this approach could be applied.  
22 What you do is you have a set of signs and

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1 symptoms that you think encompass all the  
2 meaningful features of both type 1 and type 2. You  
3 do clinical evaluations with standardized  
4 instructions for how you assess everything.  
5 Assessing all of those in patients whether they're  
6 type 1 or type 2 in your clinical belief.  
7 You get a large data set of at least 100  
8 people. You do cluster analysis, and using this  
9 two-step cluster analysis, what it will tell you is  
10 it will use the Bayesian information criteria to  
11 tell you how many clusters there are. If it pops  
12 out two clusters and you look at the features and  
13 see the patients in those, what you should see, if  
14 type 1 and 2 are meaningful, is that it should fit  
15 basically what you'd expect clinically. You can  
16 match that up statistically, if you wanted to.  
17 That's the type of thing I'm talking about,  
18 is that is a perfect use of this type approach when  
19 you've got a clinical question that is easily  
20 testable. You don't even have to know the  
21 mechanisms to do this. That's the cool thing, is  
22 you can do it totally not theory driven but just

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1 let the computer tell you this.  
2 DR. FREEMAN: Just to editorialize for a  
3 second, one of the hopes of this meeting -- well,  
4 one of the interesting things to do then would be,  
5 as I suggest to Rodica, we look at both DCCT and  
6 EDIC.  
7 One of the problems is that the entry  
8 criteria for the study are different. One of the  
9 hopes for a successful meeting would be that in the  
10 future DCCTs, future \*EDICs, similar criteria will  
11 be used so that we can make these comparisons going  
12 forward.  
13 I think it was Dan next, then Teresa, and  
14 then Rodica.  
15 DR. ZIEGLER: I would just like to come back  
16 to what Vera said. I think the problem in practice  
17 is that there is no standardization at all, and  
18 there is no way -- I agree with you completely that  
19 we need something to dichotomize the diagnosis.  
20 The problem is that if you come back to all  
21 these test, bedside tests, and the 16 different  
22 suggestions of scores, everybody is doing it in a

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1 different way. There's no way at all of  
2 standardization. If you ask the people, what is  
3 the normal cutoff for vibration perception  
4 threshold, you will hear 20 answers here, even  
5 here, among the experts.  
6 We're starting from scratch. If there is no  
7 way to standardize this, these simple tests, there  
8 will never be an accurate and reliable diagnosis.  
9 So the question really is historically,  
10 those people suggesting all these different tests,  
11 why didn't they get together 20 years ago and try  
12 to figure out which of these tests would be the  
13 most appropriate one and come back with a consensus  
14 on what would be a reliable approach of bedside  
15 testing using appropriate cut points and  
16 dichotomizing and defining the diagnosis? I think  
17 those years are basically lost so far.  
18 DR. FREEMAN: My vision is to -- and one of  
19 the reasons why I delayed this meeting is I believe  
20 that that is absolutely necessary. It's enormously  
21 challenging, and it also requires people who have  
22 their own instruments being flexible as far as what

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1 we give and take from those instruments. But I  
2 couldn't agree more with you.  
3 As a matter of interest, Jen, Chris, how  
4 many of those instrument scales that you looked at  
5 actually do give some standardization instructions?  
6 DR. GIBBONS: This will probably be best  
7 answered by Jen, but I think as we went through,  
8 part of the challenge is everybody has their own  
9 recollection of exactly what they're thinking when  
10 they wrote their instrument. When we tried to  
11 recreate that -- and it's important to step back.  
12 As a neurologist, I have my own perception, so I  
13 came into this with some degree of recognition of  
14 what people were expecting. When Jen comes at it  
15 from a different perspective, a non-neurologist  
16 with clinical trial expertise, she looks at the  
17 language the way it's written.  
18 The standardization was severely lacking.  
19 You could assume what we all thought we meant, but  
20 you could not find the definition in most cases.  
21 It was extremely difficult to come down to a really  
22 clear answer. We had to go back and query authors

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1 about what they were meaning or what they thought,  
2 and even then, I would say we frequently still got  
3 into dicey -- we weren't sure what exactly was  
4 going on despite many people using this, not  
5 necessarily in the same way.  
6 DR. FREEMAN: Teresa, and then David.  
7 DR. JONES: First, I'm really thankful.  
8 This is a fantastic meeting, and I really  
9 appreciate all the work that's going into it. It's  
10 really nice to think about these things.  
11 Just as far as your aim statement, all of  
12 it's great, but I wish I'd seen the words "cure"  
13 because that's so powerful. From my perspective,  
14 seeing research out there, I'm hopeful. I see  
15 things that look very promising, so I don't think  
16 that's so far away.  
17 I'd like to just have my comments more on  
18 the research module aspect, which I thought was  
19 great as I was listening to Stephen's talk. I have  
20 a question about how it's actually been used in  
21 practice, but I think it's -- I'm wondering and the  
22 door's closed, so this can kind of be in here. I

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1 wonder if we should work backwards and somewhat  
2 game the system a little bit, and think what drugs  
3 are out there, what are they going to be acting on.  
4 What are some of the mechanisms? What would be the  
5 patients that you would want to see in these trials  
6 so that we could finally get a drug that would be  
7 disease modifying? What would set the thing up in  
8 the best way?  
9 Of course, it has to be valid. It has to be  
10 choosing the patients, but then work backwards.  
11 And then for this research module, which doesn't  
12 have to include primary care physicians but just  
13 for doing a research study would be your inclusion-  
14 exclusion criteria. That's all.  
15 DR. FREEMAN: Let's track David, and then  
16 Rodica, Rob, Yad, Gordon.  
17 DR. HERRMANN: Related to the point that  
18 Vera and Dan made about clinical criteria and  
19 practicing neurologists and precision, I wonder  
20 whether one way you could construct it is in your  
21 taxonomy, you have your starting set -- let's take  
22 symptoms or signs -- where you think of the signs

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1 as just elements, and so you define the elements  
2 that need to go into the diagnostic criteria, so  
3 maybe vibration or position sense, whatever the  
4 sign is.  
5 That's the starting point, but then to get  
6 to the precision, which may be what you need is  
7 greater for a trial or for research than you might  
8 need for just broad clinical practice, there can be  
9 a separate component to how to or best practice  
10 around how to measure that element. Because I  
11 think if we get to the measurement too quickly and  
12 the precision, I think we will never really get  
13 there, but if we can define the elements in the  
14 diagnostic criteria and then move to best practice  
15 around precision of measurement, I think that might  
16 be more manageable to approach it that way.  
17 DR. FREEMAN: Bob, Rodica, Gordon, and then  
18 that's it. There will be plenty of time.  
19 DR. SINGLETON: I wanted to thank Teresa for  
20 opening this piece of the discussion because I  
21 think we will inevitably be talking about this  
22 neuropathy in the context of its spectrum of

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1 disease from metabolic syndrome, from pre-diabetes,  
2 to diabetes.  
3 I really like the idea that we might have  
4 two different criteria, one that is diagnostic and  
5 another that is designed for research with the goal  
6 of finding a criteria that allows us to select  
7 participants who would best respond. I think that  
8 all of us -- I certainly think that we want to find  
9 a set point that is early in the disease progress  
10 at a time when it's reversible.  
11 So choosing definitions that allow us to, at  
12 least for research, recognize the disease very  
13 early in its course means that we have a better  
14 chance of reversing that disease when we apply  
15 whatever treatment we're going to.  
16 DR. FREEMAN: Again, to editorialize, I  
17 think that line of thinking, get it early, has been  
18 so prevalent in all of our thinking, not just with  
19 neuropathy but with many diseases. And I took  
20 something else from Teresa's point, and that is  
21 that it may be that a specific drug is not  
22 effective at that early stage of the disease, and

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1 its mechanism will only be effective at a later  
2 stage of the disease.  
3 I had the view that we really do need to  
4 look across various phenotypes. This will come up  
5 during the course of the discussion. But I do have  
6 that concern that we've always focused too early in  
7 the course of the disease and maybe the drug may  
8 not be working at that stage.  
9 DR. SINGLETON: I would disagree with regard  
10 to especially the clinical trials of the late  
11 1990s, early 2000s. Those were studies where we  
12 applied very strict criteria to diabetic neuropathy  
13 to assure that patients had diabetes, and by doing  
14 so, probably chose patients whose disease was too  
15 severe.  
16 DR. FREEMAN: Rodica, and then Gordon, and  
17 then I'm going to ask the panel if they have any  
18 comments, and then we will move on.  
19 DR. POP-BUSUI: First of all, I'd like to  
20 say that I completely agree that we are all here  
21 because whatever we've been doing so far doesn't  
22 really work to advance the field.

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1 I also agree with particularly what you  
2 said, that the only way to move this successfully  
3 forward would be that we all have to look very  
4 objectively at some measures and may need to agree  
5 that whatever we consider that might be what we  
6 like to use may not be the best way to move  
7 forward. I think that's actually a very critical  
8 component of this meeting.  
9 In addition, based on what Dan has said  
10 regarding all these signs and symptoms, if we are  
11 going to use this as a tool to define taxonomy and  
12 diagnostic, we will have to use those databases or  
13 trials where these criteria were most applied in  
14 the most organized fashion. Those are the clinical  
15 trials that looked at diabetic neuropathy because I  
16 completely agree that they are in the community the  
17 way that a particular sign or symptom is being  
18 assessed varies from one provider to another, but  
19 there is a little bit of consistency that that is  
20 in clinical trial.  
21 When I gave the example of the DCCT, I  
22 didn't say that we have to continue to do that, but

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1 that we can use as a tool to define whether our  
2 diagnostic criteria meet sensitivity, specificity,  
3 and all the validity type of thresholds that  
4 Stephen has outlined because we do have resources  
5 that we should use constructively.  
6 We cannot reproduce everything. We are not  
7 going to reproduce another 30 years' trial or study  
8 or epidemiological observation because there is no  
9 time and there are no resources. That's what I  
10 said, and I think it's very important to consider.  
11 DR. FREEMAN: Gordon, and then the panel.  
12 DR. SMITH: I want to reflect on two  
13 different comments. I think the first is Steve's,  
14 and I think our situation is particularly complex  
15 because we're dealing with a phenotypic disorder,  
16 really a syndromic entity that is largely  
17 indistinguishable from other clearly separate  
18 disorders, so HIV neuropathy, chemotherapy-induced  
19 neuropathy, and so forth.  
20 I think it's certainly quite likely that a  
21 patient with type 1 diabetes and neuropathy  
22 phenotypically may look indistinguishable from a

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1 patient with type 2-related diabetic neuropathy,  
2 yet the physiology and mechanism is different. I  
3 think we have multiple different axes of chaos that  
4 we have to deal with, including metabolic pause,  
5 metabolic risk factor, disease stage, diabetes  
6 criteria, phenotypic variability.  
7 To transition, I really loved Dan's comment,  
8 and I'm glad someone's writing it down. I'm not  
9 going to try and restate it, but I completely  
10 agree. To channel my inner Vera Bril -- which is  
11 something I like to do all the time, and I rarely  
12 succeed --  
13 (Laughter.)  
14 DR. SMITH: -- but hopefully, I'll  
15 approximate that now.  
16 I think the signs are not uniformly applied  
17 well, and even if one looks at the way -- like the  
18 MRC scale, it's a terrible scale. How do we assess  
19 vibration?  
20 I think using existing data sets, we're a  
21 hostage of this imprecision that has been talked  
22 about. And I am going to talk a little bit about

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1 Peter's study at the Mayo Clinic, which I think is  
2 instructive in many ways.  
3 DR. FREEMAN: I like the notion of a meeting  
4 in Washington in which the term "axis of chaos" is  
5 used.  
6 (Laughter.)  
7 DR. FREEMAN: -- which is different from  
8 axis of evil, of course.  
9 (Laughter.)  
10 DR. FREEMAN: Anything from the panel?  
11 DR. GIBBONS: Sure. I have been frantically  
12 jotting down lots of thoughts about everybody's  
13 comments, which have been outstanding. I think  
14 we're really getting some juicy bits of things to  
15 work on here as we move forward.  
16 One of the things -- as I was hearing the  
17 comments about how do we decipher and the axis of  
18 chaos, as Gordon and Roy just put, but certainly,  
19 the criteria that we can think about, and we  
20 haven't really discussed, but the definitions  
21 possibly of possible, probable, and definite and  
22 some relation to whether that is clinical research

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1 based or how we loosen or expand our criteria to  
2 include that, particularly as going on to Stephen's  
3 discussion about how we want to frame the core  
4 diagnostic criteria. There is definitely some  
5 flexibility in there.  
6 DR. FREEMAN: Jen, anything to add?  
7 DR. GEWANDTER: Yes, I think a couple of  
8 things as someone who is not a neurologist or even  
9 a clinician listening to you guys talk about this,  
10 I would encourage you to think about the two  
11 different sets of criteria, clinical and research,  
12 and experimenting on how well they mirror each  
13 other for specific items, kind of like what Steve  
14 put up there. Because I think even from my  
15 perspective as a researcher, I might not have  
16 access to a neurologist for my inclusion criteria  
17 for my effectiveness study or my cohort study, and  
18 if there was a good level of reliability between  
19 the two entry criteria, it would be really helpful  
20 for me. Also, when it comes to generalizing the  
21 results of your clinical trials to the real world,  
22 it would be useful top have that. So if there is

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1 time, I think that would be really useful.  
2 Then the other thing, when Roy said to try  
3 to standardize the individual items, some of us  
4 would have to put our feelings aside because there  
5 are so many different measures, I didn't see a lot  
6 of standardization at all in the measures in terms  
7 of the individual items. So I'm not sure that that  
8 necessarily would be a barrier in saying, oh, this  
9 scale doesn't do it right or this scale doesn't do  
10 it right because there wasn't that much  
11 standardization, so maybe that's not as much of a  
12 barrier as you think it might be.  
13 DR. FREEMAN: You'd be surprised.  
14 (Laughter.)  
15 DR. BRUEHL: A couple of points here. With  
16 the reliability issue and the idea that nobody  
17 measures things the same way, something I didn't  
18 mention in giving the presentation about the CRPS  
19 criteria is those were all dichotomous  
20 intentionally because it was our impression from  
21 reading other things that it is much easier to get  
22 two people to agree on presence or absence than it

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1 is to get them to agree on some scaling. So if  
2 you've got a 5-point scale and reliability means  
3 you've got to agree on where on that 5-point scale  
4 they are, that is much harder to achieve than yes  
5 or no, is it abnormal.  
6 Now, that's cheating, honestly. We're  
7 hoping that the error in measurement washes out  
8 across people and we end up with some meaningful  
9 information in that dichotomous decision. But I  
10 would recommend, given the circumstances, you  
11 consider not confining yourself to measures that  
12 are too fine grained where nobody is going to be  
13 able to agree.  
14 Also, the idea of working backwards from  
15 drug targets to come up with criteria, I don't  
16 really see that as backwards because if you think  
17 about it in the bigger picture, these drugs were  
18 developed because they thought they affected a  
19 mechanism that's relevant to the disease. So  
20 really what you're saying is we should be working  
21 from the presumed mechanisms, creating the  
22 criteria, and that's exactly what I'm saying.

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1 If you wanted to look at it like what  
2 mechanisms should we be focusing on, if you wanted  
3 to look at drug targets that are being tested, now,  
4 that might make perfect sense because these  
5 companies have invested a lot of money in trying to  
6 identify meaningful clinical targets that are  
7 modifiable. Maybe not restrict yourself to that,  
8 but that might not be a bad starting point where  
9 you'd want to identify the mechanisms that you  
10 could assess clinical features that might be  
11 reflective of those.  
12 DR. FREEMAN: Thank you, panel. Thank you,  
13 audience.  
14 One of the pleasures of this meeting is that  
15 you don't need to introduce most of the people  
16 because just everybody knows everybody, and the  
17 next talk will be given by Gordon. It will be the  
18 last talk before lunch, and I think this talk is  
19 the critical talk, and there will be a lot after  
20 lunch of similar kind of discussion.  
21 Before doing so, two quick points. One, I  
22 said that if you send out more than three articles,

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1 nobody reads them. Stephen criticized me for not  
2 sending out another article, which I'm sure would  
3 not have been read, either. This is, I think, very  
4 relevant to the discussion we've just had on  
5 reliability and validity, and he's going to email  
6 us or give it to Andrea, who will email us, so that  
7 we are all aware of another article. But this time  
8 I think after this discussion, you really should  
9 read. That's the one point.  
10 The other point is we need to take the  
11 obligatory photograph, and what I'm asking is did  
12 anybody -- this is Washington. It's the nation's  
13 capital. It's the axis of chaos.  
14 Did anybody come here with a good camera?  
15 Yes?  
16 DR. POP-BUSUI: I have a good camera.  
17 DR. FREEMAN: A good camera, great. Because  
18 I was going to ask if not, is there any early  
19 adopter who has an iPhone 10? Yes?  
20 DR. POP-BUSUI: I have the iPhone 10.  
21 DR. FREEMAN: Have both. Whoa! Well, on  
22 that note, let me introduce Gordon.

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1 I think we should have the photograph -- Jim  
2 is leaving. I think we should do it today before  
3 he leaves, and I think before lunch, if you can  
4 hold out, that would be a good time to do it.  
5 Gordon Smith.  
6 Presentation – Gordon Smith  
7 DR. SMITH: I sure wish that I had listened  
8 to this morning's discussion before making my  
9 slides. I'm not going to have a taxonomy at the  
10 end, I'm afraid, but rather what I hope to do is go  
11 through the taxonomic process, as it were, and  
12 bring up issues for discussion.  
13 It's actually nice having had this  
14 discussion that we just went through before the  
15 slides because many of these themes are woven in  
16 the slides. I really hope that what I'm going to  
17 show you will really serve as more fuel for that  
18 discussion.  
19 We've already gone through that, so I'll  
20 stop. I think the one issue that's already brought  
21 up, of course, is that diabetic neuropathy isn't a  
22 single syndromic entity. We have multiple

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1 different forms of neuropathy. This is a nice  
2 figure from an article that Amanda wrote on painful  
3 neuropathy in BMJ, which is really fantastic. I'm  
4 sure she hand-drew this.  
5 We're going to be talking about many of  
6 these over the course of the day. I think the  
7 distal symmetric polyneuropathy is really in many  
8 ways the most challenging for reasons that I  
9 brought up in my last comment.  
10 I think there are also issues in terms of  
11 core principles of what diagnostic criteria ought  
12 to look like, and I think it's worth going through  
13 these. Many of them were highlighted this morning,  
14 but ideally, the taxonomic criteria we come up for  
15 polyneuropathy and the other entities ought to be  
16 respectful of these attributes, so biologically  
17 plausible, exhausted in that the system should  
18 encompass but yet still be distinct, mutually  
19 exclusive. We've talked about reliability a lot in  
20 the discussion, and I'm going to show you some of  
21 the data that Vera was speaking of.  
22 I think clinically useful is really

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1 important. This is abuts against the challenges in  
2 the neurological examination, and Roy referred to a  
3 meeting we had about CIPN earlier this year. If we  
4 struggle with this, I think it's right up in front  
5 of the challenges in creating a taxonomy, if you  
6 will, for CIPN where oncologists are not as  
7 comfortable with neurological examination skills as  
8 are our endocrinology colleagues. Then simplicity  
9 is an issue. I'm going to bring my own perspective  
10 on this in a moment.  
11 Of course, the first issue that Amanda  
12 brought up, even before we talk about the taxonomy  
13 of neuropathy is the taxonomy of diabetes. I feel  
14 embarrassed showing this slide with a bunch of  
15 endocrinologists in the room, but we need to  
16 decide, is type 1 diabetes neuropathy different  
17 from type 2.  
18 Below are the criteria for pre-diabetes as well as  
19 diabetes.  
20 So we have these two competing questions or  
21 not two competing questions but issues we need to  
22 deal with. And what I thought I would do is work

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1 through the first, which is type 1 versus type 2.  
2 Now, we say or at least neurologists will  
3 typically say, well, trials should only enroll  
4 patients with type 1 or type 2. This just shows  
5 recent neuropathic pain trials in diabetic  
6 neuropathy, and you can see more of our recent  
7 trials include patients with type 1 and type 2  
8 diabetes. You may say, well, that's just  
9 neuropathic pain, but many of the disease-altering  
10 trials we're participating in now and have in  
11 recent years, and one that I'm in the process of  
12 planning includes type 1 and type 2 at the  
13 insistence not only of the company but one of their  
14 very well known external advisors. So I don't  
15 think it is all established out in the real world  
16 that trials should include only type 1 versus type  
17 2.  
18 What are the reasons that these might be  
19 separate entities? This is a really nice figure  
20 from Rodica's article that's been referenced a  
21 number of times this morning that points out that  
22 there are different inputs into the mechanistic

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1 pathways. These may converge on issues such as  
2 mitochondrial dysfunction or other final common  
3 pathways, but there are obviously different points  
4 of entry with insulin resistance and dyslipidemia  
5 as opposed to reduced insulin and C peptide and so  
6 forth.  
7 I just made sure I had pictures from  
8 everyone's articles.  
9 (Laughter.)  
10 DR. SMITH: Another way of thinking of this  
11 is more mechanistic from a really great article  
12 that Eva wrote for Neuron, which highlights that  
13 these different front-end entry point mechanisms  
14 can field down to a final common pathway and what  
15 may look syndromically clinically similar.  
16 I think other data that these are separate  
17 disorders, of course, comes from the response to  
18 therapy, and this is, of course, one of the first  
19 vials of insulin from Banting and Best at the  
20 University of Toronto. We've known since the DCCT  
21 that aggressive glycemic control is effective for  
22 mitigating type 1 diabetes-related neuropathy.

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1 This just summarizes the data you already  
2 know. If you just look at the intensive versus  
3 conventional, and these are the percent at closeout  
4 and at year 13 and 14 of EDIC of these various  
5 criteria. I don't need to walk you through the  
6 data about this.  
7 This is a figure from EDIC up to year 8,  
8 which not only highlights the difference at entry,  
9 but this concept of metabolic memory. So very  
10 clearly, aggressive glycemic control is impactful  
11 in type 1 diabetes.  
12 What about type 2 diabetes? This is data  
13 from the UKPDS cross-sectional data that shows a  
14 relationship with A1C and hazard ratio for various  
15 outcomes. The relationship between A1C and  
16 amputation or death, overall microvascular  
17 endpoints, cataracts, so forth, is impressive.  
18 But what about treatment of hyperglycemia?  
19 The story is not the same. So this is data from  
20 the ACCORD study and shows the hazard ratios  
21 favoring intensive control versus standard control.  
22 And you can see in some diabetic endpoints, there

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1 is a significant difference, particularly in renal  
2 function. But if we look at the neuropathic  
3 endpoints in ACCORD, you'll see that for neuropathy  
4 defined by MNSI, loss of vibration, loss of ankle  
5 jerks, there was no significant risk reduction.  
6 There was a slight benefit in regards to loss of  
7 sensation to light touch, and even though this  
8 barely reached statistical significance, you can  
9 see the hazard ratio is not all that reduced.  
10 This actually mirrors other studies, so I  
11 think in what must have been a Herculean effort,  
12 Brian did a very nice Cochrane review in this. And  
13 he's having PTSD from his Cochrane review, so give  
14 him a drink of water, Eva.  
15 (Laughter.)  
16 DR. SMITH: These show the forest plots for  
17 type 1 and type 2. They look deceptively close  
18 just because of how they're constructed, but if you  
19 look at the hazard ratios here, or the risk ratios,  
20 for type 1 versus type 2, dramatically different.  
21 So clearly, these disorders respond differently to  
22 moderation of one of the main inputs to diabetic

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1 neuropathy.  
2 It may be that this is because of either  
3 different mechanisms or differential prevalence of  
4 risk factors in obesity and dyslipidemia. These  
5 are data from the Utah diabetic neuropathy study,  
6 so this is a population of a couple hundred  
7 diabetics where we looked at the risk ratio of  
8 having neuropathy if one had these various  
9 endpoints. You can see obesity and dyslipidemia or  
10 the aggregated metabolic syndrome conferred a  
11 twofold risk in this cross-sectional study. If one  
12 looks only at very well controlled diabetics, the  
13 risk ratios become even higher.  
14 So I'm not necessarily saying that type 1  
15 and type 2 diabetes are definitely different,  
16 although I suspect that they are, but it's very  
17 clear that these metabolic risk factors that are  
18 important are very different in these populations  
19 and therefore, something to be mindful of.  
20 Then there's the whole issue of pre-  
21 diabetes, which I'm going to unabashedly punt to  
22 Rob later on, and I know he's going to solve all of

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1 this for you. But this is data just from Dan's  
2 cohort study showing that in patients who are  
3 phenotyped based on glycemic status, that there is  
4 an increasing prevalence of neuropathy as one moves  
5 through increasing degrees of glucose dysregulation  
6 and that the phenotype is really disproportionately  
7 a painful neuropathy; and again, highlights the  
8 importance of these other metabolic risk factors.  
9 And I'm going to touch on this issue a few more  
10 times but not really dig into it because I don't  
11 want to steal Rob's thunder.  
12 This slide is actually timely because of  
13 Steve's construct here because it's likely that  
14 these different metabolic inputs into the  
15 neuropathy pathogenetic cascade, if you will,  
16 impact our endpoints differently.  
17 This is data from the same cohort I  
18 described earlier, and just to walk you through it,  
19 this shows the relationship between different  
20 biomarkers, skin biopsy, sural sensory amplitude,  
21 and motor conduction velocity, and BMI and  
22 hemoglobin A1C.

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1 So you can see, for instance, that peroneal  
2 motor conduction velocity is not at all related in  
3 this cohort to BMI, but there is a relationship to  
4 A1C, whereas if we go up to a structural small  
5 fiber axonal metric, epidermal nerve fiber density,  
6 it's the opposite. There's no relationship with  
7 A1C, but there is with BMI. And interestingly,  
8 with sural sensory amplitude, it really correlates  
9 with both.  
10 So this suggests that our endpoints may be  
11 related to different metabolic attributes of the  
12 disorder. This, I think, does touch on the  
13 diagnostic framework, and in particular, how we  
14 might rely on these different biomarkers within our  
15 criteria for diagnosis. And it clearly has impact  
16 on our choice of endpoints in clinical trials going  
17 forward.  
18 To answer these two questions, I'm punting  
19 to Rob a little bit, although I have teed it up a  
20 bit, but we have really high expectations for your  
21 talk. But I would posit that at this point, type 1  
22 and type 2 diabetes really are and for our

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1 taxonomic endeavor today need to be viewed as  
2 different disorders.  
3 I suppose one might view this differently in  
4 regard to the taxonomy of painful diabetic  
5 neuropathy, which we could talk about. As I'll  
6 allude to, there's a separate taxonomic, or Roy  
7 mentioned, process going on for painful  
8 neuropathies that is addressing this issue.  
9 Of course, the main taxonomic challenge we  
10 have -- now we've got the easy stuff, I think, out  
11 of the way -- are the core criteria for diabetic  
12 peripheral neuropathy. And one that again, I'm  
13 going to touch one now and again, particularly at  
14 the end, is, is painful diabetic neuropathy really  
15 a syndromically different entity? Is that separate  
16 in our taxonomy? Is it a subtype? What diagnostic  
17 criteria should we use? We've talked already about  
18 structured signs and symptoms and then the  
19 electrophysiologic aspects of this.  
20 I really do think, all joking aside, we have  
21 multiple different axes that we need to consider.  
22 We've talked already about the metabolic axes that

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1 not only includes the role of obesity and other  
2 metabolic issues, but it touches on the criteria  
3 for diabetes, which I expect will evolve over time.  
4 Then we've got these other axes we need to think  
5 about.  
6 I want to just summarize this study that I  
7 think most of you are familiar with it, that Vera  
8 brought up. I think it's really critical, so I'm  
9 just going to go through this. I think many of you  
10 were smart enough not to come to this, but I was.  
11 I looked younger then because I was.  
12 (Laughter.)  
13 DR. SMITH: The concept, which was, I think,  
14 really prescient and really brilliant on Peter's  
15 part, was to bring experts and to do sequential  
16 examination on patients that it turned out were  
17 randomly selected from the Rochester diabetic  
18 neuropathy cohort. After the first day, I went to  
19 Peter and I said, "You did a fantastic job of  
20 selecting these patients because it was really  
21 tough." And he said, "I didn't select them at all.  
22 It was just a subset of our cohort." And I think

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1 that tells you one thing.  
2 So what we did was examine them in the  
3 Kahler Hotel the first day. They were disguised  
4 and had microphones, and we had headphones that  
5 plug in that would distort their voice. So while  
6 there were some people you could kind of identify  
7 the next day when we reexamined them in their  
8 street clothes without voice distortion, it was  
9 quite difficult, so this worked.  
10 The first day, we saw each one of these  
11 individuals, and I merely had to say did they have  
12 signs and symptoms of neuropathy. We used whatever  
13 rules we wanted to have. I'll tell you what I did  
14 in a moment.  
15 Then the next day, we came back and did the  
16 same thing. I remember having a lovely steak  
17 dinner with James at Michael's, which I'm told is  
18 no longer there, so I'm glad I got it back then.  
19 It was a lovely meal. We were very happy. We  
20 thought we had done a good job, but when the data  
21 were released, they were really dreadful.  
22 So over there shows the number of times the

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1 12 experts got the right answer, and I don't even  
2 think it's the right answer. It's the number of  
3 times we agreed with Peter's answer, which as I  
4 recall, was really based on electrophysiologic  
5 criteria, I think some seven or something. But it  
6 doesn't matter, right?  
7 You can see that one of us thought 20 of  
8 them --  
9 DR. DYCK: NIS also.  
10 DR. SMITH: It was NIS plus seven.  
11 DR. DYCK: I think it was both as exam --  
12 DR. SMITH: Okay. And it almost doesn't  
13 matter. That probably explains why some of us  
14 thought lots of them had neuropathy and some of us  
15 thought very few had neuropathy. But the fact is  
16 we were all over the board as experts, which is the  
17 point that Vera brought up and Dan brought up much  
18 more eloquently than I can.  
19 If one looks at the kappa statistic, which  
20 Steve talked about, with intra-rater reliability,  
21 so the test/retest reproducibility, there was  
22 several of us that didn't even have a significant

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1 kappa statistic. So we didn't agree with each  
2 other, and a quarter of us were irreproducible day  
3 to day. So this was alarming.  
4 I don't know who I am, but I think I'm one  
5 of these two because the way I approached this, I  
6 thought this was going to be easy. I just used the  
7 UENS because we use it all the time. I know the  
8 cutoff value, and I'll show you the ROC curve for  
9 the UENS. I'm not saying the UENS is right or  
10 wrong. I just used the same way of doing it, which  
11 meant I over-diagnosed relative to the NIS plus 7,  
12 but I was reproducible.  
13 There were people there with their  
14 monofilaments and everything. I'll tell you the  
15 end of this story a little later on, but I think  
16 this highlights the need for what we're doing right  
17 now, because as experts, if we can't look at a  
18 cohort of 20-some patients and come to some  
19 agreement left to our own devices, then we need  
20 taxonomic intervention, as it were.  
21 What are the criteria that are existing? So  
22 the first set to talk about are the old San Antonio

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1 criteria, which were published in 1988. These  
2 capture, I think, some of the challenges over time.  
3 First of all, the concept was that they should  
4 include a validated questionnaire, interview  
5 technique and examination with two classes, no  
6 signs or symptoms or signs and/or symptoms.  
7 Without getting into it, you can see that  
8 these include electrodiagnostic autonomic  
9 functioning and QST data. You can just look at  
10 this from afar and realize that this is going to be  
11 extremely difficult to deploy clinically, and we're  
12 certainly not going to get people in primary care  
13 environments to use these criteria.  
14 Another attempt was made by a consensus from  
15 the AAN, and John England was first author on it  
16 and published in 2005. I think there's some  
17 concepts in here that are important to highlight.  
18 So the first concept was that -- and this was based  
19 on a literature review, so they were somewhat  
20 hostage to what had been published. But that  
21 electrodiagnostic studies were considered an  
22 objective outcome, symptoms have poor accuracy,

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1 signs are better, and that ideally, patients should  
2 have combinations of symptoms, signs, and  
3 electrodiagnostic studies.  
4 They created a rank order of certainty,  
5 essentially, that discordant signs and nerve  
6 conduction studies would be the lowest threshold  
7 for possible neuropathy. The highest would be  
8 multiple symptoms, multiple signs, and abnormal  
9 nerve conduction studies. So it makes conceptual  
10 sense. It really isn't a criterion in the  
11 taxonomic sense that we're dealing with today.  
12 I think some of their conclusions are really  
13 driven by the Rochester diabetic neuropathy study,  
14 which, of course, is incredibly important, and was  
15 founded in a population-based survey in Olmsted  
16 County starting in '86 where they examined the  
17 patients in Olmsted County that had diabetes. Now,  
18 two-thirds of these patients had some evidence of  
19 neuropathy, but only 13 percent had symptoms of  
20 neuropathy, and only 10 percent had neuropathy  
21 based on the NSS.  
22 There's some quotes, I think, that actually

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1 I pulled out are the foundation for the England  
2 paper. One is "because symptoms are not constant  
3 but tend to come and go, for purposes of following  
4 course, it's useful to have an overall measurement  
5 of severity excluding symptoms and that the  
6 frequency of abnormality was higher for attributes  
7 of nerve conduction than for individual clinical  
8 abnormalities."  
9 This concept that nerve conduction studies are  
10 important and signs trump symptoms, and therefore,  
11 the gold standard was the NIS-LL plus 7, which is,  
12 as you know, a composite score.  
13 The most recent criteria from which we've  
14 been working on that I actually think work pretty  
15 well that Solomon authored from our meeting that  
16 Vera was kind enough to host in 2009, the Toronto  
17 criteria. This paper and that meeting categorized  
18 neuropathies into typical, length-dependent,  
19 distal, symmetric, polyneuropathy, and atypical  
20 neuropathy.  
21 I will say that some people have said that  
22 painful neuropathy is atypical in the literature,

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1 which I find a little surprising because that's  
2 certainly clinically the most common scenario I  
3 deal with. In my practice, that's certainly not  
4 atypical.  
5 These are the criteria which makes --  
6 DR. DYCK: Which is not surprising because  
7 patients with numb feet aren't going to go to  
8 doctors.  
9 DR. SMITH: Right, they're --  
10 DR. DYCK: Patients with painful feet will  
11 go to doctors. So if you're calling typical versus  
12 atypical percentage of a community cohort who have  
13 signs of neuropathy, typical neuropathy would be  
14 painless, numbness, whereas if you're going to  
15 review patients who are going to come to doctors,  
16 they're going to be painful.  
17 DR. SMITH: I would say that's not typical,  
18 that it's a matter of prevalence.  
19 DR. DYCK: Or atypical --  
20 DR. SMITH: Yes. I'm more or less -- I  
21 don't like the term "atypical" in this context.  
22 DR. DYCK: I don't either actually, but I

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1 think it makes sense.  
2 DR. SMITH: No, no. That's, I think, the  
3 foundation for the way that term is being used.  
4 Here are the criteria, and then again,  
5 you're all familiar with. These are basically  
6 England-like in that they start with possible and  
7 go into probable and then confirm. So possible are  
8 symptoms or signs. Probable symptoms and signs  
9 that include two or more -- sorry for the  
10 "or" -- of the following, so "Symptoms, decreased  
11 sensation, or abnormal deep tendon reflexes."  
12 This, I think, probably makes Steve feel  
13 pretty good that we can operationalize this. And  
14 then confirmed requires the presence of a  
15 confirmatory test. So nerve conduction studies are  
16 a validated measure of small fiber function.  
17 The first problem, just to echo Dan, is that  
18 I don't think -- and I think Peter's study clearly  
19 showed it -- even amongst ourselves, we probably  
20 aren't very good at our reproducibility for  
21 individual exam metrics, and clearly, putting a  
22 reflex hammer in an endocrinologist's office and

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1 expecting reproducibility -- and this is no way an  
2 indictment of endocrinologists -- is just not going  
3 to work particularly well. So we need to think  
4 through these issues. I think neurologists have a  
5 hard time with that.

6 What about painful neuropathy? So the  
7 Toronto criteria really adopted the ISP definition  
8 of neuropathic pain with distal, symmetrical,  
9 nocturnal exacerbations, these characteristics and  
10 the following nested criteria.

11 DR. PELTIER: Gordon, can I make one  
12 interjection?

13 DR. SMITH: Yes.

14 DR. PELTIER: One of the issues also that  
15 comes up is -- and I think Peter or Jim, I forget  
16 which of you, published -- was that nerve  
17 conduction studies are not actually terribly  
18 reliable either. So people are better as far as  
19 within themselves, but if you compare one  
20 electrophysiologist to another, we're absolutely  
21 horrid at that, also, so looking at reliable  
22 confirmatory tests is also an issue.

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1 DR. SMITH: I'm going to touch on nerve  
2 conduction studies in some length, not the  
3 reproducibility, but just to comment on that, I  
4 think reproducibility in nerve conduction studies,  
5 particularly for a clinical trial and by extension  
6 for diagnostic purposes, really requires a great  
7 deal of attention. One can do it in a clinical  
8 trial. It's just quite challenging.

9 The idea that we're going to reliably deploy  
10 nerve conduction studies in a community practice to  
11 diagnose neuropathy, I think we're going to run  
12 into even bigger problems than we are relying on a  
13 reflex hammer.

14 I'm trying to think of an MRI joke I can use  
15 to get Brian --  
16 (Laughter.)

17 DR. SMITH: In any case, I think there are  
18 several assumptions that I've alluded to in our  
19 existing criteria. I think the first is that signs  
20 are more reliable than symptoms, and I think this  
21 is a feature of what Jim talked about in terms of  
22 the typical phenotypic spectrum of free-range

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1 diabetic neuropathy patients where many of them are  
2 minimally or asymptomatic and therefore, signs by  
3 default are going to be the main metric we use.

4 On the other hand, patients who have painful  
5 neuropathy, small fiber neuropathy, will be lost  
6 using an over-reliance on signs. It's in some  
7 ways, the flip of what Steve was talking about in  
8 terms of complex regional pain syndrome.

9 There is this concept that nerve conduction  
10 studies are a very early, usually preclinical and  
11 core feature, which we'll explore in a moment, and  
12 that we talked a little bit about this painful  
13 neuropathy. I think this touches on the issue of  
14 whether painful neuropathy deserves its own  
15 diagnostic category or is it a subtype of distal  
16 symmetric polyneuropathy.

17 DR. TESFAYE: I think the painful neuropathy  
18 in the Toronto consensus is actually typical,  
19 typical. Atypical is the acute painful neuropathy.  
20 Actually, the painful neuropathy that occurs in the  
21 distal symmetric chronic varieties is typical  
22 neuropathy.

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1 DR. SMITH: You're right. So I think the  
2 way the Toronto paper reads is there's DSP, there's  
3 painful, and then there are atypical neuropathies.  
4 But I think what's happened is the term "typical"  
5 and "atypical" has leaked out into the literature  
6 in different ways and is interpreted differently.

7 To go to Amanda's point on nerve conduction  
8 studies, what are the data about diagnostic utility  
9 of nerve conduction studies and skin biopsy? So  
10 nerve conduction studies are abnormal at about  
11 70 percent of patients, all comers with neuropathy,  
12 looking across multiple studies, not just diabetic  
13 neuropathy. Although they're frequently normal,  
14 maybe 40 percent, maybe even more in patients who  
15 have primarily small fiber burning feet.

16 Unfortunately, we don't really have good  
17 specificity data on nerve conduction studies. I'm  
18 going to show you some in a moment.

19 For skin biopsy, we have pretty good  
20 sensitivity and specificity data that are 70 to  
21 80 percent, but there is an issue regarding  
22 diabetes. And this is also true with nerve

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1 conduction studies where patients with diabetes who  
2 have no clinical features of neuropathy, signs or  
3 symptoms, have reduced intra-epidermal nerve fiber  
4 density.  
5 Is that nascent neuropathy? Is that  
6 laboratory neuropathy, or does that mean there's  
7 something else going on? I think it's unclear.  
8 And regardless of that, where we are now, it raises  
9 issues in terms of using tests like skin biopsy as  
10 part of our core diagnostic criteria.  
11 These are data looking -- I'm going to show  
12 you two different sets of data that more or less  
13 show the same thing, and then I'm going to do a  
14 little bit of Bayesian gymnastics with it.  
15 These data come from several pooled cohorts  
16 from cross-sectional and natural history studies  
17 that we've done in Utah. This is probably like 500  
18 patients with diabetes. It's skewed towards early  
19 neuropathy, and it shows the ROC curves for sural  
20 amplitude, peroneal motor conduction velocity, and  
21 skin biopsy with two gold standards. One is the  
22 combination of signs and symptoms, and the other is

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1 the signs, symptoms, and a confirmatory test that  
2 couldn't be the test being evaluated, so keep that  
3 in mind.  
4 For instance, for a positive diagnosis of  
5 neuropathy using sural amplitude, it would require  
6 one of the others to be abnormal. But they look  
7 similar, and you can see the areas under the curve  
8 are okay but really not that great. These are the  
9 sensitivity and specificity data, which don't look  
10 too bad, over here 70 and 76 percent.  
11 Apropos of what I think we've been talking  
12 about earlier, the positive predictive values are  
13 dreadful, but the negative predictive values are  
14 quite good. So from a framework perspective, these  
15 are usually used as inclusion criteria.  
16 This is sort of a tomato/tomahto [ph] thing,  
17 but one probably ought to think of nerve conduction  
18 studies if one were to use them in enrollment  
19 criteria as an exclusion. If it's normal, the  
20 likelihood of you having neuropathy just dropped a  
21 great deal.  
22 This sounds great so far if we deploy it

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1 that way, but I'll get to the problem in a moment.  
2 This shows data from another cohort of about 150  
3 people, I think, in this. These patients are  
4 categorized -- our gold standard of neuropathy is  
5 really based on signs or symptoms in a clinical  
6 evaluation by a neurologist. It's more  
7 qualitative.  
8 Not surprisingly, the UENS and a symptom  
9 scale, the NTSS6, perform extremely well in that  
10 environment because we're using a purely  
11 clinically-based diagnostic criteria. But if we  
12 look at sural amplitude, peroneal motor amplitude,  
13 or conduction velocity, skin biopsy, and CCM  
14 metrics, you can see they generally don't perform  
15 particularly well, although sural amplitude  
16 performs actually best. I don't have predictive  
17 values, but I think it would look pretty similar to  
18 what we saw with the other data.  
19 I think the point I want to bring up,  
20 though, has to do with something that Steve raised,  
21 which is the issue of pretest probability. So if  
22 we're going to use nerve conduction studies to

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1 exclude people who don't have neuropathy, we need  
2 to really think about the impact of the pretest  
3 probability of neuropathy in the group we're  
4 screening and the impact that has on the negative  
5 and positive predictive values.  
6 We modeled this using the sensitivity and  
7 specificity data, and to walk you through it, this  
8 shows the negative predictive value of sural  
9 sensory amplitude. Let's just say 6 has a cutoff  
10 with different pretest probabilities. So the  
11 pretest probability in our cohort was 18 percent  
12 had a neuropathy, and you can see the negative  
13 predictive value was about 90 percent.  
14 Here's what happens if 50 percent were to  
15 have neuropathy, and I would posit in the patients  
16 we're screening for a clinical trial, the pretest  
17 probability that they're going to have neuropathy  
18 is going to be a lot higher. So the diagnostic  
19 performance of these in an enrollment criteria  
20 setting or diagnostic setting even is going to be  
21 quite different, which is why I don't feel so bad  
22 about these data because in clinic, it's probably a

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1 lower pretest probability.  
2 This shows it in tabular form. So I think  
3 this is something that, David, you wrote something  
4 awhile ago on this way of thinking in carpal tunnel  
5 syndrome, if I recall correctly.  
6 I think we need to be mindful of it. We  
7 can't just slavishly use our standard cutoffs in  
8 clinical trial enrollment criteria without at least  
9 thinking through this concept.  
10 There was a remedial trip to Rochester,  
11 Minnesota. As I recall, a year later, we came  
12 back, and there was a really big snowstorm. The  
13 Mayo Clinic actually was amazing. They sent people  
14 out to bring these patients back again, and we did  
15 the same study one more time with one difference.  
16 We met the night before and had a discussion about  
17 how we were going to judge whether or not the  
18 people had neuropathy.  
19 We weren't given a set of criteria, but the  
20 concept was that we were only going to capture  
21 unequivocal evidence of neuropathy. There was some  
22 specific discussion about how to factor in age in

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1 relation to ankle jerks and vibration assessment.  
2 That conversation, which wasn't very long, and I've  
3 got some lovely pictures of people like Peter  
4 showing us how to check ankle reflexes on people  
5 using one of the Mayo examination tables, we did  
6 much better. In fact, these statistics all  
7 improved dramatically, which is, I suppose, good  
8 news in that it took relatively little intervention  
9 to bring us along, but it still feels sort of  
10 MacGyver'ed to me that we scotched taped this thing  
11 together with agreeing on unequivocal.  
12 Then, of course, the issue that Rob brings  
13 up I think is important because this may not  
14 capture patients who have earlier or milder  
15 neuropathy, so keep in mind that issue.  
16 In terms of the core diagnostic criteria,  
17 painful DPN, there is another ACTTION paper in  
18 process that is delayed by a particularly slow  
19 co-author, I'm told, to remain nameless.  
20 (Laughter.)  
21 DR. SMITH: That will be coming up very soon  
22 after this meeting, I think.

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1 DR. FREEMAN: Just to let you know, the  
2 aspects of that paper are --  
3 DR. SMITH: But the author will catch up.  
4 I think as a general construct, the Toronto  
5 criteria work very well, and I think they have  
6 attributes that we'll be able to pull out in  
7 service of a taxonomic scheme at the end of this  
8 meeting.  
9 I do have concern about using a structured  
10 specific instrument as part of these criteria for  
11 reasons that have been brought up, but I think the  
12 individual components make sense.  
13 I have a lot of concern about how we deploy  
14 nerve conduction studies and skin biopsy. I didn't  
15 show skin biopsy data. It looks the same as nerve  
16 conduction data, the same issue as very poor  
17 positive predictive value, very good negative  
18 predictive value. Looks very similar.  
19 So I think there are real concerns about how  
20 we do this, and I'm sure we're going to have a  
21 robust discussion about it. I'm not going to get  
22 into that now.

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1 The other issue that I haven't talked about  
2 is dealing with other causes of neuropathy. This  
3 is one of the other axes we need to think about.  
4 It's very common for patients who have diabetes and  
5 neuropathy to have other common risk determinants,  
6 so alcohol use, for instance, or other issues. So  
7 it is likely that we're going to need to include  
8 not only the safety clause that Steve advised us to  
9 use, we may want to have a little more specific  
10 safety clause in reference to that. I'm not really  
11 talking about that at all.  
12 I think the other issue, of course, we have  
13 to deal with is the prevalence of idiopathic  
14 neuropathy, which is quite high, phenotypically  
15 looks like diabetic neuropathy. This starts to  
16 abut against Rob's definitive talk coming up later  
17 today, and it's going to answer that for us.  
18 What about lifespan issues? I think this  
19 goes to subcategories of neuropathy. Jim already  
20 brought this up. Most patients who have neuropathy  
21 have a relatively painless neuropathy. Now, we  
22 have in our mind that this may occur later in the

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1 course with years of hyperglycemia and may have  
2 more motor conduction velocity abnormalities,  
3 whereas earlier, we see painful neuropathy due to  
4 small fiber involvement. Then there's asymptomatic  
5 neuropathy, so this concept of abnormal nerve  
6 conduction studies or abnormal skin biopsy.  
7 There's another I'll get to in a second.  
8 Now, I'm going to challenge that a little  
9 bit as we go along, and I think we have a bit of  
10 anchoring bias in this scheme that I think we  
11 really need to take a close look at.  
12 Then in terms of painful neuropathy and core  
13 clinical features, there are a variety of different  
14 symptoms our patients have, and I think part of the  
15 challenge in defining painful neuropathy is many  
16 patients who don't have painful neuropathy, yet  
17 have symptomatic neuropathy have milder versions of  
18 this that they don't self-describe as pain. You  
19 can look across these, and they'll all be familiar.  
20 There are, of course, significant comorbid  
21 conditions which touch on Dimensions 3, 4, and 5,  
22 including depression and anxiety, sleep

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1 disturbance. I'll get to those in a moment because  
2 they're not only important in our full framework,  
3 but they probably have impact certainly on how we  
4 design clinical trials.  
5 This is a screening tool slide similar to  
6 the one that Jennifer and Chris put together  
7 showing the frequency with which various positive  
8 neuropathic symptoms show up in commonly used  
9 neuropathic instruments. The gray boxes show when  
10 they're used in more than three instruments, and  
11 the lighter gray, two.  
12 I bring this up in part just to emphasize  
13 the challenge in reading the literature because  
14 we're hostage to the instruments that had been used  
15 in earlier studies. I think this is an issue that  
16 supports Dan's contention that I think we need to  
17 take a fresh look at this, and I think it's  
18 probably true in symptoms. I think it would be  
19 very interesting to know in an authentic starting  
20 from scratch approach, what are the distribution of  
21 symptoms, the frequency of symptoms, do they differ  
22 between type 1 and type 2 and other forms of

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1 neuropathy.  
2 The other concept that was implied in a  
3 couple of slides ago is that early neuropathy is  
4 painful and later neuropathy is more large fiber,  
5 loss of protective sensation, foot ulceration.  
6 Clearly, foot ulceration and amputation, which I'm  
7 not going to talk much about because it's such a  
8 distal endpoint, it's clearly related to  
9 longstanding disease.  
10 I think the question is this shift, as I'll  
11 show in the next slide, from early small fiber,  
12 later large fiber, something we need to think  
13 about. One of the reasons I think we have this in  
14 our mind is that 10 or 20 percent of patients who  
15 have diabetes have evidence of neuropathy at  
16 diagnosis, and then there's a whole separate  
17 narrative around pre-diabetes.  
18 I think what tends to happen is this idea  
19 that we lay on our clinical experience as an  
20 anchoring bias of thinking of this. So the idea is  
21 that type 1 diabetes, which I think has informed  
22 historically some of our concepts of neuropathy,

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1 natural history, and risk, obviously related to  
2 hyperglycemia, gets worse and more prevalent over  
3 time, and it involves mainly large myelinated  
4 axons, which also happens in type 2 diabetes. But  
5 there's this separate issue of metabolic syndrome  
6 and obesity, which we think may cause more small  
7 fiber injury, therefore, earlier pain. These kind  
8 of merge together to make type 2 diabetes look  
9 somewhat different than type 1 with earlier small  
10 fiber involvement in pain, later more large fiber  
11 involvement, and ultimately, risk of painless  
12 injury, foot amputation, and so forth.  
13 This makes some sense, but it's anchored in  
14 our clinical experience, as Jim pointed out.  
15 Patients who don't have neuropathic pain generally  
16 don't come to see a neurologist and say I'm worried  
17 that I have asymptomatic neuropathy. So I think we  
18 need to really think about this in a fresh way.  
19 I'm not sure it's really true, but there are  
20 reasons to think that aspects of it might be.  
21 I did want to talk a little bit about the  
22 physiology of these different fiber classes. Large

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1 myelinated axons -- this is Theodor  
2 Schwann -- obviously, have fast conduction  
3 velocity, but they are also relatively protected  
4 from the environment by their myelination. Yet  
5 when injured, it's difficult for them to regenerate  
6 for fairly obvious reasons whereas unmyelinated  
7 axons -- this is a picture of Robert Remak -- seem  
8 to be particular susceptible to injury, yet they're  
9 uniquely capable of regenerating.

10 Ahmet brought up the question this morning  
11 of the natural history of epidermal nerve fiber  
12 density in early diabetic neuropathy, and several  
13 groups have found that there's a decline in  
14 epidermal nerve fiber density in early neuropathy.  
15 Our work and others suggest that interventions can  
16 actually provoke improvement, stabilization, and  
17 this biomarker.

18 This also, I think, serves as part of our  
19 anchoring bias for the concept I showed in the  
20 earlier slide. It certainly has implications for  
21 the endpoint measures or the biomarkers we might  
22 use in clinical trials, but it has mixed

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1 implications for how we might deploy skin biopsy,  
2 for instance, which we're never going to do, but  
3 were we to in diagnostic framework. CCM is  
4 actually much more conceivable at least from a  
5 patient compliance and tolerance perspective that  
6 we might do that, yet the equipment is expensive  
7 and so forth.

8 I think there's data to suggest that this  
9 whole framework I've given you is perhaps not true.  
10 This is a recent study looking at sensory  
11 phenotypes and risk of neuropathy. If the  
12 framework I gave you was true, we would expect that  
13 there would be a disconnect between objective  
14 severity of neuropathy and the presence and  
15 severity of neuropathic pain.

16 It turns out that there are multiple studies  
17 suggesting that's not the case. So this shows in a  
18 very nice paper that just came out earlier this  
19 year, this is the modified Toronto scale looking at  
20 no neuropathic pain, mild, and severe. There are  
21 other studies that show this, that as we look at  
22 patients with diabetic neuropathy when they have

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1 more pain, they have more severe neuropathy.  
2 Again, we have our preconceived notions, and  
3 in the past, I think we've tended to argue back and  
4 forth about this. But I think these data make me  
5 really want to understand for certain what the  
6 natural history of this is. Clearly, the  
7 implication is the patient who has painful  
8 neuropathy or neuropathy that's not painful but has  
9 dominant positive sensory symptoms, is that a  
10 different disorder from the silent majority that  
11 Jim talks about of painless diabetic neuropathy?  
12 Are those different? Are they subtypes?

13 I'm not going to get into that right now,  
14 but it's something that we need to hash out in our  
15 discussions. I'm going to skip over that in the  
16 interest of time.

17 Epidemiology -- I don't want to skip back  
18 over that because I think it's really neat. The  
19 concept here is that what may be determining pain  
20 is less axonal loss but axonal regeneration. This  
21 is, I think, work from Dan's group, that looked at  
22 GAP 43 staining and in skin biopsies and showed

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1 that essentially patients who have a higher  
2 percentage of epidermal axons in a regenerative  
3 phenotype have more neuropathic pain.

4 We found something quite similar in  
5 collaboration with Eva's group a number of years  
6 ago. So I think there are other reasons to think  
7 about or other ways of thinking about neuropathic  
8 pain.

9 I wanted a slide that color, and that was  
10 just to show Doug that we do a little bit of  
11 discovery science in what we do.

12 The epidemiology is something that I don't  
13 need to emphasize too much to you. This is a  
14 worldwide epidemic. Over 8 percent of Americans  
15 and Europeans, yada, yada, yada; you know all of  
16 that.

17 I did want to show this because diabetic  
18 neuropathy is a global health problem, and this  
19 shows the prevalence of diabetes in 13, projected  
20 in 35. It shows the growth by region, and this  
21 displays that visually.

22 The reason I show this is if you think it's

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1 challenging to get primary care doctors in the UK  
2 or in the United States to use nerve conduction  
3 studies or use their CCM machine or do a skin  
4 biopsy, I think we need to be mindful in what we're  
5 doing that this is an international exercise, and  
6 that the criteria we're developing, at least base  
7 criteria, ought to be applicable in Africa or the  
8 western Pacific, or other places that may be more  
9 resource limited.

10 So I think it's fine to have biomarkers that  
11 we'll use in clinical trials and in parts of the  
12 world that have access to those tools, but we ought  
13 to be thinking about how one can go about  
14 diagnosing reproducibly neuropathy and following it  
15 from a clinical perspective using tools that are  
16 easily deployed in resource-limited environments.

17 I personally haven't been in discussions or  
18 heard people talk a lot about this, but I think  
19 it's important thinking of this as a global health  
20 issue. I think I would be remiss sitting in  
21 Washington, DC not to recognize that global health  
22 is right outside our front door. As James sees in

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1 his patients from east Baltimore, we don't need to  
2 go to Africa to see these resource-limited  
3 environments. We have them in our cities and rural  
4 areas right now in this country.

5 What about common medical comorbidities,  
6 going to Dimension 3. Some of these are self-  
7 evident, and I'm not going to belabor them in terms  
8 of metabolic risk, which I want to remind you Rob  
9 is going to definitively solve later today in a  
10 highly anticipated talk.

11 DR. SINGLETON: Tomorrow.

12 DR. SMITH: Tomorrow. So we're going to be  
13 awake all night waiting for the answer to the  
14 questions that I raise.

15 I want to point out one issue -- or two  
16 issues. One is the role of the central nervous  
17 system in diabetic neuropathy, and a related issue,  
18 depression, anxiety, and sleep disorders.

19 Clearly, cerebrovascular disease and what  
20 appears to be an increased risk for CNS nerve  
21 degeneration probably impact the way in which  
22 patients experience neuropathy and the way in which

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1 we might measure it. It's possible that these in  
2 part underlie some of the other behavioral or  
3 mental health issues.

4 I promised Brian I was going to display to  
5 him the role of MRI scan in diagnosis of  
6 neuropathy, and so this is from Solomon's group.  
7 But there is a literature now looking at what's  
8 happening in the brain in patients who have  
9 neuropathy, in particular painful neuropathy.

10 Solomon can explain all of this to you, but this is  
11 looking at areas of differential cortical atrophy  
12 in patients who have peripheral neuropathy.

13 These are probably secondary effects, but we  
14 also have independent things going on in the  
15 central nervous system, both in terms of vascular  
16 problems and also in the neurogeneration that we're  
17 just beginning to scratch at. Thos I don't think  
18 are going to be in our core diagnostic criteria  
19 that Roy tells me we're going to have at the end of  
20 tomorrow, but it's something that I think deserves  
21 a lot more study as we try to understand covariance  
22 in terms of the neuropathy experience and how we go

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1 about measuring it.

2 I'm going to skip this, and just show this  
3 is a recent summary from Dan's team about risk  
4 factors and the level of evidence. The reference  
5 is on this slide, and here are the references  
6 underlying it. They did a very nice job looking at  
7 the roles of various risk factors, and obviously,  
8 diabetes duration and hyperglycemia, age are large  
9 determinants. But there are many other of these  
10 that are risk determinants, and I think in talking  
11 to Brian over the break, one of our real challenges  
12 is, is obesity a risk determinant? Is it a  
13 separate pathway? What do we make of idiopathic  
14 neuropathy patients who have obesity? Is that  
15 really the same as type 2 diabetes and whatnot?

16 I won't go through all of these, but I do  
17 want to spend a little bit of time talking about  
18 genetics because I think this is a critically  
19 important area. There are clearly generic  
20 determinants of risk in diabetic neuropathy, and  
21 this is just a table of them.

22 My read of this literature -- and there are

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1 people in the room who know infinitely more about  
2 this than I do -- is that these are of modest  
3 impact in terms of risk for neuropathy. So looking  
4 at single gene variants and polymorphisms, they  
5 don't really individually confer a great deal of  
6 risk.

7 Now, there's not been a lot of work looking  
8 at the more complicated systems-based approach, but  
9 there are a few indications that this is at least  
10 useful from a mechanistic perspective. I think the  
11 biggest and best really comes from Eva's team where  
12 they looked at sural nerve biopsies, categorized  
13 them into progressors and non-progressors and did a  
14 really fantastic genetic and bioinformatic study  
15 that essentially came up with 530 differentially  
16 expressed genes in progressors versus non-  
17 progressors that really conformed to several  
18 different themes, lipid metabolism, immune response  
19 and inflammation, and axogenesis.

20 Others have done this with smaller numbers  
21 of patients. There's a micro RNA study that came  
22 up with the same sort of thing. This was looking

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1 again at smaller, I think about 12, nerve biopsies  
2 from an available database in progressors and non-  
3 progressors.

4 Then an even smaller study just recently  
5 published looking at, I think, 6 patients with and  
6 without neuropathy, suggesting that there were  
7 differences in gene expression and multiple steps  
8 in the pathway for neurotrophin MAP case signaling.

9 I think these sort of analyses are going to  
10 be much more informative than going on a hunt for  
11 monogenic influences of neuropathy risk, and I  
12 don't think we're at a point where this literature  
13 is able to drive our enrollment in clinical trials.

14 It's certainly informing our understanding of  
15 mechanism, and clearly, more work is needed there.

16 Now, what about functional consequences of  
17 neuropathy? So obviously, these are enormous.  
18 There's enormous costs associated with neuropathy.  
19 Older data suggests about a quarter of direct  
20 healthcare costs attributable to diabetes are spent  
21 on neuropathy-related complications and outcomes.  
22 Painful neuropathy is second only to amputations in

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1 terms of impacting quality of life in neuropathy.  
2 I wanted to comment on a couple of other  
3 issues. First, gait, and we don't spend a lot of  
4 time talking about this, but it turns out to be an  
5 enormous issue for our patients. So diabetic  
6 neuropathy have a three to five times greater risk  
7 of falling, and as I'll show you in a moment, there  
8 are multiple contributors to this, including  
9 sensory loss, loss of strength, joint and range of  
10 motion, and certainly, central nervous system  
11 determinants like I had talked about earlier. It  
12 turns out that abnormal gait is strongly associated  
13 with depression, and the opposite is true as well.

14 This just shows in a study of about 170  
15 patients the difference in various measures between  
16 those who had neuropathy and those who did not.  
17 You can see there are changes in strength, range of  
18 motion. The ABC score is a score of balance  
19 confidence essentially, and it's a good metric for  
20 fall risk. You can see that there's a significant  
21 difference in the ABC score in those who have  
22 neuropathy and those who don't. This leads to a

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1 higher fracture rate and clearly is a main driver  
2 or one of the main drivers of reduced quality of  
3 life. It's something that we don't often think  
4 about and all too often isn't measured in clinical  
5 trials.

6 This is actually a nice example of this  
7 relationship between neuropathy severity and  
8 balance. This is the MNSI, which we're all  
9 familiar with, and the BERG Balance Scale. It just  
10 shows a scatter plot on a cohort of people with  
11 diabetes, and you can see that there is a clear  
12 relationship.

13 What's particularly interesting is this is  
14 sort of the threshold for overt neuropathy, and it  
15 really intersects nicely with the threshold of BERG  
16 Balance that predicts a moderate risk of fall. But  
17 you'll see that even with very low MNSI scores, the  
18 risk of fall increases, and those in this quadrant  
19 have a significant increase in fall risk despite  
20 mild neuropathy.

21 I think James published a long time ago that  
22 patients that have pre-diabetes and neuropathy,

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1 which we think of as being small fiber predominant  
2 and milder in terms of proprioceptive dysfunction,  
3 have very significant abnormalities in sense of  
4 postural position and so forth. I think this going  
5 back, this challenges our concept of the time  
6 evolution of diabetic neuropathy.  
7 This is actually an interesting paper that  
8 looked at the relationship between functional  
9 status and quality of life, and it's basically a  
10 mediation analysis that shows that not only does  
11 diabetic neuropathy directly change in quality of  
12 life but measures such as the 5 times sit to stand  
13 mediate change in quality of life through measure  
14 of balance confidence with the ABC scores.  
15 These are important determinants, and I can  
16 tell you that we're starting a trial in metabolic  
17 syndrome-associated neuropathy. We're using a  
18 timed up and go as opposed to this with an ABC  
19 score, which will be interesting to see how those  
20 perform in a clinical trial setting of a disease-  
21 altering agent.  
22 I think the last issue before I start to

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1 wind up is that of anxiety and depression. There's  
2 a 50 percent relative increased risk of depression  
3 in patients who have neuropathy. It's actually  
4 work from Brian that is similar between those who  
5 have CSPN or idiopathic neuropathy and those how  
6 have diabetic neuropathy. Fifty percent of  
7 patients with painful diabetic neuropathy have  
8 depression or anxiety, and a quarter have both of  
9 these.  
10 These really, and pain, as I pointed to  
11 earlier, are really drivers of these issues. They  
12 almost certainly are going to impact outcomes in  
13 clinical trials and something that one needs to be  
14 mindful of.  
15 This is data from Bruce Perkins looking at  
16 long surviving type 1 patients. These are patients  
17 who've had type 1 for, I think, 50 years, very long  
18 survivors. It looks at two measures of depression,  
19 essentially. This is a measure. The pain score is  
20 a measure of distress, and this is the Geriatric  
21 Depression Score. The point here is that while  
22 painful neuropathy patients are more depressed, are

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1 more distressed than those who don't have  
2 neuropathy, non-painful neuropathy patients also  
3 have increased levels of distress and of  
4 depression. So it's not purely pain that's driving  
5 this. It's probably gait or perceived gait and  
6 balance issues, and other issues that are probably  
7 incompletely explored.  
8 I think really the concept behind this is  
9 that there are probably if not different forms of  
10 diabetic neuropathy, there are different  
11 phenotypes, and there are probably micro phenotypes  
12 that really we ought to be thinking about in  
13 service really of personalized -- not only  
14 personalized medicine but personalized clinical  
15 trials.  
16 We've started to do this in a very crude way  
17 in just thinking of type 1 versus type 2, duration  
18 of diabetes, whether or not patients have  
19 particularly severe neuropathy, and other measures  
20 here. I wanted to talk a little bit about  
21 neuropathic pain, though, and Solomon actually  
22 brought this to my attention. I was familiar with

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1 these articles, but he sent a few of them. He  
2 sent -- you sent four, and I actually had read a  
3 couple. I read the others, so I think there's a  
4 modification to your rule. If you've read two and  
5 you get four, you'll probably read them.  
6 The idea here is that in the neuropathic  
7 pain literature, there is indication that one can  
8 use pain phenotyping to predict response or that  
9 pain phenotyping might predict response. So this  
10 is one trial of oxcarbazepine in neuropathic pain  
11 that shows that the response was much better in  
12 those who had an irritable nociceptor phenotype.  
13 This is the early phenotype that I was  
14 alluding to earlier with neuropathic pain in the  
15 absence of small fiber dysfunction as opposed to  
16 non-irritable nociceptor where there is axonal loss  
17 and pain as well.  
18 There are other studies suggesting this.  
19 One that I think is particularly nice is Solomon's  
20 COMBO-DN trial, which just to remind you,  
21 randomized patients to duloxetine or pregabalin.  
22 Then those who did not respond where randomized

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1 then to either an increase in dose, a high dose  
2 duloxetine, a high dose pregabalin, or combination  
3 therapy.  
4 Then the take-home point was I think  
5 duloxetine did a little better and combination  
6 therapy did better than high dose monotherapy. But  
7 very soon after this was published, they went back  
8 and looked at a cluster analysis of pain  
9 phenotypes, which really seemed to inform the  
10 response to therapy. I won't get into the details  
11 and Solomon can tell you about it if you have  
12 questions, but I think this is an interesting idea  
13 that I think also supports Roy's notion that we  
14 ought to take an unbiased look at our data.  
15 Here, this is taking a look retrospectively  
16 at data, but one could imagine that ultimately, we  
17 may do clinical trials in neuropathic pain in  
18 diabetes either specifically in subtypes or  
19 stratifying in these different subtypes of  
20 neuropathic pain categories. There may be a  
21 similar lesson in thinking about diabetic  
22 neuropathy more broadly.

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1 Right now, when we do disease-altering  
2 trials, if you have severe pain, that's great. If  
3 you don't have pain but you meet the neuropathy  
4 criteria we're using, great, whatever. It may be  
5 that we need to be more thoughtful or at least go  
6 back and look at the response to therapy in  
7 different disease categories, not just duration of  
8 disease or how early, but different phenotypes.  
9 Clearly, the neuropathic pain literature suggests  
10 this might be a fruitful endeavor.  
11 I'm going to ignore the conclusions because  
12 I made them on the airplane, and they're  
13 meaningless. I have a couple of attribution  
14 slides.  
15 This is the first two generations of  
16 Michigan diabetic neuropathy. I show it more as a  
17 statement of gratitude to Eva and Rob and James and  
18 Rodica and then the rest, and then of course, I  
19 think we all owe Chris --  
20 (Photo shown.)  
21 (Laughter.)  
22 DR. SMITH: -- an enormous debt of gratitude

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1 for taking this on. I think this was a selfie when  
2 he was getting ready for the meeting, but it's  
3 turning out really well.  
4 (Laughter.)  
5 DR. SMITH: With that, I'll end because I'm  
6 the only thing between you and lunch.  
7 (Applause.)  
8 DR. FREEMAN: I think that's an appropriate  
9 segue into the obligatory photo, so put on your  
10 best faces, see if you can reproduce or how  
11 reliable Chris can be with regard to  
12 reproducibility of his image.  
13 Rodica, can we use your camera?  
14 Carlos, how steady is your hand?  
15 Why doesn't everybody come up? I think  
16 probably this is the best place to do it. The  
17 light is reasonable.  
18 (Whereupon, at 12:10 p.m., a lunch recess  
19 was taken.)  
20  
21  
22

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1 AFTERNOON SESSION  
2 (1:03 p.m.)  
3 Q & A and Panel Discussion  
4 DR. FREEMAN: The figure ground separation  
5 is not clear at all, in fact, barely visible. Now  
6 is the time when the figure ground separation  
7 becomes a little clearer.  
8 Can I get the first slide, or are you going  
9 to do it for me?  
10 This is the reminder. The reminder is at  
11 the end of this meeting, we are going to need to  
12 come up with something like this. "Every patient  
13 entered into a research project, be it a drug trial  
14 or study of pathophysiology or biochemistry, must  
15 fulfill a set of diagnostic criteria."  
16 We need the diagnostic criteria. We need  
17 Dimension 1, the core diagnostic criteria, and it's  
18 got to look like something this. The formatting is  
19 gone. We'll improve on that, but it needs to look  
20 something like that. This is the menu, and we're  
21 going to need to come up with something.  
22 We do need to leave this meeting with that

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1 framework, and there are several possible  
2 approaches, which Gordon introduced. One might say  
3 he punted a little, but he almost got there.  
4 (Laughter.)  
5 DR. FREEMAN: In terms of the approaches,  
6 there are really several. I personally think we  
7 should actually do more than one of these and  
8 perhaps all of them, but I want you to begin to  
9 think in these terms.  
10 There is the possible, probable,  
11 definite -- I prefer clinically confirmed just  
12 because nothing is ever definite, which is one  
13 approach -- one approach which the Toronto criteria  
14 are used, not in quite the way that I would like  
15 them to be used, but at least used. There's the  
16 preclinical, subclinical, mild, moderate, and  
17 severe, and there is the small fiber, large fiber,  
18 and mixed.  
19 Why I think that we should consider doing  
20 more than one of these is just imagine you have  
21 somebody, for example, who is interested in looking  
22 at NAV 1.7 polymorphisms in patients with small

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1 fiber diabetic neuropathy or diabetic neuropathy  
2 with predominantly small fiber features. We want  
3 to give them the criteria that they can use.  
4 If somebody wants to do a study on the  
5 likelihood of developing ulceration and amputation,  
6 we want to give them the criteria for severe  
7 diabetic peripheral neuropathy. So I think more  
8 than one of these approaches may be required.  
9 Then the settings, we need to think in terms  
10 of the settings, and this has come up, but we  
11 haven't concretized this yet. Tertiary care  
12 centers where there will be QST and corneal  
13 confocal microscopy and nerve conduction studies  
14 and autonomic testing versus the field, Central  
15 Africa, where we would like them to have criteria  
16 for diabetic neuropathy and all of the range in  
17 between, a multicenter trial for disease  
18 modification in diabetic peripheral neuropathy  
19 where there may not be corneal confocal microscopy  
20 or autonomic testing.  
21 Epidemiological studies, cohort studies,  
22 case control studies where perhaps the criteria may

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1 not, if we think of the continuum from signs to  
2 symptoms to special investigations, be quite as  
3 rigorous, may not be quite as specific.  
4 Components of the menu. Symptoms, which  
5 symptoms? Signs, which signs? Special  
6 investigations, which special investigations? Then  
7 finally, and this is the heavy lifting, the menu  
8 that Gordon is going to include in his manuscript,  
9 which I remind you, is going to look like that.  
10 So that's the setting. That's where we are.  
11 Let the panel begin.  
12 Eva, you're in the corner there. Why don't  
13 you start?  
14 DR. FELDMAN: Could I suggest then -- and I  
15 guess you're probably not going to like this, but I  
16 think we could divide up in three or four smaller  
17 groups and each take one of those. Our expertise  
18 is fairly homogenous, I mean fairly homogenous, and  
19 we could probably in an hour have migraine with  
20 aura 1.2.  
21 We could actually produce, get real  
22 documents done if that is your goal, or is your

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1 goal now just for all of us to continue to talk  
2 about it?  
3 (Laughter.)  
4 DR. FREEMAN: I would like --  
5 DR. FELDMAN: I mean really because we  
6 could -- this is too big of a group, I think. If  
7 you wanted to do all of that --  
8 DR. FREEMAN: I think that's a very  
9 reasonable point. What I think we could do maybe  
10 is to make sure that we are on the same playing  
11 field initially, and as you put it in such a  
12 denigrating fashion --  
13 (Laughter.)  
14 DR. FREEMAN: -- I think we should talk  
15 about it.  
16 DR. FELDMAN: I wasn't being denigrating. I  
17 was just --  
18 DR. FREEMAN: No, I take --  
19 DR. FELDMAN: ACTTION, isn't that our  
20 acronym?  
21 (Laughter.)  
22 (Crosstalk.)

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1 DR. FREEMAN: I think that's a great idea.  
2 Is everybody onboard with that, by the way?  
3 DR. SMITH: We talked a little bit about  
4 this. I think to do that before hearing Rob's  
5 presentation puts us at some disadvantage.  
6 DR. SINGLETON: I actually was going to  
7 say -- I think that's true, but I would actually  
8 say I'm going to advance the idea tomorrow that the  
9 phenotypic diagnostic criteria for metabolic  
10 syndrome neuropathy, pre-diabetic neuropathy, are  
11 basically identical to the ones that we'll choose  
12 for diabetes.  
13 DR. PELTIER: Which type? I guess that's  
14 the first --  
15 DR. SINGLETON: Type 2 diabetes. If we're  
16 going to have two, but I say that because I think  
17 spending time, as Eva's suggesting, in actually  
18 hammering these out will save time later, for me at  
19 the very least, because I suggest that we're going  
20 to -- it won't be that different, if at all  
21 different.  
22 I really like the idea, Roy, that you have

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1 of those different forms of this. I think have one  
2 that's a form of diagnostic certainty because I  
3 think we need that. Having one that's a form of  
4 severity because that's really what we're talking  
5 about, those two aspects when we consider diabetic  
6 neuropathy versus metabolic syndrome neuropathy.  
7 They are undifferentiable in terms of their  
8 phenotypes. What's different is the attribution of  
9 the neuropathy.  
10 DR. FREEMAN: I think that that's fine. So  
11 are we on the same page that we can actually do  
12 this without hearing Rob's talk, and we can make  
13 life easy for him?  
14 DR. SINGLETON: Again, what I'm going to  
15 talk about tomorrow is not about the phenotype.  
16 Small fiber versus large fiber, I think there's  
17 room for that discussion a little bit. But mostly  
18 what I need to do, I think, is to get consensus  
19 from this group that there is such a thing as pre-  
20 diabetic neuropathy, that the attribution is  
21 sufficient that you guys think that that's  
22 something that we can talk about.

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1 DR. FREEMAN: You think that it will  
2 be -- if things go according to your plan, it will  
3 be on the continuum, and we might as well decide  
4 this --  
5 DR. SINGLETON: That's right, right.  
6 DR. FREEMAN: -- these different pies today.  
7 I'm totally fine with that. But I think we should  
8 talk a little bit about the component so that when  
9 we break up into these small groups, and we can  
10 decide how many small groups we can break up into,  
11 we're actually going to be, to some extent, on the  
12 same page. But I do love the suggestion.  
13 I want to go back to this just a little  
14 because I broke this down really into three  
15 separate approaches, the level of certainty, as Rob  
16 said or said something like that --  
17 DR. GIBBONS: Roy, they're going to get very  
18 upset in the back when they can't copy your speech.  
19 DR. FREEMAN: The level of certainty, the  
20 severity continuum, and then the phenotype. Those  
21 are the three, but I've made them discrete.  
22 They're actually not -- they're not really separate

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1 because each one of those apply. Level of  
2 certainty with severity is quite important, too.  
3 I think we need to have some kind of  
4 discussion on that and then also some kind of  
5 discussion on the components because those are  
6 going to be common. If signs, which signs? If  
7 symptoms, which symptoms? If signs, which signs?  
8 And if special investigations, which special  
9 investigations? What role do they play? How do we  
10 incorporate it?  
11 I think it would be good to do this in the  
12 room rather than come up with something that may  
13 not quite mesh.  
14 Having set that stage -- and, Eva, I'm glad  
15 I asked you first because I think that's a great  
16 suggestion, first of all, anything else to say?  
17 DR. FELDMAN: Let me understand one point,  
18 and that is, what you're envisioning is that we  
19 actually come up with a set of diagnostic criteria  
20 for possible, probable, clinically confirmed  
21 separately for preclinical, mild, moderate, severe  
22 separately for small fiber and large fiber. And

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1 then we look at these in aggregate and see if we  
2 can agree upon one set of diagnostic criteria.  
3 Is that the idea?  
4 DR. FREEMAN: I think that would be the  
5 easiest way to do it.  
6 DR. FELDMAN: I do, too. I do, too.  
7 DR. FREEMAN: I think we can then mix and  
8 match if we wish, but I think that would be the  
9 easiest way to do it.  
10 DR. FELDMAN: I actually really agree with  
11 you because I think we'll get a lot of very good  
12 input, and one group will think of something that  
13 another group has not.  
14 DR. FREEMAN: Sounds good.  
15 DR. POP-BUSUI: I have a question. So what  
16 is the evidence that we are going to use when we  
17 are going to make these decisions? Because that's  
18 actually very important to decide --  
19 DR. FREEMAN: I think all of our --  
20 DR. POP-BUSUI: -- is going to be again our  
21 expert or --  
22 DR. FREEMAN: I think Gordon is going to be

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1 our resource on what the evidence is, and I think  
2 all of us know the studies. But one of the points  
3 that I didn't make, which was at the end of the  
4 study, we want to come up with something, as I say,  
5 something definite, and part of it is going to be  
6 evidence based. Some of it is going to be  
7 consensus. Some of it is going to be expert based.  
8 But it must be testable and refutable so that going  
9 forward, we can say, you know, we decided that  
10 sensory distortion should be one of the symptoms or  
11 allodynia should be one of the symptoms. That  
12 didn't work at all. We should drop that.  
13 I think we want this to be a testable set of  
14 hypotheses, and that's absolutely critical to the  
15 process.  
16 Any other questions?  
17 DR. POP-BUSUI: But then we will have to  
18 have a way to test, right, because we need to  
19 derive a set of criteria based on evidence, let's  
20 say, obtaining a particular setting, whether it's a  
21 trial, whether it's an epidemiological observation,  
22 and see how reproducible that type of definition is

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1 in a completely different population. That's the  
2 way we have to do it. I think there is a lot of  
3 data there, but we have to agree how are we going  
4 to use the data.  
5 DR. FREEMAN: I think we have a lot to do at  
6 this meeting. I think what I would prefer is in  
7 the discussion that we have at the end of the  
8 meeting is next steps, going forward, how are we  
9 going to test? What kind of studies do we need to  
10 do? How's the DNC going to do this, or whatever  
11 we're calling ourselves. How is CONCEPPT going to  
12 do this? What are the ways forward?  
13 But I think at this point, we're going to  
14 accept that we have a good sense of the literature;  
15 that where we don't, we have opinions; and we're  
16 going to have to come up with something, and then  
17 we'll move forward on that.  
18 DR. POP-BUSUI: I agree. One more small  
19 comment regarding the settings, and I completely  
20 agree that, yes, there are tertiary centers that  
21 have much more resources in general. But I think  
22 that we should not forget that diabetes care is

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1 extremely expensive even in countries like ours or  
2 western Europe. So we have to be also pragmatic  
3 here and take into account what does it cost just  
4 to treat hyperglycemia today and how complicated it  
5 is for providers to think about 15 classes of  
6 agents, for instance, that are available to treat  
7 hyperglycemia as well as other risk factors.  
8 I think that we should think about it not  
9 only because diabetes is such a prevalent condition  
10 throughout the globe and there are countries that  
11 have not the same economic power, but even here in  
12 U.S., it's actually very expensive to treat  
13 diabetes. The access to care or diagnostic  
14 procedure, also, it's extremely not equal among  
15 nations.  
16 DR. FREEMAN: David?  
17 DR. HERRMANN: To add to that, I would agree  
18 with the approach that you're taking in terms of  
19 defining the phenotype according to those  
20 dimensions, but the other thing one might think  
21 about from a diagnostic approach is just to also  
22 come up DPN-1, which may be type 1 diabetes being

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1 the precursor to the phenotype; and then DPN-2,  
2 perhaps, adult onset diabetes in the context with  
3 that metabolic syndrome; and then DPN-3, adult  
4 onset diabetes with metabolic syndrome. So that  
5 you might have three or four types to put the  
6 phenotype in the particular context, and then that  
7 could be used or selected from for a particular  
8 trial.

9 DR. FREEMAN: I think that that's fine. But  
10 I think that that is subsumed under these groups.  
11 Solomon, any --

12 DR. TESFAYE: I think that is perfectly  
13 reasonable.

14 DR. FREEMAN: Gordon?

15 DR. SMITH: I think what David said is  
16 really important. We're starting this NeuroNEXT  
17 trial in cryptogenic neuropathy in patients who  
18 have metabolic syndrome, and we self-made our  
19 criteria. But there was a lot of negotiating with  
20 NINDS and others about the boundaries.

21 For instance, we said patients initially  
22 just with neuropathies in the Toronto criteria who

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1 also had metabolic syndrome. Then someone said,  
2 "Well, what if they're non-obese?"

3 Then we said, well, okay. They need to be  
4 obese with metabolic syndrome. We've created  
5 criteria for the individual trial, but to your  
6 point earlier, the next trial may choose a  
7 different BMI cutoff for obesity.

8 Maybe they use waist circumference, and I  
9 think these things become really important. And  
10 maybe that isn't something that we need to decide  
11 right now, and that would come after Rob's  
12 discussion tomorrow. But I think defining  
13 particularly -- type 1, type 2 take care of  
14 themselves, but the pre-diabetes, obesity,  
15 metabolic syndrome discussion, I think, has some  
16 important granularity to it to achieve the  
17 objective that David talked about.

18 DR. FREEMAN: The way I would envision that  
19 is clarification notes where all of these secondary  
20 aspects come into that, and being, again, as  
21 prescriptive as possible.

22 Stephen?

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1 DR. BRUEHL: I just wanted to throw out  
2 something to think about here. One of the issues  
3 that we encountered with CRPS as a reaction to the  
4 definition of CRPS in the new criteria was  
5 clinicians would come back to us and say, well,  
6 what about the people that I've always diagnosed  
7 CRPS that have X, Y, and Z but are missing this  
8 factor? So they don't receive the diagnosis  
9 anymore.

10 That is an uncomfortable conversation to  
11 have because -- and my only response is, well,  
12 we've defined it differently, so they don't have  
13 it. That's not terribly helpful.

14 The example you just brought up was a good  
15 example of what can happen. You keep adding on  
16 more criteria, and eventually, you define it so  
17 narrowly that there are large sets of people that  
18 might not get it. What are we going to do about  
19 those that don't fall into that category now? Just  
20 something to think about.

21 DR. POP-BUSUI: This is actually a very  
22 important point, especially when it comes to

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1 clinical trials because if you make our criteria  
2 too granular, then we will never enroll our  
3 patients for trials. That's why it's so important  
4 to do it right.

5 DR. BRUEHL: I agree, and one option, kind  
6 of the in-between option, which we used, was to  
7 have the set of clinical criteria that are less  
8 specific so we capture more of those people, and  
9 then a specification that doesn't change the  
10 underlying criteria. It just changes the decision  
11 rule to narrow it down a little more for clinical  
12 trial purposes.

13 DR. SMITH: That was a question I have, is  
14 can you nest these, right? So what you just talked  
15 about is having a classification that may create,  
16 let's say, presence and severity with a measure of  
17 certitude built underneath that, if I'm  
18 understanding correctly.

19 DR. BRUEHL: I don't like the levels of  
20 certainty idea in diagnosis because to be  
21 clinically useful, it really needs to be  
22 dichotomous. You force it to be either a yes or a

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1 no. Traditionally, that's the way it's done.  
2 Now, if you wanted to be a little different,  
3 you certainly could have some limited type of  
4 ranking of probabilities. It wouldn't be my  
5 preference because it makes things like trying to  
6 determine reliability if you were to try to test  
7 that, makes it harder to do because then what -- if  
8 you have somebody who's probable, do you count them  
9 in the definite or non category if you're trying to  
10 determine reliability of diagnosis?  
11 DR. FREEMAN: Vera and Brian.  
12 DR. BRIL: The comment again is the setting,  
13 right? If we want to impact the greatest number of  
14 patients with diabetes, we will use a simple  
15 screening method, something like we did, normal or  
16 abnormal. You have it, or you don't.  
17 This is what we did years ago when we used  
18 the pinprick or the tuning fork to try to detect  
19 neuropathy present or not, with all the issues  
20 around, and very simple yes-no answers to get the  
21 diagnosis in the greatest number of people no  
22 matter how specific it is, but just to get the

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1 diagnosis. But then as you step up, you get into  
2 the other things. Because if people are not taking  
3 footwear off, they're not asking about symptoms,  
4 and they're not examining. Mostly, they're not  
5 diagnosing unless it's a painful patient that has  
6 brought themselves to attention.  
7 That's why the simple screening study we did  
8 was important for the large majority, I would say,  
9 of diabetes patients, if people actually use those  
10 screening methods, but otherwise, all of this is  
11 more into endocrinology clinics, neurology clinics.  
12 And we all know what we would be asking the  
13 patients and what we would be examining because we  
14 all pretty much do the same thing.  
15 DR. FREEMAN: I think if we take Dan's  
16 point, which I think many of us do, I'm not so  
17 sure. I do think that in some way, we need to  
18 combine the setting -- doing the study in Central  
19 Africa -- [inaudible - off mic] -- look at those  
20 three groups and I accept Steve's point about  
21 dichotomy being ideal.  
22 DR. GIBBONS: To the microphone, you're not

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1 getting heard.  
2 DR. FREEMAN: Okay. So I accept Steve's  
3 point about dichotomy being ideal, but I think each  
4 one of those three approaches should be shaded by  
5 the setting. If done in setting X, then this is  
6 what would be; however, if done in Central Africa,  
7 then.  
8 Dan, then Brian.  
9 DR. ZIEGLER: I think that that's a  
10 fundamental question. The question is whether we  
11 add clinical practice to the settings or not,  
12 because as it stands now, it's research. In the  
13 clinical practice setting, what Vera is addressing,  
14 is a fundamentally different scenario. But I agree  
15 that we should address that.  
16 We should give some recommendation or  
17 whatever or statement about what is appropriate for  
18 screening and what is appropriate in the clinical  
19 practice setting because that is --  
20 DR. FELDMAN: Could I say something? Isn't  
21 that we just did? That is what we just did with  
22 the ADA criteria.

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1 DR. ZIEGLER: Yes, that's what we did. The  
2 question is whether we want to repeat that in this  
3 --  
4 DR. FELDMAN: No, I don't think so. I think  
5 the whole goal of this meeting -- I feel like we're  
6 mixing -- we're losing our focus or our goal.  
7 DR. POP-BUSUI: I agree.  
8 DR. FELDMAN: The whole goal of this meeting  
9 was to come up with a taxonomy, very specific  
10 definitions primarily for tertiary centers,  
11 multicenter trials, drug trials, epidemiological  
12 trials. So this is more of a research goal or  
13 focus.  
14 We did a very nice job, I think, with the  
15 ADA criteria for the clientele, for the population  
16 you're discussing. I don't think we can easily do  
17 both in a day and a half here.  
18 DR. POP-BUSUI: I also agree with that. I  
19 think that our scope right now, if we want to get  
20 out something of this two-day meeting, is to try at  
21 least to understand what are the best criteria for  
22 research studies, whether they are epidemiologic or

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1 they are clinical trials, and come up with a set of  
2 measures that can be applied even in 10,000-patient  
3 trials in a standardized and approachable way.  
4       Once we identify these methods and criteria  
5 and we see that they indeed have a lot of validity,  
6 then we can think whether it's needed to rethink  
7 the clinical practice recommendations, but there is  
8 no point to try to overrule everything right now  
9 because, in fact, you don't have anything to offer  
10 those patients, whether you are going to propose  
11 very expensive evaluations or not. The standard of  
12 care of diabetes, it's not going change.  
13       DR. RUSSELL: Couldn't we maybe take a vote?  
14 Can we take a vote and see if we all agree that we  
15 should just have clinically confirmed and that's  
16 what we should focus on as part of this meeting?  
17 So in other words, if this is going to be research  
18 criteria, we should decide on focusing on  
19 clinically confirmed.  
20       DR. FREEMAN: Typically, clinically  
21 confirmed with a special investigation. That's the  
22 confirm. That's the so-called definite, so not

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1 just symptoms and signs. The standard approach is  
2 possible signs, probable signs plus symptoms,  
3 clinically confirmed with a special investigation,  
4 whereas I do think this is for research, but I  
5 think it's research epidemiology and not only  
6 research multicenter trial and research tertiary  
7 care center.  
8       I don't know if epidemiology Central Africa,  
9 which I do think this must play a role in those  
10 kinds of studies, I don't think they're clinically  
11 confirmed. That would be my view, but let's hear  
12 what others think.  
13       DR. ZIEGLER: Epidemiology can never be  
14 confirmed. I think the simple question is whether  
15 we restrict our research or not, and we can vote  
16 about this. My feeling is that the majority feels  
17 that it should be restricted to research.  
18       DR. TESFAYE: The ADA criteria as they stand  
19 focused on clinical exam in clinical practice to  
20 diagnose neuropathy, but the problem we have in  
21 clinical practice at the moment is we're  
22 under-diagnosing the patients. So we're not doing

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1 a good job of -- we're diagnosing in about 10, 20  
2 percent of patients' neuropathy using very crude  
3 measures. And that's not fit for purpose when you  
4 compare it with retinopathy now with digital  
5 camera. You can achieve precise -- in the old  
6 days, we used to fiddle with the ophthalmoscope,  
7 and we didn't know what we were doing, but now in  
8 the UK, everybody undergoes retinal photography  
9 annually, and you diagnose the condition in a much  
10 higher proportion.  
11       The clinical practice that we are engaged in  
12 at the moment and is actually using monofilament,  
13 is useless. It's diagnosing the patients at risk  
14 of foot ulceration, but it's not diagnosing the  
15 condition early, which is what we want. So the  
16 clinical practice measures -- using Toronto, we  
17 managed to diagnose neuropathy in around 30  
18 percent, which is twice that of monofilament, but  
19 we need more confirmed.  
20       The confirmed neuropathy shouldn't just be  
21 for research purposes, but in well developed  
22 countries such as the US, UK, Europe, actually we

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1 do need to do better. We need to use confirmed  
2 neuropathy as a proper standard of diagnosing  
3 neuropathy annually in our diabetic patients.  
4       DR. FREEMAN: Brian?  
5       DR. CALLAGHAN: I think we have a good  
6 framework from Toronto and ADA on how we think of  
7 neuropathy. I think the settings kind of naturally  
8 fall out of clinical trials and tertiary centers,  
9 looking at confirmed neuropathy versus  
10 epidemiologic ones, being more in the possible and  
11 probable.  
12       I think where we can take it to the next  
13 step after Toronto and the ADA is to start focusing  
14 on the components, which are what's the  
15 questionnaire that we want to standardize to use as  
16 our symptom definition? What exam tool do we want  
17 to use to be our signs definition? How can we  
18 standardize the skin biopsies and nerve conduction  
19 definitions such as that doing it at Utah is the  
20 same as doing it at Michigan, same as doing it in  
21 Germany, et cetera?  
22       I think that's how -- I feel like we have a

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1 framework, and we can build on that by becoming  
2 more precise.  
3 DR. FREEMAN: Let's talk a little bit about  
4 then the symptoms, and I think at this point in the  
5 whole process, my bias -- and I think this is where  
6 views may not be unanimous, and I really do  
7 anticipate this is where the controversy emerges.  
8 My bias would be to be agnostic at this  
9 point in terms of instruments and not say that this  
10 specific symptom score or this exam score is our  
11 ideal unless this is absolutely unanimous and  
12 rather look at the components as individuals.  
13 What symptoms are we interested in? What  
14 signs are we interested? And not even at this  
15 point talk about how do elicit these signs, and  
16 that is work that needs to be done. I think none  
17 of us would disagree with the point that Dan made.  
18 Then finally, what special investigations.  
19 Stephen, you've got something to say.  
20 DR. BRUEHL: With that issue that you're  
21 just talking about there, you have all these  
22 measures that have been already validated, and I

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1 guess the question I would raise, because I'm  
2 ignorant of exactly what's on these -- what I would  
3 ask if you've gone back and done these reviews as  
4 was presented earlier showing these measures cover  
5 these aspects of things and these differentiate  
6 better than others, instead of looking at the full  
7 measures, can you look at the item level? If you  
8 get seven measures that all are the best predictors  
9 and you look at the items and they've got 85  
10 percent overlap, that tells you that's the symptoms  
11 and signs that you would want to address in here.  
12 I'm just saying maybe go at it not so much  
13 from the scale perspective, but look at the item  
14 level at the overlap, and that might be helpful.  
15 The other issue -- and I just want to raise  
16 this because it's going to come up with the  
17 investigations -- is I thought it was pretty  
18 profound when I saw the receiver operating  
19 characteristics curve that was presented showing  
20 that the confirmation test, the value of the  
21 confirmation test, had a negative predictive value  
22 that was virtually worthless.

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1 For research purposes, that's what you're  
2 really concerned with is are we weeding out the  
3 people that don't really have it. I would argue  
4 that if we're trying to optimize this for research,  
5 and that's the only justification for including  
6 these tests, why would you do that if they're not  
7 predictive? Just to be provocative because I don't  
8 work in this area --  
9 (Crosstalk.)  
10 DR. FREEMAN: Gordon, you shared this slide,  
11 so what do you think?  
12 DR. SMITH: I agree. It was actually the  
13 negative predictive value is low, but if you model  
14 it --  
15 DR. BRUEHL: It depends on the base rate.  
16 DR. SMITH: -- so the negative predictive  
17 value is high. Positive predictive value is  
18 terrible, but if you model it for a highly  
19 prevalent population, it stinks. So I agree. I am  
20 actually ambivalent about using nerve conduction  
21 studies or skin biopsy to confirm neuropathy. It's  
22 not clear to me that it really adds value.

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1 I think they are definitely valuable tools.  
2 They're essential tools in monitoring disease  
3 progression. They're clinically useful when  
4 applied judiciously, but our foundational almost  
5 religious belief that these tools convey a higher  
6 certainty of neuropathy in an individual patient in  
7 a screening setting for a clinical trial I think is  
8 suspect at best.  
9 DR. FREEMAN: That is the question. What  
10 about the pretest probability, which in those  
11 patients, there was a relatively high pretest  
12 probability?  
13 DR. SMITH: Well, it was 18 percent in that  
14 group, so if it's that low, it's good. The problem  
15 is once the pretest probability goes up, then your  
16 risk of having a false result goes up as well, so  
17 then the negative predictive value starts to  
18 decline as the false positive goes up.  
19 DR. CALLAGHAN: I think part of the problem  
20 is our constructs don't all overlap. In some ways,  
21 maybe we shouldn't be trying to lump tests and a  
22 clinical definition together but have our best

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1 clinical definition, our best large fiber  
2 quantitative definition, our best small fiber  
3 quantitative definition. Maybe part of the reason  
4 we're struggling and why we get some of these  
5 strange results is because we're meshing these  
6 things that don't overlap as well as we would all  
7 like.  
8 DR. FREEMAN: Can I just ask Jen to  
9 say -- because Jen's looked at signs. And you've  
10 looked at symptoms as well, and symptoms, I think,  
11 is one of the critical pieces.  
12 Can you talk to us a little -- and I'm sorry  
13 for putting you on the spot. Maybe you should have  
14 some time to think about it. Can you talk now, or  
15 do you want me to hear from somebody else first?  
16 DR. GEWANDTER: Do you have a question?  
17 DR. FREEMAN: The question is, if I were to  
18 say I want five symptoms that, to address Stephen's  
19 point, are present in the vast majority of tests.  
20 We can't answer Rodica's point yet whether there's  
21 overlap, which is the most likely to predict the  
22 presence of disease. We can test that later. But

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1 we can answer Stephen's point.  
2 DR. GEWANDTER: Oh, can I have a minute?  
3 DR. FREEMAN: Of course. So it was Dan, I  
4 think.  
5 DR. ZIEGLER: I'd just like to comment to  
6 that, to Gordon's statement. We did a number of  
7 studies in recently diagnosed type 1, type 2  
8 diabetes. That's the first -- that's the earliest  
9 time you can go. What those measures show, nerve  
10 conduction and also skin biopsy, is that these are  
11 sensitive. These are the gold standards for large  
12 fiber and small fiber, and these detect abnormality  
13 very early. They are very sensitive, and  
14 therefore, they will detect more abnormality in  
15 people who do not have neuropathy.  
16 So that all these test sensitivity and  
17 specificity discussion is a little bit questionable  
18 because if it's the gold standard, it is the best  
19 thing. This is our impression, that those tests  
20 actually are the gold standards for small and large  
21 fiber deficits.  
22 DR. SMITH: That was my impression, too,

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1 going into it, but the fact remains there's still  
2 false positives with the gold standard.  
3 DR. FREEMAN: Amanda, then Rayaz, then  
4 anybody else other than Jen who has -- James. So  
5 Amanda.  
6 DR. PELTIER: I think one of the things that  
7 you have to think about if you're designing your  
8 criteria for either the clinic or research is that  
9 what you want to think about actually are the  
10 syndromes that are going to be confused with  
11 neuropathy and how do you differentiate those. I  
12 think that's really where you want to think about  
13 it.  
14 Because as Dan suggested, you can have a lot  
15 of preclinical patients who are going to have  
16 abnormal tests and very few symptoms and maybe only  
17 a handful of signs. The bigger issue is how do you  
18 rule out the person with plantar fasciitis? How do  
19 you rule out the person with a tarsal tunnel or  
20 some other mononeuropathy of the foot and making  
21 sure that they're not included in your trial and  
22 they're not confused with having polyneuropathy?

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1 DR. FREEMAN: Rayaz?  
2 DR. MALIK: With regard to this  
3 sensitivity/specificity issue, we look at this  
4 data, and we don't actually think about what goes  
5 behind the test. What goes behind the test is the  
6 definition that you use to define a condition. So  
7 if you're using criteria which are weighted towards  
8 a particular -- I don't know -- maybe large fibers  
9 and you're looking at skin biopsies, of course,  
10 it's not going to do well.  
11 That's the thing that we forget because we  
12 just generically say, oh, this has got a bad  
13 negative or positive predictive value, but it's the  
14 definition that you use. I think that is again  
15 going to be useful for what comes out of this as do  
16 we need to think about how we define diabetic  
17 neuropathy. Do we need to incorporate a more  
18 holistic approach as opposed to the previous  
19 approach that we've had?  
20 DR. HARATI: In ALS, in definition of the  
21 different classes of ALS, we have definite,  
22 possible, probable, but there is also a category of

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1 laboratory-supported diagnosis. There is nothing  
2 wrong to include that, and we may choose for a  
3 particular research to use only definite or  
4 possible or we may want to choose all four  
5 categories.  
6 DR. FREEMAN: I think of definite as  
7 autopsy, and clinically -- of course, that's the  
8 only definite.  
9 DR. PELTERI: Not really, though, Roy,  
10 because if you think about it, if you do an autopsy  
11 and you do the sural nerve biopsy, and you just say  
12 a lot of loss of nerve and you didn't have all the  
13 other information, how would you know that that  
14 loss of nerve was really due to their diabetes?  
15 DR. FREEMAN: But the point about it is I  
16 like the clinically confirmed because that's what  
17 it is. It's accurate. You don't know whether this  
18 patient definitely has a neuropathy. You've  
19 confirmed it clinically, and I think most criteria  
20 actually do have the autopsy if you look at Lewy  
21 body dementia, Parkinson's, so most of the central  
22 neurodegenerative processes use that approach.

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1 DR. SMITH: Can I comment, though, because I  
2 think Amanda hit the nail right on the head, and it  
3 goes to Dan's point. The problem with these tests,  
4 first is not everyone who has obvious neuropathy  
5 has an abnormal nerve conduction or an abnormal  
6 skin biopsy, and there are reasons for that.  
7 There may be changes if we had been able to  
8 see those metrics from their pre-disease state, but  
9 the fact is we're enrolling for trials now where we  
10 look at these patients and say they obviously have  
11 neuropathy, yet they don't quite meet the criteria.  
12 So there are false negatives, and it's just the way  
13 the tests are constructed.  
14 The real issue is what Amanda talked about,  
15 is trying to prevent enrollment of patients who  
16 have plantar fasciitis, and people with diabetes,  
17 they're allowed to have plantar fasciitis. Because  
18 of the frequency with which there are preclinical  
19 abnormalities of these tests, using them as a  
20 positive enrollment, a confirmatory criteria, runs  
21 the risk of enrolling patients who don't have the  
22 clinical phenotype, whereas relying on them also

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1 will exclude patients who clearly have the clinical  
2 phenotype.  
3 I think the real major problem is the one  
4 that Amanda talked about, and it shows in the  
5 performance data where the positive predictive  
6 value is terrible, and that's because it's based on  
7 clinical criteria.  
8 DR. FREEMAN: There was James and then  
9 Jennifer.  
10 DR. RUSSELL: Roy, in part answer to the  
11 question that you actually posited to Jennifer, we  
12 already have this information. So in 2015, we  
13 looked at seven of the major scales that are used  
14 across the board, and what turns up from that study  
15 is that the positive predictive value, the negative  
16 predictive value, the sensitivity and the  
17 specificity turns out to be best for the modified  
18 Toronto Clinical Neuropathy Scale. The two top  
19 scales were that and the Total Neuropathy Scale.  
20 The thing that drives the overall sensitivity is  
21 actually the presence of the symptoms.  
22 Now, if you look actually at the validity of

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1 the different domains, the thing that determines  
2 the validity is actually the sensory signs. If  
3 you're going to look at a scale and you want to  
4 make it more sensitive, you are going to have to  
5 include symptoms, but if you actually want perhaps  
6 to make that scale more valid and more  
7 reproducible, then you're really going to have to  
8 focus actually on the signs.  
9 We already do have some of that information.  
10 Now, I would suggest that we can probably actually  
11 come up with clinically confirmed based on symptoms  
12 and signs. We're going to have to decide which of  
13 those signs and symptoms we're going to use, and  
14 then prospectively in coming years, we're going to  
15 have to test those objectively in trials conducted  
16 by this group.  
17 DR. SMITH: An autopsy.  
18 (Laughter.)  
19 DR. SMITH: An autopsy maybe.  
20 DR. GEWANDTER: So you wanted to know what  
21 were the most common symptoms and signs in the  
22 scales. So as far as symptoms go, by far most

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1 common is numbness and tingling. It is in all of  
2 them.  
3 DR. FREEMAN: So that one slowly.  
4 DR. GEWANDTER: Numbness and tingling is in  
5 all. I can't find the total, and I'm having  
6 trouble. But it's 17 of them. We only reviewed, I  
7 think, 18.  
8 Then the next most common is pain, and that  
9 was in seven of them. Then the next most common  
10 was altered warm and cold perception was in six.  
11 Allodynia was in six, and specifically sharp pain  
12 was in six. Then difficulty feeling your feet or  
13 instances when walking was five.  
14 So these scales mix functional report as  
15 well as symptoms, so after this, it gets a little  
16 murky, so I'll stop there.  
17 As far as the signs go, the most common are  
18 vibration, reflex, pinprick, and then to a little  
19 bit lesser extent, muscle strength, and touch  
20 pressure.  
21 DR. FREEMAN: All right. So should we  
22 divide into those groups? It looks like it's

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1 roughly -- what's up?  
2 DR. FELDMAN: This is just a suggestion  
3 because it's a quarter till 2:00, and we have two  
4 talks. What do you think about having the two  
5 talks, taking a break, and then dividing into the  
6 groups? You've got another discussion session  
7 planned --  
8 DR. FREEMAN: You know what? Here's what I  
9 thought --  
10 DR. FELDMAN: -- just based on time, what  
11 would be most efficient?  
12 DR. FREEMAN: What I thought is that we  
13 would do the discussion because that is so tightly  
14 connected to this most previous session. We can  
15 then do the next talks. We do have time, and if we  
16 only do Jim's talk, that will be okay, too, or if  
17 we do the session on the Diabetic Neuropathy  
18 Consortium tomorrow or later, that will be time.  
19 But I think we're all geared up for doing this, and  
20 I think we can do that.  
21 I think roughly a half an hour should be  
22 enough. I'll walk around and see.

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1 It looks like the way we are seated is  
2 pretty random, so why don't we say -- and I think  
3 of the panel, pick your group that you're going to  
4 go with, but one, two, three, four, five, six,  
5 seven, up to is one group.  
6 Maybe that group -- Chris, you were telling  
7 me where?  
8 DR. GIBBONS: We're going to split up into  
9 three rooms. There's the eating room here on the  
10 right. There's a small room for about seven or  
11 eight people right behind the check-in desk over  
12 there; they'll direct you over. These will be the  
13 three spaces we'll move to.  
14 DR. FREEMAN: That group who I called out  
15 plus one or two panelists, you'll go to the small  
16 room.  
17 Jen, one, two, three, four, five, six,  
18 seven, up to Jim Dyck, go to the dining room with  
19 one or two panelists, and then the rest stay here.  
20 And remember that you are going to shape your views  
21 on what you want from the setting.  
22 (Whereupon, at 1:47 p.m., a breakout session

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1 occurred.)  
2 Breakout Discussion  
3 DR. FREEMAN: Here is the story. To be  
4 quite honest, I was worried that we would finish  
5 early because nobody would say anything. I really  
6 had no idea this was going to go, let's say, so  
7 well.  
8 (Laughter.)  
9 DR. FREEMAN: What we're going to do this  
10 afternoon, just the big picture, everybody will  
11 come up, at least the representatives from each  
12 group will come up, give their spiel. There will  
13 be discussion about that. I have no idea how long  
14 that's going to take, but let's say it will be  
15 somewhere around 30 minutes, maybe more.  
16 I want to give the perspective on this that  
17 this is not yet cast in stone. Gordon will have  
18 the onerous task of merging this, sending round  
19 questions for voting. We once did something, I  
20 think which was very effective, using the Delphi  
21 method where people voted, and we came down to  
22 definitive conclusions, which may be an approach

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1 for doing this. But let's try and get as close to  
2 final as we can this afternoon with this.  
3 We will then have Jim Dyck give his talk,  
4 and depending on timing, perhaps Chris give his  
5 talk. And then we may have a working dinner,  
6 depending on the timing, where the Diabetic  
7 Neuropathy Consortium -- somebody said the DPNC.  
8 Is that the new name?  
9 DR. GIBBONS: We're still working on --  
10 DR. FREEMAN: Still working on it?  
11 That consortium -- what's that?  
12 DR. FELDMAN: I was just going to ask Troels  
13 Jensen if maybe we can have the name.  
14 DR. FREEMAN: If we can have his name?  
15 Okay.  
16 DR. FELDMAN: Because the consortium is just  
17 David Bennett, myself, and Troels, so it's a small  
18 --  
19 DR. FREEMAN: It's small. We're happy to  
20 include Troels, so then we'll -- yeah, okay.  
21 Whatever it's called, they will -- we will  
22 meet over dinner, possibly.

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1 Let's go with group 3, which is -- Chris,  
2 going to do the presentation?  
3 DR. GIBBONS: Sure. I might need some help  
4 scrolling since I put this on Word.  
5 We were basically coming up -- our focus  
6 was, again, small fiber, large fiber, mix, and some  
7 of the discussion. We actually came up with a very  
8 simple solution. We decided there was no small  
9 fiber. There was no large fiber. It was all  
10 mixed, and that was pretty much it. We're done.  
11 (Laughter.)  
12 DR. GIBBONS: Actually, it gets in a little  
13 more detail. So what we tried to do was come  
14 through and define a little more clearly. We  
15 thought again, small fiber did exist, in gest, but  
16 it's going to be less likely.  
17 One of the things we were looking for were  
18 symptoms, which had to be bilateral, symmetrical,  
19 length-dependent, positive symptoms. We thought  
20 for an isolated diabetic small fiber neuropathy, we  
21 had to have one of the following symptoms: burning  
22 pain; prickling, tingling, lightning, stabbing

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1 pains; hypersensitivity; or paradoxical temperature  
2 sensations, so hot being cold, et cetera. So those  
3 were the presenting symptoms, one of those.  
4 Negative symptoms were not required, but  
5 they were supportive. Again, for my group, if I  
6 typed this incorrectly, please correct me, but lack  
7 of feeling temperature, pain was supportive but not  
8 diagnostic.  
9 Signs, we thought they needed one of the  
10 following signs: either loss of pinprick being the  
11 predominant one. We really all felt that cold  
12 temperature, although it's really been used  
13 historically, was so far down on the bottom of  
14 utility as a clinical bedside test that we didn't  
15 want to recommend it. Warm temperature, also  
16 pretty far down from a clinical bedside test, so we  
17 thought pinprick was really the way to go.  
18 Then allodynia or hyperalgesia were things  
19 we wanted to use in addition to pinprick as one of  
20 the following, and it was primarily pain and  
21 hyperalgesia or a loss of pinprick that would put  
22 you in the positive sign.

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1 Then the negative, if one of these were  
2 abnormal, this would move you to the mixed  
3 neuropathy by definition. So if you had abnormal  
4 reflexes, abnormal vibration, proprioception, or  
5 motor, that would automatically move you into the  
6 mixed category.  
7 The other comment we had --  
8 DR. PELTIER: We did have the age caveat.  
9 DR. GIBBONS: Oh, right, I have the age  
10 caveat a little later. But the age caveat for  
11 reflexes, and, again, we have to --  
12 MALE VOICE: And vibration.  
13 DR. GIBBONS: -- and vibration. So there's  
14 some variability, but I think absent vibration,  
15 would still not fall into that. There would some  
16 definitional operation there.  
17 Then light touch we thought was not  
18 particularly valuable. We did have comments about  
19 whether validated quantitative sensory testing  
20 should be used in place of examination. We thought  
21 not on a routine clinical approach, but something  
22 for discussion maybe afterwards in terms of where

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1 the QST fit into all of this.  
2 From an investigational standpoint, not  
3 required but supportive, we thought confirming, so  
4 autonomic testing, so just thermoregulatory sweat  
5 testing or QSART showing a length-dependent loss  
6 would confirm or be supportive of the other  
7 diagnoses.  
8 If you can move to the next slide or scroll  
9 up, if it's possible.  
10 Or on the confirmatory testing skin biopsy  
11 with abnormal intraepidermal nerve fiber density,  
12 and in this case, it requires an and normal nerve  
13 conduction studies. Again, we're going to  
14 require -- we'll have to operationalize what those  
15 actually mean by age, et cetera.  
16 Then we move to the large fiber --  
17 DR. FREEMAN: I think it might be worthwhile  
18 just to stop now and discuss that.  
19 DR. POP-BUSUI: I actually have a comment  
20 regarding the need of using positive and negative.  
21 We did have our discussion around those same terms  
22 as well, and I think it reflects maybe in some

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1 providers or even patients, negative feeling or  
2 mixed feeling or confusion.  
3 Why do we need to use positive, negative?  
4 DR. FREEMAN: Can you scroll back?  
5 DR. GIBBONS: To the other page.  
6 DR. POP-BUSUI: Why not just symptoms?  
7 Because I think they are relevant symptoms of  
8 neuropathy, but that I don't think that we can gain  
9 anything by using positive, negative.  
10 DR. GIBBONS: Yes. I think from an  
11 operational standpoint as long as we understand  
12 what we mean, we can rephrase that. I don't think  
13 we need to indicate a connotation to the positive  
14 or negative, but it's the presence or absence may  
15 be a better way of thinking about it, which is  
16 fine.  
17 Jim?  
18 DR. DYCK: So we had lots of discussions  
19 about symptoms and the role of symptoms indicating  
20 the presence of neuropathy. We're mostly talking  
21 about severity.  
22 Now, most people think of small fiber

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1 neuropathy almost by definition as being a  
2 symptomatic neuropathy. Theoretically, one could  
3 have a small fiber neuropathy where you don't have  
4 symptoms and you might have reduced pinprick and  
5 you might have reduced epidermal nerve fibers.  
6 Maybe it's not so important because they don't have  
7 symptoms, but your first thing required one of  
8 those symptoms. I don't know if that should be  
9 absolutely necessary.  
10 DR. GIBBONS: Yes, we had a lot of debate  
11 about that, and I may have captured it incorrectly.  
12 I think one of the things I didn't have a chance to  
13 do is actually to phrase this in a way that made  
14 sense from a presentation standpoint. But we were  
15 thinking that the positive would really put us into  
16 the painful small fiber neuropathy. A symptom  
17 would move us into that category.  
18 The absence of a symptom would not  
19 necessarily move us into a mixed category, but it  
20 would move us out of the painful small fiber  
21 neuropathy category. I didn't actually get to that  
22 point, and that's a great interlude.

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1 DR. FREEMAN: The one thing it should say,  
2 again, I'm thinking of this from the clinical trial  
3 standpoint, drug company X within that 1.7 blocker  
4 will want a --  
5 DR. GIBBONS: Painful, right.  
6 DR. FREEMAN: -- symptomatic small fiber  
7 neuropathy, and then drug company Y with a drug to  
8 treat, say, Rob's pre-diabetic neuropathy will not  
9 care about symptoms necessarily but would be quite  
10 happy to just have an asymptomatic small fiber  
11 neuropathy.  
12 Maybe you want to subdivide it into  
13 symptomatic and --  
14 (Crosstalk.)  
15 DR. PELTIER: We also talked about  
16 practically that it's very rare to see an  
17 asymptomatic small fiber predominant neuropathy.  
18 It's possible but like --  
19 DR. GIBBONS: I think we had disagreement on  
20 that. I think the referral to a physician for  
21 treatment of pain, you're not going to have it.  
22 But I did mention in my own clinics where I get

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1 general neuropathy referrals, I see that not  
2 uncommonly. So it depends on who's seeing what.  
3 DR. ZIEGLER: Definitely. I could even say  
4 it's more frequent, more common than the painful  
5 entity. So it just depends on --  
6 DR. SMITH: Is it the same thing? I think  
7 that's the question. Because I agree, if you look  
8 carefully, you find this all the time, particularly  
9 using abnormal pin sensation and abnormal skin  
10 biopsy, but is that the same condition as a  
11 symptomatic or painful small fiber predominant  
12 neuropathy? Or does it matter?  
13 DR. ZIEGLER: But still I think you should  
14 have a heading for that, a name for that kind of  
15 neuropathy. So I would agree with Roy's suggestion  
16 to call this asymptomatic predominantly or  
17 symptomatic predominantly small fiber.  
18 DR. GIBBONS: Yes, I think that's perfect  
19 and yes --  
20 DR. DYCK: Or preclinical.  
21 DR. FREEMAN: Can I ask a neurologist or  
22 anybody a question? Non-painful prickling and

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1 tingling, is that small fiber or large fiber?  
2 DR. GIBBONS: We've got some mixed  
3 discussion.  
4 (Laughter.)  
5 DR. ZIEGLER: Yes, we don't know. We don't  
6 know.  
7 DR. GIBBONS: We had a lot of debate about  
8 that.  
9 DR. FREEMAN: But one of the questions is do  
10 we want to add this then as one of your one  
11 positive symptoms, and is one enough? Do you want  
12 two? I don't know the answer to this, and here we  
13 get into the possible, probable, definite story,  
14 perhaps.  
15 DR. ZIEGLER: You could also define  
16 painless. You could also call it painless if it's  
17 numbness, paresthesias.  
18 DR. FREEMAN: With the small fiber. Now,  
19 numbness I think most neurologists would say maybe  
20 it's [inaudible – off mic]. The question is really  
21 related to small fiber modalities. I don't know  
22 the answer to the question, but I wondered.

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1 Anybody have a definite view on that?  
2 MALE VOICE: There may be answers, but I'd  
3 be worried about putting tingling as a small fiber  
4 symptom.  
5 DR. FREEMAN: You'd be worried?  
6 MALE VOICE: Yes.  
7 MALE VOICE: I do see tingling in both  
8 large --  
9 DR. GIBBONS: Yes, we were getting into the  
10 question of painful tingling and that operational  
11 definition --  
12 DR. ZIEGLER: That would be dysesthesia.  
13 That would be dysesthesia if it's --  
14 MALE VOICE: You might even say --  
15 DR. ZIEGLER: No, not even that. That's  
16 unpleasant paresthesias would be dysesthesias.  
17 DR. HERRMANN: What we did in the discussion  
18 one way we thought about it was say tingling or  
19 prickling wouldn't put you in a small or large  
20 fiber category. It's an acceptable symptom. You  
21 would make the determination of small versus large  
22 based on your signs.

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1 DR. SMITH: How do you know this isn't just  
2 early neuropathy? Because we know that if you  
3 follow these patients, most of them develop large  
4 fiber findings, and you're also making the judgment  
5 that they don't have large fiber findings at a  
6 single point in time, not knowing what the  
7 quantitative evaluation of their large fiber  
8 sensation would have been 6 or 12 months ago, and  
9 we know 6 or 12 months later, it's likely to  
10 change.  
11 Does that matter, the --  
12 FEMALE VOICE: It's the earlier comment that  
13 we said, okay, it's just all mixed. It really  
14 doesn't matter.  
15 DR. GIBBONS: There was that impression.  
16 DR. SINGLETON: You weren't joking? Are you  
17 really going to get to the point that it's all  
18 mixed, and you're just taking time?  
19 (Crosstalk.)  
20 DR. GIBBONS: No. So we're --  
21 FEMALE VOICE: -- we did discuss that.  
22 DR. GIBBONS: Yes, we are operationalizing

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1 this for a point in time theoretically for an entry  
2 to a trial. It's an isolated small fiber  
3 neuropathy at this point in time with the  
4 understanding that it will progress, and we expect  
5 that there will be at some point large fiber,  
6 theoretically.  
7 DR. SINGLETON: I think we can think about  
8 the idea that small fiber or small fiber  
9 predominant neuropathy is also early diabetic  
10 neuropathy for many people.  
11 DR. ZIEGLER: It's simply not true. It's  
12 not true.  
13 DR. SINGLETON: I said for many people, not  
14 for everyone.  
15 DR. ZIEGLER: Yes, it's --  
16 DR. SINGLETON: It's the natural history to  
17 go from --  
18 DR. ZIEGLER: I don't think so.  
19 DR. SINGLETON: -- for many patients to go  
20 from small fiber to --  
21 DR. ZIEGLER: No, no, no. I don't think  
22 there is enough evidence to support that notion.

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1 DR. HERRMANN: In the Rochester diabetic  
2 neuropathy study, my father did this really nice  
3 study 10 years ago that I think most of us have  
4 read where he looked at the heat pain thresholds  
5 and saw in normal and abnormal people with and  
6 without neuropathy that there was a shift to people  
7 toward -- in early diabetes toward the  
8 hyperalgesic. As time passed, it shifted to the  
9 hypoalgesic. So it went originally towards having  
10 increased pain thresholds, and then it went just to  
11 the other extreme.  
12 I think that actually is an argument that it  
13 is early diabetic neuropathy giving you almost a  
14 painful small fiber neuropathy and then it goes the  
15 other direction.  
16 DR. ZIEGLER: I think there's no support for  
17 that. You have always that selection bias, and you  
18 have to consider that. So if you want to study  
19 early diabetic neuropathy, you have to go to the  
20 early stage of the disease, and that is at the time  
21 of diagnosis or at least within the first year from  
22 diagnosis, and then to follow the patients

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1 prospectively. And only by doing this, you can say  
2 this comes first or not.  
3 We've done some thousands recently diagnosed  
4 type 1 or type 2 patients, and we see very, very  
5 little allodynia or hyperalgesia in those patients.  
6 So this is clearly not documenting that this is an  
7 early feature, and very few patients actually among  
8 these have pain. That's a minority.  
9 If you think of type 1, most of them have  
10 subclinical neuropathy, that is, nerve conduction  
11 deficits. And if you think of type 2, they have at  
12 best -- the most frequent category you see is  
13 possible neuropathy in those patients, but very  
14 rarely, you see the gain phenomena in those  
15 patients.  
16 DR. HARATI: I agree. I think that's the  
17 neurologist's bias. Neurologists --  
18 DR. ZIEGLER: Yes, definitely, there is a  
19 bias.  
20 DR. HARATI: Diabetologists see the  
21 different group of patients, so I agree.  
22 DR. ZIEGLER: It's the same -- we will

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1 discuss that tomorrow. It's the same with  
2 pre-diabetic neuropathy. You're coming from a very  
3 different angle. If you're a tertiary center, and  
4 a patient with idiopathic neuropathy comes to you  
5 and it is painful, and then you do your OGGT on  
6 them, of course, the OGGT will be frequently  
7 abnormal because this is an abnormal phenomena.  
8 This is the case in the general population that  
9 they have pre-diabetes. And in addition, they may  
10 be multi-morbid patients with polypharmacy and so  
11 on, so that the likelihood is very high that they  
12 would have pre-diabetes.  
13 So you have to come from the other side.  
14 You have to go to the population level and then see  
15 how frequent pre-diabetic neuropathy is.  
16 The same thing here, you have to start at  
17 the early stage of diabetes and have a  
18 representative population, and see whether those  
19 phenomena are found or not. We have a very, very  
20 meticulously phenotype population with several  
21 hundreds of people recently diagnosed, and I think  
22 that's the best way to see which phenomena of

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1 diabetic neuropathy will be painful or not, early  
2 or not. I don't know there is another appropriate  
3 way to look at that.  
4 DR. FREEMAN: Just in the interest of time -  
5 -  
6 DR. ZIEGLER: Sorry.  
7 DR. FREEMAN: -- it does exist whether it's  
8 highly prevalent, early, late, fixed, static, part  
9 of a window in time, if you catch it at one point  
10 and look at it the next day, or it will become  
11 large. Let's just accept that there is this  
12 entity.  
13 I want to give Gordon enough to work with,  
14 so I'm not quite sure what you mean by "supportive,  
15 lack of feeling of temperature or pain."  
16 We're trying to have the menu, the Chinese  
17 menu --  
18 DR. FELDMAN: Roy, could you use the  
19 microphone? We can't hear you.  
20 DR. FREEMAN: Sorry. It's funny. I always  
21 thought I spoke so loudly.  
22 I want to give Gordon enough to work with,

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1 so I want to clarify a couple of things. Have we  
2 agreed that prickling and tingling is painful  
3 prickling and tingling, whatever we're going to  
4 call it?  
5 DR. ZIEGLER: It's not. It's painless.  
6 It's painless. It's not painful.  
7 DR. FREEMAN: In small fiber neuropathy,  
8 we're talking about?  
9 DR. ZIEGLER: I think there is no agreement.  
10 DR. GIBBONS: We're talking about a symptom  
11 that's enough to be reported as painful.  
12 DR. FREEMAN: As painful?  
13 DR. GIBBONS: Yes. That was our operational  
14 definition. And again, this is quick shorthand.  
15 DR. FREEMAN: No, I understand that.  
16 Clarify "negative symptoms, supportive lack of."  
17 Is that part of the menu, or is that just --  
18 DR. GIBBONS: Negative symptoms were  
19 supportive. They weren't going to --  
20 DR. FREEMAN: Didn't matter one way --  
21 DR. GIBBONS: -- modify the definition.  
22 DR. FREEMAN: -- were not part of. Okay. I

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1 think that that's probably enough for Gordon to --  
2 DR. GIBBONS: Again, I can clean this up to  
3 revise --  
4 DR. SMITH: You're saying that there needs  
5 to be one positive symptom and one sign, positive  
6 sign? I'm not sure I understand --  
7 DR. GIBBONS: One positive symptom, one  
8 positive sign, and in absence of the other things  
9 that could move it into a mixed.  
10 DR. FREEMAN: And it was an "and." Could we  
11 scroll down? It was "and skin biopsy."  
12 DR. GIBBONS: The investigations were  
13 confirming; they weren't required.  
14 DR. FREEMAN: The biopsy?  
15 DR. GIBBONS: Right, exactly. So you could  
16 use --  
17 DR. FREEMAN: Before skin biopsy --  
18 DR. GIBBONS: You could use again autonomic  
19 sudomotor function testing or skin biopsy and a  
20 negative nerve conduction study. Again, these were  
21 confirming.  
22 DR. FREEMAN: And negative, Gordon, is going

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1 to have to work, what, negative means --  
2 DR. ZIEGLER: Normal.  
3 DR. FREEMAN: I understand that, but normal  
4 is --  
5 DR. DYCK: How about QST?  
6 DR. GIBBONS: We had a long debate about QST  
7 and how it might be a positive or negative. We  
8 didn't come to an answer I think was the shorthand.  
9 We determined that it might be a substitute for the  
10 examination, but we weren't sure that it was  
11 necessarily going to substitute for one of the  
12 other tests that were confirming.  
13 It could substitute for the exam, but we  
14 weren't sure that that was necessarily going to be  
15 a reason enough to do QST instead of the exam.  
16 DR. DYCK: In my institution, I have  
17 thermoregulatory sweat test, which I think is the  
18 best test for small fiber neuropathy. Now, I  
19 understand most of the world doesn't have that.  
20 DR. GIBBONS: That's why we said QST or  
21 thermoregulatory --  
22 (Crosstalk.)

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1 DR. GIBBONS: Sorry. It was on the other  
2 scroll, thermoregulatory sweat testing or QSART,  
3 yeah.  
4 DR. BRUEHL: The things that you put like  
5 the negative being supportive, that is what goes in  
6 Dimension 2. So any things like that that are  
7 common enough that you would consider it  
8 characteristic but not is important that it's  
9 diagnostic, just falls down to Dimension 2?  
10 DR. FREEMAN: The only question, I suppose,  
11 is one and one or -- maybe I should sit closer.  
12 The only question I think that we need to resolve  
13 is one enough of each of the one sign, one symptom,  
14 or more than that?  
15 DR. GIBBONS: Yes, we had some debate, and  
16 at this point, we also thought it would be  
17 important to go back and see a little bit more in  
18 terms of the data from the literature to try and  
19 get at that. We didn't have that on hand.  
20 DR. FREEMAN: I may be wrong on this, but I  
21 know I can look at my slides. But I think that  
22 Giseppi's study, he had QST or skin biopsy, or skin

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1 biopsy the definitive. Does somebody know?  
2 MALE VOICE: It's QST and skin biopsy.  
3 DR. FREEMAN: QST and skin biopsy. Worth  
4 looking at that, not that we need to follow that.  
5 DR. HERRMANN: In Giseppi's study,  
6 basically, it was an "or." So a QST could have  
7 been one of the elements.  
8 DR. FREEMAN: That's what I remember.  
9 MALE VOICE: It performed fairly similar  
10 to -- skin biopsy was a bit better, but QST, it had  
11 some --  
12 DR. GIBBONS: Performed similarly.  
13 DR. FREEMAN: Let's move on.  
14 DR. GIBBONS: Then --  
15 DR. SINGLETON: I was going to say the  
16 theoretical concern with QST is that it doesn't  
17 necessarily measure the function of peripheral  
18 nerve.  
19 DR. GIBBONS: Yes, so again, there was a lot  
20 of interest in defining it.  
21 We moved to the large fiber --  
22 DR. FREEMAN: Can I just ask one quick

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1 question? I'm sorry about this, but this is a  
2 really practical question, which is an ongoing  
3 issue.  
4 There are a couple of drug companies that  
5 are interested in doing trials in small fiber  
6 neuropathy. Somehow they're quite happy about  
7 doing skin biopsy. They're not happy about doing  
8 nerve conduction studies as a definitive exclusion.  
9 How strongly do we feel about that? Do we  
10 want to shade that? Are we hard nosed about a  
11 normal -- whatever normal means -- nerve conduction  
12 study?  
13 DR. SINGLETON: I think it depends on do  
14 they want a pure small fiber neuropathy. We have a  
15 --  
16 DR. GIBBONS: We address that --  
17 DR. SINGLETON: -- category of small fiber  
18 predominant neuropathy, and we would be happy to  
19 allow abnormal nerves.  
20 DR. FREEMAN: I think that's a very nice way  
21 of doing it. I like that a lot.  
22 DR. POP-BUSUI: Plus I think that we should

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1 all agree that those criteria will be like a  
2 starting point, and then based on the type of  
3 questions that a particular study or trial needs to  
4 answer, we can decide whether all these measures  
5 are needed or just a portion of them.  
6 DR. FREEMAN: Yes. Just of interest, of the  
7 Toronto meeting, Solomon's paper and Rayaz's paper  
8 actually say two different things for the  
9 definition of small fiber neuropathy. Rayaz's one  
10 is like you, predominant, and Solomon's is pure.  
11 Let's move on. Sorry about that.  
12 DR. GIBBONS: It's okay. So we moved on to  
13 large fiber as the next, and we actually had a lot  
14 of debate about if anyone had ever seen a pure  
15 large fiber diabetic neuropathy.  
16 DR. ZIEGLER: Why not?  
17 DR. GIBBONS: We just asked has anyone seen  
18 it.  
19 DR. ZIEGLER: Sure.  
20 DR. GIBBONS: You have?  
21 DR. ZIEGLER: Yes.  
22 DR. GIBBONS: Pure large fiber, no

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1 involvement of small fiber at all?  
2 DR. ZIEGLER: Yes.  
3 DR. SINGLETON: So nerve fiber density was  
4 normal in those patients?  
5 DR. ZIEGLER: Yes, that's possible. Why  
6 not?  
7 DR. GIBBONS: No. We're saying it's  
8 possible. We're asking has anyone actually in this  
9 room seen it.  
10 DR. ZIEGLER: Certainly, I can go through  
11 the data based -- I'm sure I will find those  
12 patients.  
13 DR. GIBBONS: So we're less interested in  
14 the database. We're just trying to figure out --  
15 DR. ZIEGLER: I was not particularly  
16 interested in knowing that. I don't know --  
17 DR. GIBBONS: Well, we were just wondering  
18 as we got to it. None of us can actually ever  
19 recall seeing one, ever. And so we're wondering  
20 from an operational definition how important that  
21 is. But we're trying to get there.  
22 Jim?

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1 DR. DYCK: This whole thing about your pure  
2 small fiber and pure large fiber, I think are sort  
3 of -- don't really exist as such. I think you have  
4 small fiber predominant, large fiber predominant,  
5 but very rarely are you going to have pure either  
6 of those.  
7 This obsession with pure small fiber  
8 neuropathy also seems artificial to me, too,  
9 because usually, there will be some small fiber  
10 involvement. In fact, my father's doing a study  
11 right now looking at correlations of things, and he  
12 finds that it correlates the most strongly with  
13 epidermal nerve fiber density is the sural snap.  
14 It's large fiber and small fiber correlated with  
15 each other.  
16 DR. HERRMANN: We kind of create some of  
17 these definitions. I don't think we're really  
18 implying what the percentages are in each group.  
19 We just put the categories there. For the NAV 1.7  
20 trial that Roy keeps talking about and based on  
21 other people's work, maybe they want that very  
22 small subset of pure small fiber. But for most

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1 diabetic neuropathy trials, you're going to maybe  
2 go with a small fiber predominant, which may  
3 include the few who have pure and the majority who  
4 have --  
5 DR. SINGLETON: Jim, this is our charge, so  
6 that's what we --  
7 DR. DYCK: But it seems a little artificial.  
8 DR. GIBBONS: No, we agree, and that was our  
9 decision.  
10 DR. FREEMAN: I wouldn't say artificial, but  
11 I think there's a low prevalence of that entity.  
12 Maybe it's irrelevant, but there are some who are  
13 focusing on that.  
14 DR. DYCK: I hear you. "Artificial" is the  
15 wrong term, but it's a small minority.  
16 DR. GIBBONS: At least operationally, what  
17 we tried to go through with this was that there  
18 were really no defined symptoms that were required  
19 for an isolated pure small fiber neuropathy. We  
20 thought signs, you again had to have normal pin,  
21 normal pain. There had to be abnormal joint  
22 position vibration.

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1 We talked about monofilament use, but it was  
2 difficult to actually get graded sensitivity, so we  
3 weren't sure the value of that. But by definition,  
4 it would have to have abnormal nerve conduction  
5 studies and a normal skin biopsy. But we also  
6 commented -- and that's what the yellow part  
7 is -- that frankly, we didn't think you were ever  
8 going to see this. And it also seemed like if you  
9 did see this, you really had to think this was not  
10 related to diabetes, and this was something else.  
11 You needed to be very careful about rethinking that  
12 potential diagnosis if it's a pure isolated large  
13 fiber neuropathy.  
14 DR. POP-BUSUI: Then if it's so rare, who is  
15 going to be interested to study that disease?  
16 DR. GIBBONS: That was what moved us to the  
17 next discussion point, which is the mixed  
18 neuropathies.  
19 DR. DYCK: I understand it's part of the  
20 conversation, but Hugh Garland and company would  
21 argue that the diabetic amyotrophy was a pure large  
22 fiber neuropathy.

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1 DR. PELTIER: But we're simply talking about  
2 the --  
3 DR. GIBBONS: Yes, distal axonal. We agree,  
4 but we're focused on distal axonal.  
5 DR. FREEMAN: Chris, joint position,  
6 monofilaments, one of the above, all of the above,  
7 two of the three?  
8 DR. GIBBONS: We thought that joint position  
9 vibration should be abnormal. Monofilaments, we  
10 weren't sure we actually needed. That was a  
11 debate.  
12 DR. FREEMAN: Joint position and vibration?  
13 DR. GIBBONS: Yes.  
14 DR. FREEMAN: Okay.  
15 DR. GIBBONS: For an isolated large fiber.  
16 Then going on to the mixed neuropathies,  
17 which we thought were actually the vast majority of  
18 what we're interested in, and these were going to  
19 be a length-dependent neuropathy that was not an  
20 isolated small fiber neuropathy. We, again, didn't  
21 think we'd be looking at the large fiber component.  
22 So we were talking about one symptom, length-

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1 dependent.  
2 If you want to go to the next slide. We had  
3 components that looked at these different things,  
4 but we were trying to, again, shift this into a  
5 discussion of small fiber predominant, large fiber  
6 predominant. And the way we went through this was  
7 for small fiber, again, it would meet the criteria  
8 for the small fiber neuropathy with the addition of  
9 some reduction in vibration at the toes.  
10 We had some discussion about anything else,  
11 but anything else, which included abnormal  
12 proprioception, abnormal reflexes except with the  
13 appropriate age-related discussion, would move you  
14 actually into a large fiber predominant as opposed  
15 to small fiber.  
16 DR. SINGLETON: Absent reflexes.  
17 DR. GIBBONS: Absent reflexes, yes.  
18 Then the large fiber predominant would be a  
19 big catchall there would be abnormal vibration at  
20 the ankles or above. Any proprioceptive loss at  
21 the toes would move you to large fiber. Absent  
22 ankle reflexes, again, would move you to large

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1 fiber. This would also be a length-dependent  
2 axonal neuropathy.  
3 It was sort of a catchall. You, again, had  
4 the small fiber, the small fiber predominant, which  
5 included the vibratory reduction in the toes;  
6 anything else would move you into the large fiber  
7 predominant.  
8 DR. SMITH: Do we really need criteria for  
9 small fiber predominant, large fiber predominant,  
10 small and large fiber equal, halfway between the  
11 other extremes? At some point, this gets to be a  
12 splitting exercise.  
13 I understand why there's a need for a small  
14 fiber neuropathy set of criteria given the  
15 therapeutic milieu in which we live. I'm not sure  
16 I understand the need for any of the rest of this  
17 because it all seems to be part of the spectrum of  
18 what we would all agree is distal symmetric  
19 polyneuropathy.  
20 DR. FREEMAN: Just to give my take on this,  
21 I agree that this is -- we actually are  
22 creating -- we're drawing a line in a spectrum,

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1 most likely because I think it is an evolving  
2 picture, and there's some patients that may come in  
3 or we may see for the first time who have mixed.  
4 And there are many patients who I think evolve, and  
5 this may be referral bias. I happen not to think  
6 so.  
7 In the clinical trial world, just to give  
8 that example again, there are companies that do not  
9 want to do nerve conduction studies, so they are  
10 left saying that, well, this is a small fiber  
11 neuropathy because they fulfill all of those  
12 criteria, but the Gibbons' last criteria, the nerve  
13 conduction study, that's not done. What do we call  
14 that group? I think it's reasonable to call that  
15 small fiber predominant because they may have some  
16 large fiber element, and if you were to do a sural  
17 nerve biopsy, for example, even that pure small  
18 fiber neuropathy may have large fiber loss.  
19 So I agree that all of this is artificial,  
20 but I think there needs to be some term to describe  
21 those patients who have an array of small fiber  
22 features but still will have either nerve

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1 conductions not done or mildly abnormal nerve  
2 conduction studies or mild vibration.  
3 DR. SMITH: Then why not just use the small  
4 fiber and say small fiber predominant based on  
5 clinical criteria, or one might even say probable  
6 small fiber neuropathy, and then use the nerve  
7 conduction, normal nerve conduction is confirmed  
8 or put it into the rubric that we're going to be  
9 talking about.  
10 But I get the whole small fiber thing.  
11 Where it starts to seem really irrelevant to me is  
12 in a pure large fiber or various gradations along  
13 that continuum. I totally understand the situation  
14 you're raising because we're dealing with it in  
15 trials now.  
16 DR. BRUEHL: This is a good example of what  
17 happened with CRPS is there was an argument over  
18 whether it made a difference whether you had  
19 evidence of peripheral nerve injury or not.  
20 Historically, people paid attention to that.  
21 There's no evidence that it makes any difference.  
22 What we opted to do was the criteria are for

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1 CRPS. So here the criteria would be for peripheral  
2 neuropathy. You'd have the criteria which are  
3 basically the same regardless of whether it's large  
4 or small fiber dominant, and then you'd have  
5 subtypes listed at the bottom that said small fiber  
6 predominant, specified this is XYZ conditions. If  
7 this pattern is shown, large fiber. This is shown.  
8 I'll say pragmatically from the FDA's  
9 standpoint, we encountered this with CRPS, is if  
10 you do a trial where the entry criterion is CRPS,  
11 then the indication is CRPS. You can, though,  
12 restrict it to one of the subtypes listed in there,  
13 which in this case would be like a small fiber  
14 predominant. That's who the indicator would be for  
15 would be restricted to a subtype of peripheral  
16 neuropathy.  
17 It doesn't leave anything out. There's no  
18 disadvantage to doing it this way.  
19 DR. GIBBONS: Doug?  
20 DR. ZOCHODNE: I just argue from a  
21 pathophysiological point of view that [inaudible -  
22 off mic].

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1 DR. GIBBONS: Can you use the mic, Doug?  
2 DR. ZOCHODNE: Yes. The definitions will be  
3 useful for many reasons because we anticipate if  
4 these guidelines stand, we may be able to  
5 understand disorders, why there's large fibers and  
6 large neurons become targeted later. Maybe it's  
7 for completely different reasons than small  
8 neurons.  
9 I think if these guidelines are helpful, we  
10 are going to want to know all the different types.  
11 DR. FREEMAN: Dave?  
12 DR. BENNETT: I basically agree with Gordon,  
13 that I'm comfortable with small fiber predominant  
14 and mixed. I think where I'm uncomfortable is  
15 where we get to large fiber predominant. Why  
16 should the presence of vibrations -- why should  
17 having vibrations trump other things that make that  
18 large fiber predominant? In reality, it's mixed.  
19 So I would --  
20 DR. GIBBONS: Call it mixed.  
21 DR. BENNETT: I think I'd rather have small  
22 fiber predominant or mixed, and that's it.

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1 DR. GIBBONS: It's very reasonable.  
2 DR. FREEMAN: I think this is enough to work  
3 with.  
4 Do you have more to --  
5 DR. GIBBONS: That's all.  
6 DR. FREEMAN: So this was the easy one.  
7 (Laughter.)  
8 DR. FREEMAN: I'm going to disrupt the  
9 sequence just because Jim Dyck has a plane to  
10 catch, and I think probably we should bring you  
11 on -- your plane is at 7:00?  
12 DR. DYCK: 7:00.  
13 DR. FREEMAN: We should bring --  
14 DR. DYCK: I probably need to leave at 5:00.  
15 DR. FREEMAN: Need to leave at 5:00.  
16 DR. DYCK: It's an hour and a half. I have  
17 a half an hour talk, and you want discussion.  
18 DR. FREEMAN: Well, yes. I think we  
19 should -- let's have your talk just to be on the  
20 safe side, and we'll come back to this in a while.  
21 (Crosstalk.)  
22 DR. DYCK: Sorry everyone.

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1 (Crosstalk.)  
2 DR. FREEMAN: I should say -- thank you for  
3 reminding me. This is how you spend your vacation  
4 when you are at the Mayo Clinic.  
5 (Laughter.)  
6 DR. FREEMAN: Jim, we are really fortunate  
7 to have Jim. He took a vacation day to come here,  
8 so this is -- if you ever want -- if you feel that  
9 you don't want vacation any longer, the Mayo Clinic  
10 has a place for you.  
11  
12 Presentation – James Dyck  
13 DR. DYCK: There are many very good things  
14 about working at the Mayo Clinic, but they guard  
15 their days very closely.  
16 This is a completely different topic. We  
17 have really been focusing in on diabetic  
18 polyneuropathy and small fiber neuropathies and  
19 things like that. I'm going to talk about diabetic  
20 lumbosacral radiculoplexus neuropathy, and then  
21 about diabetic radiculoplexus neuropathy more  
22 generally.

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1 I'm going to focus in on what's been written  
2 about classifications of this or lack of  
3 classifications and then about some of the  
4 controversies. It seems to me that what we've  
5 really been talking about are controversies so far,  
6 so from that point of view, I will be right on  
7 them.  
8 Radiculoplexus neuropathies are conditions  
9 involving roots, plexus, peripheral nerves, and can  
10 involve the cervical levels, the thoracic levels,  
11 lumbosacral levels, and they can involve people  
12 with diabetes mellitus and people without diabetes  
13 mellitus.  
14 I'm going to begin with diabetic lumbosacral  
15 radiculoplexus neuropathy. This condition has been  
16 described under many different names, and I think  
17 it really gets at the very thinking about it. So  
18 neuritic paralysis by Bruns, paralytic neuropathy  
19 by Leyden. Hugh Garland talked about diabetic  
20 myopathy, diabetic myelopathy, and eventually, he  
21 said, "I don't know what it is," and he called it  
22 diabetic amyotrophy. That was the term that stuck

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1 for a long time, diabetic I don't know what it is.  
2 It is known as diabetic femoral sciatic  
3 neuropathy, diabetic femoral neuropathy, diabetic  
4 mononeuropathy multiplex; proximal diabetic  
5 neuropathy, the Bruns-Garland syndrome. In my  
6 institution, they called it diabetic  
7 polyradiculopathy, painful lumbosacral plexopathy,  
8 diabetic CIEP, diabetic lumbosacral radiculoplexus  
9 neuropathy, multifocal diabetic neuropathy. So  
10 it's been known by lots of different names.  
11 There were certain features that were  
12 accepted to be classical for this that was painful  
13 by weakness, complete recovery within a year, a  
14 pure motor syndrome, a pure proximal syndrome,  
15 accompanied weight loss, affecting only people with  
16 type 2 diabetes mellitus. In general, these  
17 features are correct but maybe not quite so  
18 strongly as stated there.  
19 I'm just going to try to hit the key  
20 features that Roy gave us to hit. This is an  
21 overview of what I'm going to try to cover.  
22 There are no agreed upon standard diagnostic

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1 criteria for diabetic lumbosacral plexopathy.  
2 Every study up to this point has developed their  
3 own diagnostic criteria, or they didn't even really  
4 talk about diagnostic criteria.  
5 Hugh Garland didn't list any criteria. He  
6 talked about diabetes being short-lived, it being  
7 purely a motor syndrome, although pain was usual,  
8 that there were asymmetrical symptoms and signs,  
9 that the legs were affected first. Arms are rarely  
10 affected. Reduced reflexes. And he emphasized  
11 Babinski signs.  
12 Now, I think subsequent studies have not  
13 found this, so this has gone by the wayside, but  
14 this is probably the reason why he called this a  
15 diabetic myelopathy, that he thought typically  
16 there were extensor plantar responses.  
17 A subsequent study he did, he found many of  
18 the same features, progressive weakness and wasting  
19 of the pelvifemoral distribution muscles, most of  
20 the involvement above the knee.  
21 Raff, Sangalang, and Asbury, New England  
22 Journal of Medicine, their inclusion criteria was a

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1 rapid, asymmetrical motor greater than sensory  
2 neuropathy in diabetic patients. They included  
3 people with cranial neuropathies, and recovery was  
4 the rule.  
5 They showed infarcts in the nerve,  
6 multifocal fiber loss, occluded blood vessel. They  
7 saw some inflammation, but they felt that that  
8 inflammation was reactive. So here is a fossicle  
9 without nerve fibers. There's an occluded blood  
10 vessel, and they felt this was an ischemic event in  
11 the nerve. They showed inflammatory infiltrates,  
12 but they didn't think they were causative.  
13 Chokroverty in contrast talked about 12  
14 patients with a pelvifemoral weakness, wasting with  
15 insidious onset. So there is this debate whether  
16 it's a rapid and progressive or whether it's slow  
17 and insidious. They emphasize metabolic  
18 derangement and not microangiopathy. They felt it  
19 was different than Raff, Sangalang, and Asbury's  
20 diabetic mononeuritis multiplex.  
21 Arthur Asbury coined the term "proximal  
22 diabetic neuropathy," said it was two poles of a

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1 continuum with asymmetric weakness, rapid evolution  
2 from an ischemic basis at one end, and symmetrical  
3 weakness, slow progression from metabolic factors  
4 at the other end.  
5 At my institution, Bastron and Thomas wrote  
6 about diabetic polyradiculopathy. They said there  
7 could be involvement of the chest, abdomen, back,  
8 buttock, thigh, leg, or foot. EMG and neurologic  
9 examination would be in keeping with a  
10 polyradiculopathy.  
11 They made a distinction from what we've been  
12 talking about so far today, which is diabetic  
13 sensory motor polyneuropathy. They felt the  
14 symptoms would begin focally and then become more  
15 widespread, and they emphasized lumbar and thoracic  
16 denervation and made the point that this is not  
17 just a pelvifemoral syndrome.  
18 Subramony and Wilbourn included patients  
19 with diabetes, proximal lower limb weakness, a  
20 neurologist diagnosis of diabetic amyotrophy, and  
21 exclusion of other causes of the neuropathy.  
22 Walter Bradley and colleagues wrote about

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1 painful lumbosacral plexopathy with elevated  
2 sedimentation rate. They had six cases, three with  
3 diabetes, three without diabetes. They showed  
4 cuffs of perivascular inflammatory cells,  
5 multifocal fiber loss, and felt that it was an  
6 inflammatory ischemic condition. And they made a  
7 distinction about cases who had the elevated sed  
8 rate versus those without the elevated sed rate.  
9 They shared perivascular inflammation and  
10 multifocal fiber loss.  
11 Rick Barohn, Zarife Sahenk, Jerry Mendell  
12 wrote about the Bruns-Garland syndrome. The  
13 patients had to have diabetes; abrupt onset of hip,  
14 back, leg, thigh pain, unilateral or bilateral;  
15 lower limb weakness, proximal or proximal and  
16 distal unilateral or bilateral; EMG showing a  
17 neurogenic, not a myopathic abnormality; and  
18 imaging to exclude structural causes.  
19 Gerard Said talked about proximal diabetic  
20 neuropathy, included patients with diabetes,  
21 proximal neuropathy of the lower limbs. Other  
22 causes excluded through imaging. He broke them

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1 into forms. In the severe forms, he felt  
2 vasculitic causes predominated, and the mild forms,  
3 he felt metabolic factors predominated. They  
4 showed some inflammatory lesions in the nerve.  
5 Linda Pascoe, Tony Windebank, Phillip Low,  
6 Bill Litchy at our institution did a series. They  
7 insisted in bilateral lower limb weakness,  
8 progressive course, other causes excluded.  
9 Gareth Llewellyn, P.K. Thomas, Rosalind King  
10 wrote about diabetes. Again, a motor neuropathy,  
11 pain, weakness, muscle wasting in the lower limbs.  
12 Usually subacute onset with asymmetrical pattern.  
13 Other causes of the neuropathy excluded by CSF  
14 studies and spine imaging.  
15 In my study, we looked at diabetic  
16 lumbosacral radiculoplexus neuropathy. To be  
17 included, you have to have diabetes mellitus; a  
18 subacute developing unilateral or asymmetrical  
19 lower limb neuropathy; involvement of the buttock,  
20 thigh, leg or foot; but upper limb or thoracic  
21 could also be present. MRI or CT were used to  
22 exclude structural causes. Nerve conductions EMG

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1 were not confined to one peripheral nerve or one  
2 nerve segment. Typically, pain, weakness, and  
3 numbness were all present.

4 We found evidence of ischemic injury. We  
5 compared the nerves to nerves of diabetic  
6 polyneuropathy. We found multifocal fiber loss.  
7 We found injury neuroma. We found increased  
8 amounts of inflammation in the nerve and suggestion  
9 of microvasculitis. We saw inflammation involving  
10 vessel walls, fragmentation of the vessel walls.

11 We felt that this was a subacute painful  
12 neuropathy beginning unilaterally in the leg or  
13 thigh but progressing to be more widespread and  
14 bilateral. We felt it wasn't just a proximal  
15 neuropathy and it wasn't just a motor neuropathy,  
16 that usually sensory and autonomic fibers were  
17 involved. Ischemic injury best explains the  
18 clinical and pathological findings, and the cause  
19 of the ischemic injury is altered immunity and  
20 microvasculitis.

21 Kelkar and Gareth Perry wrote about diabetes  
22 mellitus and progressive painful asymmetrical

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1 proximal lower limb weakness and concluded that the  
2 pathology showed a PMN predominant vasculitis.

3 We didn't recognize that sometimes you'll  
4 get cases that don't have pain, so we did a study  
5 looking at a painless form of motor predominant  
6 lower limb neuropathy. These cases had diabetes.  
7 They did not have pain. They had weakness in one  
8 or both lower limbs, presence of sensory symptoms  
9 or signs, nerve conduction showing involvement from  
10 at least two different peripheral nerves from at  
11 least two different nerve roots. The findings  
12 could be demyelinating or axonal, and the patients  
13 could have upper limb or thoracic involvement.

14 That's an overview of many of the studies  
15 that have been done. As I pointed out, there is no  
16 consensus core criteria for diabetic lumbosacral  
17 radiculoplexus neuropathy. But going through those  
18 studies, there are some generally agreed upon  
19 features, and they seem to include diabetes  
20 mellitus, lower limb predominant usually  
21 asymmetrical peripheral neuropathy, motor  
22 predominance. Severe pain is usual, but not all

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1 cases have it. It can be unilateral, or it can be  
2 bilateral. There are reduced lower limb reflexes,  
3 and need to exclude other structural causes that  
4 can mimic this. So this is a diagnosis of  
5 exclusion. Other things can look a lot like this.

6 What is the differential diagnosis of  
7 diabetic lumbosacral radiculoplexus neuropathy?  
8 You can have lumbosacral radiculopathy, and it can  
9 look a lot like this. Lumbosacral radiculitis. I  
10 think the question comes up -- and I have a slide  
11 further on about this -- is radiculitis really a  
12 different disease than this? Lumbosacral spinal  
13 stenosis.

14 Then other things, peripheral nerve  
15 sarcoidosis, CIDP, neurolymphomatosis, necrotizing  
16 vasculitis, amyloidosis, infiltrating neoplasm into  
17 the lumbosacral plexus, radiation plexopathy,  
18 vasculopathies, retroperitoneal hemorrhage, and  
19 retroperitoneal abscess.

20 A lot of that can be diagnosed through  
21 imaging, but again, I think this ends up being  
22 largely a diagnosis of exclusion.

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1 What are some of the controversial issues  
2 when it comes to this diagnosis? One that I've  
3 been alluding to is, is this a pure motor syndrome?  
4 And it's interesting that we were just having this  
5 conversation about pure small fiber and pure large  
6 fiber because I think that comes up in this  
7 condition, too.

8 Garland, Chokroverty, Llewellyn, and others  
9 have emphasized that if it's not a pure motor  
10 syndrome, it's close to a pure motor syndrome.  
11 Through use of quantitative sensory and autonomic  
12 testing, I think we've fairly definitively shown  
13 it's not a pure motor syndrome, but it certainly is  
14 a motor predominant syndrome.

15 Is this just a proximal neuropathy? Again,  
16 Garland, Chokroverty, Said emphasized that this is  
17 a proximal neuropathy. But Bastron and Thomas and  
18 we have emphasized that it can also present in  
19 other locations, and it might just present with a  
20 foot drop without thigh involvement and really be  
21 the same disease. So from my perspective, although  
22 it's often commonly predominantly a proximal

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1 neuropathy, it doesn't necessarily have to be.  
2 Then this issue of rapid progression versus  
3 insidious. Asbury wrote that it's a spectrum with  
4 insidious, slowly progressive, symmetric at one end  
5 of the spectrum, and a rapidly progressive  
6 asymmetrical ischemic form at the other end of the  
7 spectrum.  
8 Pain, do all cases require pain? Probably  
9 more than 90 percent of these cases do have pain,  
10 and the pain is severe, lancinating, burning,  
11 contact allodynia. But as I've mentioned, we have  
12 a series of painless lumbosacral plexopathies with  
13 more insidious progression, more symmetrical, and  
14 more upper limb involvement.  
15 When we compared our painless cohort to the  
16 painful one, they were more subacute to chronic,  
17 they were more bilateral, and they had more distal  
18 involvement. There was more upper limb involvement  
19 as well, but the pathology really was the same.  
20 There was evidence of ischemic injury, so  
21 multifocal fiber loss was common. This is an  
22 injury neuroma; it's common. There was evidence of

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1 inflammatory infiltrates in the nerve and  
2 microvasculitis in the nerve, so big inflammatory  
3 infiltrates involving blood vessel walls. So from  
4 the pathological point of view, there really wasn't  
5 a difference in the painless form versus the  
6 painful form.  
7 We concluded that the painless lower limb  
8 motor predominant neuropathy in diabetic patients  
9 really was a form of diabetic lumbosacral  
10 plexopathy. The findings confirmed that the  
11 clinical spectrum of DLRPN is you have more rapid  
12 ones on one end and more insidious ones on the  
13 other end, and the underlying mechanisms of both of  
14 them is ischemic injury and microvasculitis.  
15 The pattern involvement, the focal versus  
16 multifocal, for our research studies, we required  
17 that EMG involvement of two peripheral nerve and  
18 two nerve root levels would be required, but again,  
19 this debate whether you're going to make everybody  
20 have an EMG and all of that, I think is apropos  
21 here as well. But we wanted to make sure it just  
22 wasn't a mononeuropathy, that it was involvement of

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1 more than one nerve and more than one nerve root  
2 level.  
3 Then I've alluded to this already, in  
4 isolated radiculitis, pain and weakness in one  
5 nerve root distribution really may be a form of  
6 this condition, but it doesn't meet those  
7 electrophysiological criteria. So what do you do  
8 with those patients as well?  
9 Similarly, should we have pathologic  
10 confirmation? I would argue probably you don't  
11 necessarily need to have pathological confirmation,  
12 but it might be nice to have nerve biopsies showing  
13 inflammatory infiltrates. But in fact, most of the  
14 cases I see, we don't do a nerve biopsy on.  
15 Then another controversial issue is the  
16 lower limb syndrome versus the whole body syndrome.  
17 What I've been talking to you so far about is  
18 diabetic lumbosacral radiculoplexus neuropathy.  
19 But in fact, a more generalized diabetic  
20 radiculoplexus neuropathy exists.  
21 Most of the published literature is really  
22 focused on the lower limb form, but you can have a

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1 lower limb form, an upper limb form, a thoracic  
2 limb form, cranial neuropathies occurring in the  
3 same patient. So maybe it's best to think of this  
4 as diabetic radiculoplexus neuropathy which is made  
5 up of the components of diabetic lumbosacral  
6 radiculoplexus neuropathy, diabetic cervical  
7 radiculoplexus neuropathy, and diabetic thoracic  
8 radiculopathy. So how one should write the  
9 criteria taking that into account also needs to be  
10 thought about.  
11 Then does diabetic cervical radiculoplexus  
12 neuropathy exist separately from diabetic neuralgic  
13 amyotrophy? I would argue it did. We did a series  
14 of 85 patients with diabetic cervical  
15 radiculoplexus neuropathy. They presented mostly  
16 as a lower trunk brachial plexopathy. Your typical  
17 Parsonage-Turner syndrome is mostly an upper trunk  
18 brachial plexopathy, so the clinical pattern is  
19 different.  
20 Half of these patients had other forms of  
21 radiculoplexus neuropathy occurring in the same  
22 patients. So half of them had contralateral other

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1 limb involvement and other segments involved.  
2 These conditions present very similarly to the  
3 diabetic lumbosacral plexopathy with pain,  
4 weakness, sensory loss. They usually begin  
5 unilaterally, and half of them become bilateral.  
6 They usually begin in the subacute fashion. They  
7 have pain, typically neuropathic pain. They have  
8 weakness. They have sensory symptoms. Twenty  
9 percent or so have recurrent episodes.  
10 As I mentioned, other segments are often  
11 involved, often the contralateral limb, often  
12 thoracic, often lumbosacral plexus in these  
13 patients. So the fact that they're getting so many  
14 other segments involved I think means it's really  
15 part of the diabetic radiculoplexus neuropathy.  
16 They also had ischemic injury and upper limb  
17 nerve biopsies as shown there, multifocal fiber  
18 loss. They also had inflammatory collections in  
19 the nerves as shown there.  
20 We feel that diabetic cervical  
21 radiculoplexus neuropathy is a subacute monophasic  
22 painful neuropathy beginning unilaterally in the

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1 upper limb, sometimes becoming bilateral. It has  
2 many similar features to the lower limb syndrome.  
3 It's not a pure motor syndrome. Sensory and  
4 autonomic fibers are involved. The pathological  
5 basis is ischemic injury from microvasculitis  
6 occurring at roots, plexus, and nerves, and it's  
7 part of this clinical spectrum of diabetic  
8 radiculoplexus neuropathy.  
9 What role does diabetes mellitus itself play  
10 in all of this? We classify them as forms of  
11 diabetic neuropathy. However, non-diabetic forms  
12 occur. So it seems that diabetes is a risk factor,  
13 but the precise role is unknown, and should we, in  
14 fact, classify them as diabetic neuropathies?  
15 Proposed core diagnostic criteria for  
16 diabetic lumbosacral radiculoplexus neuropathy  
17 alone or more generally diabetic radiculoplexus  
18 neuropathy. I took a shot at this, and of course,  
19 we can change this after having all of our  
20 conversations. I said one lower limb motor  
21 predominant neuropathy primarily involving the  
22 back, buttock, thigh, leg, or foot either

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1 unilaterally or bilaterally.  
2 Either they need to have the presence of  
3 diabetes mellitus; three, usually a rapidly  
4 developing neuropathy in a subacute fashion in an  
5 asymmetrical distribution with a monophasic course,  
6 but it may be insidious or recurrent. Of course,  
7 this gets at this whole issue that it's usually  
8 that, but it may not always be that. So it's sort  
9 of contradictory to say that, but in fact, that is  
10 the truth. I don't know how you get around that.  
11 It's usually one way, but it's not always that way.  
12 Weakness and pain are almost always present.  
13 In fact, you might say weakness has to be present  
14 really to have this. Sensory loss is typical.  
15 Then again, are you going to insist that everybody  
16 have nerve conductions and EMG? Nerve conductions  
17 and EMG show neuropathic involvement in the  
18 distribution of two peripheral nerve from two  
19 lumbosacral roots. I'd say an upper lumbar  
20 plexopathy would count as two nerve root levels.  
21 Then I think you always have to have  
22 exclusion because you don't want to include lumbar

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1 radiculopathies and all that. So I don't know how  
2 you handle this in third world countries and all  
3 that because other neurologic diseases are going to  
4 be excluded through imaging of the spine and the  
5 plexus to make sure you don't have a structural  
6 lesion causing that or you don't have an  
7 infiltrative tumor. I think CSF is also a good  
8 thing to make sure your cytology of that is  
9 negative.  
10 Anyway, that is my attempt at lumbosacral  
11 plexopathy. Then for more generalized diabetic  
12 radiculoplexus neuropathy, diabetic radiculoplexus  
13 neuropathy is a motor predominant syndrome of  
14 weakness, pain, and sensory loss occurring in lower  
15 limbs, upper limbs, or thoracolumbar levels.  
16 It can be present in isolation, or it can be  
17 present in a combination of those syndromes. There  
18 needs to be presence of diabetes. Usually, the  
19 neuropathy is rapidly progressing in a subacute  
20 fashion in an asymmetrical distribution with a  
21 monophasic course, but on occasion, may be  
22 insidious or recurrent.

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1 Again, nerve conduction studies, EMG show  
2 involvement of two different nerve roots and two  
3 different peripheral nerves, and other causes are  
4 excluded through imaging.  
5 Next turning to features that may be present  
6 but not necessarily part of the diagnostic  
7 criteria, weight loss is a very common feature of  
8 this. In our series, we found weight loss of 10 or  
9 more pounds in 28 of 33 patients. So again, I  
10 don't think you require weight loss to be there,  
11 but it is certainly a very commonly recognized part  
12 of this disease.  
13 Most of these patients have type 2 diabetes  
14 mellitus, but type 1 patients certainly can present  
15 with this. So last week in the Mayo Clinic, we had  
16 a severe type 1 with a raging lumbosacral  
17 plexopathy. Nonetheless, 32 of our 33 patients had  
18 type 2 diabetes mellitus.  
19 Compared to the regular population, there is  
20 less insulin use, less retinopathy, and less  
21 cardiovascular disease, so they probably have less  
22 complications of diabetes, better metabolic control

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1 than your typical diabetics do.  
2 Again, I've already brought this up, but  
3 what role does elevated blood sugar have? The  
4 non-diabetic lumbosacral radiculoplexus neuropathy  
5 occurs with very similar electrophysiological and  
6 pathological findings. Should these illnesses be  
7 classified as forms of diabetic neuropathy or  
8 inflammatory neuropathy or other?  
9 To date, there haven't been epidemiological  
10 studies done. People assume that diabetes is a  
11 risk factor for developing these. Peng-Soon Ng,  
12 our fellow last year at Mayo Clinic, we have been  
13 doing an incidence study of lumbosacral  
14 radiculoplexus neuropathy in Olmsted County in  
15 Rochester, Minnesota to look at this question to  
16 see if diabetes mellitus is a risk factor for this.  
17 We defined lumbosacral radiculoplexus  
18 neuropathy by the criteria presented above. We  
19 defined diabetes by the American Diabetes  
20 Association criteria. We reviewed 1800 medical  
21 records.  
22 Fifty-nine patients, 33 men, 26 women had

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1 lumbosacral radiculoplexus neuropathy. 52  
2 definite, 7 probable. The average age was 70  
3 years. 39 of those patients had diabetes. 20 were  
4 non-diabetic. 10 of those were pre-diabetic. The  
5 mean hemoglobin A1C was 7.8 in the diabetics and  
6 6.2 in the non-diabetics, including the pre-  
7 diabetics.  
8 Overall, the incidence of lumbosacral  
9 radiculoplexus neuropathy was 4.13 per 100,000 per  
10 year. Incidence of diabetic lumbosacral  
11 radiculoplexus neuropathy was 2.57 per 100,000 per  
12 year. The incidence of non-diabetic lumbosacral  
13 radiculoplexus neuropathy was 1.6 per 100,000 per  
14 year.  
15 The odds of having lumbosacral  
16 radiculoplexus neuropathy among diabetic patients  
17 was 6.35. The odds of having lumbosacral  
18 radiculoplexus neuropathy among pre-diabetics was  
19 1.0.  
20 Lumbosacral radiculoplexus neuropathy is a  
21 common inflammatory neuropathy, and I think this is  
22 something that the world just doesn't understand.

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1 This is three times more common than Guillain-Barre  
2 syndrome. People talk about Guillain-Barre  
3 syndrome all the time. You never hear about  
4 lumbosacral radiculoplexus neuropathy.  
5 This is an important inflammatory neuropathy  
6 that is ignored by the world. We're talking about  
7 having a neuropathy crisis and all that. I think  
8 this is something that is largely ignored. It's an  
9 important -- this causes major morbidity.  
10 Diabetes mellitus clearly is a risk factor  
11 for developing lumbosacral radiculoplexus  
12 neuropathy, and because of that, I think it's  
13 probably okay to classify this as a diabetic  
14 neuropathy.  
15 Lifespan considerations, there is no data  
16 about life expectancy, so I'm going to look at all  
17 these patients I told you about, and maybe we'll  
18 have some data on that, but I don't have any data  
19 about that. It clearly is a disease of middle and  
20 old age.  
21 How about comorbidities? Well, of course,  
22 diabetes is a comorbidity. As I mentioned, there's

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1 less complications than in the general population.  
2 But there's little other data existing about other  
3 problems in this.  
4 Gordon mentioned that in diabetic  
5 polyneuropathy, depression is very common. I  
6 didn't list that here on a separate slide, but  
7 depression is incredibly common in these patients.  
8 They almost get all depressed, the severe ones, and  
9 it makes sense. They're doing very well. Their  
10 life is going along great, and suddenly, they get  
11 this horrendous disease where they get this  
12 terrible pain, weakness, and it knocks them off.  
13 They often can't work, and they almost all get  
14 depressed with this disease.  
15 I'm sure that Chris is going to talk about  
16 this in his treatment-induced diabetes neuropathy,  
17 but this is also is a treatment-induced diabetic  
18 neuropathy. I think it's somewhat ironic that  
19 attempts to be more healthy and often will  
20 precipitate attacks of the diabetic lumbosacral  
21 plexopathy.  
22 Triggers for this include overzealous

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1 correction of the hyperglycemia, overzealous  
2 exercise routine, overzealous weight loss program,  
3 and post-surgical reaction.  
4 So a typical patient will find out they're a  
5 mild type 2 diabetic. They will be fat,  
6 overweight, and they'll get on an exercise routine.  
7 They'll go on a diet. They'll be feeling really  
8 good about themselves. They'll go on treatment for  
9 their diabetes. They'll start losing a lot of  
10 weight. Everything will great, and then they won't  
11 be able to control that, and they'll develop pain,  
12 and they'll continue to lose weight, and it's very  
13 frequently induced by good intentions.  
14 Nathan Staff and I in Mayo Clinic reported  
15 21 cases of biopsy confirmed, post-surgical  
16 inflammatory neuropathy, a third of whom, 33  
17 percent, could be classified as diabetic  
18 radiculoplexus neuropathy. All the biopsies showed  
19 inflammatory infiltrates.  
20 This is microvasculitis from one of the  
21 diabetic lumbosacral plexopathies from these post-  
22 surgical inflammatory neuropathies. So these

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1 patients will get a surgery. They'll wake up with  
2 a post-op neuropathy that will continue to progress  
3 after the operations.  
4 Functional consequences. The usual belief  
5 is that diabetic lumbosacral radiculoplexus  
6 neuropathies are monophasic illness and most  
7 patients will have complete recovery in a year.  
8 This is not the case. In our prospective cohort of  
9 33 patients, most were improved, but most did not  
10 recover over time. So initially, half of them or  
11 16 were in wheelchairs, 14 were using walkers or  
12 canes, and only 3 were walking normally  
13 independently. At two years, 3 were still in  
14 wheelchairs, 16 used aids, and 12 walked  
15 independently. So they get better, but they are  
16 often left with long-term morbidity.  
17 Falls are common. Most patients with  
18 diabetic lumbosacral plexopathy will fall, and they  
19 often fracture bones with this. So hip fractures  
20 are not uncommon in diabetic lumbosacral  
21 plexopathy.  
22 Some patients have ongoing long-term pain

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1 from this, too. Long-term morbidity from weakness,  
2 pain and ongoing needs for walking aids is a very  
3 common problem with these patients.  
4 In conclusion, there are no established  
5 criteria for diagnosis of diabetic lumbosacral  
6 radiculoplexus neuropathy. I think there are lots  
7 of controversial areas in this. Is this a pure  
8 motor syndrome? What's the role of pain? What do  
9 you do with rapid versus insidious, symmetric  
10 versus asymmetric, need for nerve biopsy, need for  
11 EMG, and whether we just should have criteria for  
12 the lower limb.  
13 I've given you some proposed criteria for  
14 both diabetic lumbosacral radiculoplexus neuropathy  
15 as well as diabetic radiculoplexus neuropathy. I  
16 think they can be fairly easily definable and  
17 usable.  
18 Diabetes mellitus clearly is a risk factor  
19 for developing diabetic lumbosacral plexopathy.  
20 These syndromes are precipitated by over-correction  
21 of blood sugars, exercise, or weight loss similar  
22 to treatment-induced diabetic neuropathy, and long-

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1 term morbidity from pain and weakness is common.  
2 Thank you all for including me.  
3 (Applause.)  
4 Q & A  
5 DR. FREEMAN: That was really great. I'm  
6 going to move things along. So let's have  
7 questions, and then I want to get back to the core  
8 criteria so that we can actually come up with  
9 something operational.  
10 Just to give the perspective for where we  
11 want to be at the end of the presentation, Jim did  
12 a trial on a diabetic lumbar radiculoplexopathy  
13 with methylprednisolone. Vera wants to replicate  
14 or show that it actually does work at some point in  
15 time. She needs to have the cookbook, no usually,  
16 no maybe, no sometimes, 1, 2, 3, 4. So that's  
17 where we want to be at the end of the session so  
18 that we can be in the situation that we can do  
19 another clinical trial using that cookbook.  
20 Vera, off you go.  
21 DR. BRIL: Thanks. It was an excellent  
22 presentation. My question is a little bit off. So

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1 these are, what, 60 to 70 years old, these  
2 patients, and you do an MR of them. Almost  
3 everybody has spinal degenerative disease at  
4 multiple levels.  
5 I understand if it's in the upper limb or  
6 thorax, and I know when you've done the biopsy, but  
7 now you're not doing biopsies. How are you so  
8 clearly distinguishing between degenerative spinal  
9 disease? Because they don't have clean MRs, most  
10 of them.  
11 DR. DYCK: No, they don't. Most people  
12 don't have clear MRs.  
13 I think what you do is you do your MRI. You  
14 look at their findings. You look at their EMG. A  
15 little bit of degenerative change in the spine is  
16 not going to cause it. If they have an upper  
17 lumbar plexopathy and there's a big disc pushing on  
18 the L3 nerve root at that level, then you think,  
19 well, maybe that is due to that, and then you have  
20 them see a surgeon.  
21 I've had patients who I'm convinced have  
22 diabetic lumbosacral plexopathy who I've then sent

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1 to surgeons and had operations that helped them.  
2 And I've had the opposite happen much more where a  
3 patient will present with pain and weakness in the  
4 lower limbs, have an MRI on the outside before they  
5 ever see me. Go to a surgeon, have an operation;  
6 that doesn't help them, and they progress, and then  
7 they come to see me.  
8 DR. BRIL: I think there's a contradiction  
9 in there when you say they clinically have a  
10 plexopathy and then say, oh, but they have L3 --  
11 DR. DYCK: Yes.  
12 DR. BRIL: -- so I think you can do it by --  
13 DR. DYCK: That's the issue. I agree with  
14 you.  
15 DR. BRIL: -- exam and/or by EMG to show  
16 that it's outside one nerve root.  
17 DR. DYCK: Yes. So this is the whole issue  
18 of the EMG criteria for involvement of more than  
19 one nerve root. The real problem of that comes  
20 with the upper lumbar plexopathy, and that's why I  
21 used the L3 as an example.  
22 L3, if you do an EMG and you find

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1 involvement of the adductor longus and L2-3 muscle  
2 of rectus femoris in L3-4 muscle, vastus medialis  
3 L3-4 muscle, you could say, well, there are two  
4 different nerve root involvement, there are two  
5 different nerves, the obturator nerve and the  
6 femoral nerve. But that still could potentially be  
7 an L3 radiculopathy. But the problem is that you  
8 will get pure upper lumbar plexopathies that are  
9 part of this, so I don't think you can exclude  
10 them.  
11 So these attempts to try to differentiate  
12 them are imperfect. I don't know a way around  
13 that.  
14 DR. FREEMAN: Yad, then Nathan [sic], then  
15 Doug.  
16 DR. HARATI: Is there a place for spinal  
17 fluid studies positive or negative, sorting it out?  
18 DR. DYCK: I went through a lot of stuff  
19 very quickly. Again, I think this whole issue that  
20 we brought up in the past of the criteria for the  
21 practicing physician in the community and the  
22 criteria for research studies probably are going to

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1 want to be somewhat different. But for me, the  
2 work-up I do -- either I do it or it's been done,  
3 an MRI of the lumbosacral spine, an MRI of the  
4 lumbosacral plexus. The spine to make sure you  
5 don't have some compressive spinal stenosis disc  
6 pushing on something. The plexus to make sure  
7 there's no infiltrating tumor. I do a CSF.  
8 The average CSF protein is elevated in these  
9 patients, but the bigger reason you're doing it is  
10 you want to make sure they don't have lymphoma,  
11 they don't have some tumor infiltrating the nerve.  
12 So I do a CSF for the cytology predominantly.  
13 I do blood work-up looking for other causes.  
14 I do the EMG to meet that criterion to make sure  
15 it's not some other disease, and then I may or may  
16 not do a nerve biopsy. I'm doing a nerve biopsy  
17 mostly when I think it might not be this, if it's  
18 gone on too long to judge disease activity, that,  
19 and potentially treat them.  
20 DR. FREEMAN: So this is a disorder -- and I  
21 just want to again keep us focused -- that is rare  
22 enough that I think our goal over here is not to

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1 give clinical criteria for the practicing  
2 neurologist or diabetologist, but to come up with  
3 criteria if somebody wishes to do a clinical trial,  
4 immunomodulation, one kind of another, that they  
5 have a cookbook, the recipe.  
6 Nathan [sic]?  
7 DR. KOLB: Along those lines, if you want to  
8 include people, it looks like the hemoglobin A1C  
9 for the non-diabetic group, the mean was 6.2, so do  
10 you think a lot of those patients are pre-diabetic  
11 and --  
12 DR. DYCK: A lot of those patients are  
13 pre-diabetic. So there are 20 patients; 10 of them  
14 were pre-diabetic. I actually gave you that data,  
15 but I agree, I went through this quickly. So yeah,  
16 they were.  
17 DR. KOLB: So do you think that we should  
18 reconsider in the pre-diabetic people that  
19 definition?  
20 DR. DYCK: Well, again, we used controls.  
21 What I showed you there was from the  
22 Rochester -- the odds ratio of the pre-diabetic was

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1 1.0 compared to the population. So it was an  
2 increase in the pre-diabetic.  
3 DR. FREEMAN: Sorry, Jim.  
4 DR. DYCK: Doug.  
5 DR. ZOCHODNE: I don't want you to miss your  
6 plane.  
7 DR. DYCK: My plane's at 7:00. It's okay.  
8 DR. ZOCHODNE: My proposal would be to  
9 accept your carefully one criteria as is. I think  
10 they look pretty good. I wouldn't have any  
11 difficulty with them.  
12 I may be a little out of line here, but a  
13 sidebar, which is you got this kind of cohort of  
14 these people in Rochester, what are we doing to  
15 look at the etiology of this condition in terms of  
16 autoantibodies? I think you're perfectly set up  
17 with Vanda Lennon or substitute. We just had Jan  
18 Willem Tervaert join us at U of A who discovered  
19 ANCA, so let's push this along to the next step. I  
20 think it would be a major breakthrough if we could  
21 identify what the etiology of this --  
22 DR. DYCK: In fact, we did look for some

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1 several years ago and didn't find any.  
2 DR. ZOCHODNE: I think we should keep at it  
3 because the technology is charging ahead, too.  
4 DR. FREEMAN: David, and then Solomon.  
5 DR. HERRMANN: Two questions. You mentioned  
6 most of the time there's some proximal involvement,  
7 but you did define some patients who had foot drop.  
8 In a foot drop, wouldn't you exclude patients who  
9 just have a mononeuropathy --  
10 DR. DYCK: I would.  
11 DR. HERRMANN: You would?  
12 DR. DYCK: I would.  
13 DR. HERRMANN: Even though it probably can  
14 occur, you want to make sure that --  
15 DR. DYCK: Whoa, whoa, whoa.  
16 DR. HERRMANN: -- plexus or root is  
17 involved?  
18 DR. DYCK: I have argued that -- I wouldn't  
19 exclude mononeuritis multiplex, but they do have to  
20 have two nerves involved and two roots involved.  
21 DR. HERRMANN: Have the roots involved.  
22 DR. DYCK: Yes. Well, two roots involved.

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1 So if you had some focal proximal process and a  
2 focal distal process, then you get that. An  
3 isolated foot drop just in and of itself probably  
4 isn't going to meet those criteria, but really  
5 what's more common is they'll present with a foot  
6 drop, and then with time, it evolves into having  
7 more than that.

8 DR. HERRMANN: One other question, just a  
9 really short one to Doug's point. Are there  
10 exclusionary blood tests? I don't know who had  
11 mentioned the ESR. Are there exclusionary blood  
12 tests for this diagnosis?

13 DR. DYCK: Exclusionary --

14 DR. HERRMANN: Yeah, in other words --

15 DR. DYCK: No, no, I'm thinking about that.  
16 You do blood tests to look for other causes, so you  
17 may find things that then may lead you -- for  
18 instance, you might do a monoclonal study. You'll  
19 find a monoclonal approach, and you'll do a nerve  
20 biopsy, and you find amyloid in there.

21 The blood tests by themselves, are the  
22 exclusionary, probably not. If you had all kinds

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1 of inflammatory rheumatological things and you  
2 ended up finding that this person really had  
3 rheumatoid arthritis, maybe this is mononeuritis  
4 multiplex in rheumatoid arthritis and not due to  
5 the diabetic syndrome.

6 I don't know if there are exclusionary blood  
7 test in and of themselves, but I think you're doing  
8 those blood tests to look for other conditions.

9 DR. FREEMAN: Solomon, then Gordon. Then  
10 we're going to go back to the slide, and we're  
11 going to put both Stephen and Jim on the spot, and  
12 we're going to fix those criteria.

13 DR. TESFAYE: The question for me is, is  
14 there a pattern of recovery? Is there a natural  
15 history? I always say to the patients -- and I  
16 have seen about a dozen of these patients over many  
17 years -- that the pain will get better. I  
18 reassure. They're profoundly depressed. They're  
19 completely devastated when they see you. The pain  
20 will get better. Weakness will improve. Reflexes  
21 appear to be the last ones that recover.

22 Do we have a naturalist?

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1 DR. DYCK: Well, so I have a lot of  
2 experience seeing these people over time, but then  
3 again, that's -- so I'm going to look at this  
4 cohort that I just showed you, the preliminary  
5 stuff, to try to get some of that information.

6 I think it is clear -- so back to my  
7 original prospective study in '99, I did follow-up  
8 with them, and it was really interesting to me that  
9 where many of them had been in a wheelchair  
10 originally, now almost all of them walked, but many  
11 of them still had foot drop. And I think in some  
12 ways this makes sense.

13 Proximal nerve segments reinnervate, and they  
14 can walk. The thigh muscles come back in almost  
15 all of them, but they're often left with that foot  
16 drop. I think that makes sense. Proximal segments  
17 reinnervate better and more completely than distal,  
18 so patients are often left with a foot drop where  
19 they are not usually left unable to walk, which is  
20 good.

21 Most of the pain gets better, but some of  
22 these people do develop chronic pain state. So I

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1 think it is not correct to tell patients that their  
2 pain necessarily will get better. Almost all of  
3 them, the pain gets better, but some of them are  
4 left with chronic pain situations.

5 Quadricep reflexes usually come back. Ankle  
6 reflexes often don't come back, not that it really  
7 matters if you regain your reflexes or not. But  
8 often what these patients look like years down the  
9 road is a severe length-dependent diabetic  
10 polyneuropathy because it's all distal and they  
11 might have foot drop, and then the proximal stuff  
12 is all reinnervated.

13 DR. FREEMAN: Let's have Gordon, who I think  
14 was next, then Yad. That will be the last  
15 question, and if we could start moving back, maybe  
16 about eight slides back, and I'll let you know when  
17 to stop.

18 DR. SMITH: This is all making me a  
19 taxonomic catastrophizer.

20 (Laughter.)

21 DR. SMITH: Thinking about David's question,  
22 a patient who was diabetic, who has a subacute

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1 onset of a foot drop, who has denervation in  
2 multiple nerve roots, does that fit the criteria?  
3 Because I can start to see where if one aligns the  
4 typical features, let's say a progressive onset,  
5 let's say absence of pain, let's say distal  
6 predominant, one could end up with a lot of  
7 confusion with other disorders.  
8 DR. DYCK: Well, again, I think one  
9 important thing in this -- and if it's not clear  
10 the way it's written, it should be -- is that this  
11 is a diagnosis of exclusion. So other conditions  
12 that this could be need to be excluded, and if they  
13 are those, then they're those.  
14 I think we absolutely need to write it in  
15 such a way because -- and I say that when I get up  
16 and give talks about this, this is a diagnosis of  
17 exclusion.  
18 Most of these patients will have proximal  
19 involvement, but they don't all have proximal  
20 involvement. And I think we would be wrong to  
21 exclude those patients who don't have proximal  
22 involvement.

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1 DR. FREEMAN: Yad, and then can we get the  
2 presentation back on, please? This one.  
3 DR. HARATI: I just wanted to add, doesn't  
4 the improvement coincide on those who have lost  
5 weight with the resumption of the weight, normal  
6 weight?  
7 DR. DYCK: Usually. So improvement, I often  
8 will tell patients that when their pain goes away,  
9 that's a good sign. When the weight loss stops,  
10 that's a good sign because that usually is an  
11 indicator that the disease activity isn't so much.  
12 But that's not a hard and fast rule.  
13 DR. FREEMAN: Sorry. Amanda, you have  
14 something? No.  
15 DR. PELTIER: I was going to comment on the  
16 criteria --  
17 DR. FREEMAN: Remember, we want this to  
18 look like the migraine with aura, so 1, 2, 3, 4.  
19 The principle, these are core criteria, so we're  
20 focusing on specificity. If there are variants  
21 that fit the picture but are not quite typical,  
22 that's okay. Those will be the variants, and those

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1 will be discussed. We can't deal with -- I get the  
2 feeling that this is diabetic radiculoplexus  
3 neuropathy, what smells like it, therefore, it is.  
4 This is so somebody who's not an aficionado can say  
5 these are the patients I want to include in the  
6 trial.  
7 DR. CALLAGHAN: It's hard to operationalize  
8 number 3, right?  
9 DR. FREEMAN: Sorry. I can't hear that.  
10 DR. CALLAGHAN: It's hard to operationalize  
11 number 3 because it's --  
12 DR. DYCK: I agree with you, but I don't  
13 know what you'd do with it. It gets to be like his  
14 point about there's some preceding damage or injury  
15 in patients with complex regional pain syndrome.  
16 It's been recognized for 50 years that most  
17 of these patients are subacute rapidly evolving,  
18 but some of them are insidious. You could leave it  
19 out completely, but I think you're missing the  
20 flavor of the disease if you completely drop it,  
21 and I don't know how to get around that.  
22 DR. PELTIER: I would actually make the

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1 argument --  
2 DR. FREEMAN: Amanda and then we'll have  
3 Stephen. Amanda?  
4 DR. PELTIER: I just was going to make the  
5 argument actually, I would get rid of the insidious  
6 and the recurrent because I think those are a  
7 different population.  
8 DR. BRUEHL: Stephen, fix this for us.  
9 DR. BRUEHL: All I'm going to do is I'm  
10 going to give you the same feedback that I gave  
11 [inaudible - off mic]. The things that I see that  
12 you would want to consider changing, one is whether  
13 you want even the lumbar versus cervical because to  
14 me, if it doesn't really change the basic  
15 description, the basic clinical features, it would  
16 make more sense to have just the one.  
17 DR. DYCK: Not two criteria but one  
18 criteria?  
19 DR. BRUEHL: Yes, just one set of criteria.  
20 DR. DYCK: I wrote them both, and we can  
21 open up. The lumbosacral is probably the most  
22 common thing, the thing that has the most agreement

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1 to, and that's part of the reason why I wrote it  
2 that way, because I think that's the one that  
3 everybody agrees with, and then the other one, you  
4 know.  
5 DR. BRUEHL: That makes perfect sense.  
6 That's fine.  
7 Number 1, motor predominant neuropathy, how  
8 do you operationalize that? What does that mean?  
9 DR. DYCK: It is you're weak.  
10 DR. BRUEHL: So it would be associated with  
11 weakness, right?  
12 DR. FREEMAN: Yes, and he means, I think,  
13 motor greater than sensory or autonomic. I think  
14 that's what he means.  
15 DR. DYCK: That is.  
16 DR. BRUEHL: You just need to have it worded  
17 in a way where somebody who isn't an expert --  
18 DR. FREEMAN: -- all of that because we do  
19 more if feels like this is the entity, it smells  
20 like it's in the entity. So help us operationalize  
21 it.  
22 DR. BRUEHL: I would just say on number 1,

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1 since the back, buttock, thigh, leg, and foot could  
2 all be considered lower limb, for complexity  
3 reasons just say lower limb or back --  
4 DR. GIBBONS: Motor greater than sensory --  
5 DR. BRUEHL: Yes, neuropathy, yes.  
6 DR. BRIL: Or could you just say weakness?  
7 DR. BRUEHL: Yes, weakness associated with -  
8 -  
9 DR. BRIL: Pain and --  
10 DR. DYCK: That's number 4, but you might be  
11 able to --  
12 DR. BRUEHL: Yes, so you might just combine  
13 those. So the definition would be weakness and  
14 pain with weakness predominant in a lower limb or  
15 back. You don't need to get into unilateral or  
16 bilateral if it could be either one. You don't  
17 need the specific body areas.  
18 I think 4 and 1 could be combined pretty  
19 easily there to capture the essence of it. Number  
20 2's perfect.  
21 DR. FREEMAN: Can I just ask, Jim, can you  
22 live with weakness and pain, that pain is part of

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1 the core diagnostic criteria?  
2 DR. DYCK: Well, I think that --  
3 DR. FREEMAN: Or do we need to say variants,  
4 painful and painless?  
5 DR. DYCK: Well, I think you have to at some  
6 point take into account that there is a painless  
7 variant. I don't know how you want to do it. It  
8 just needs to be taken into account somehow.  
9 DR. BRUEHL: I would just say then  
10 neuropathy associated with lower limb weakness as  
11 number 1.  
12 DR. DYCK: Yes, but the problem is then  
13 you've got ALS.  
14 (Crosstalk.)  
15 DR. DYCK: Pain is a very stereotypical  
16 component of this in 95 percent of the cases, but  
17 it's 95 percent of the cases.  
18 (Crosstalk.)  
19 DR. FREEMAN: And that's what we want to  
20 live with --  
21 DR. BRUEHL: Then you lose the 5 percent and  
22 figure out later what to do with that.

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1 DR. DYCK: This is what Amanda is saying,  
2 but they exist.  
3 DR. BRIL: Can you put a note at the bottom  
4 saying up to 5 percent are painless?  
5 DR. DYCK: I wouldn't have a problem with  
6 that.  
7 DR. FREEMAN: We have a section for  
8 variants, and that would be under variants. So I  
9 think that's great.  
10 DR. BRUEHL: Other than that, the number3,  
11 that is not very clear to me.  
12 DR. DYCK: No. Again, it's this exact same  
13 issue. Most of these patients will present in a  
14 subacute fashion quite asymmetrically.  
15 DR. TESHAYE: Subacute for weeks and months?  
16 DR. DYCK: Exactly, so subacute weeks.  
17 DR. TESHAYE: It's got to be weeks --  
18 DR. FREEMAN: Can you give us usually end  
19 rapidly? What do we mean? We need a time frame?  
20 DR. DYCK: Yes, I think they hit their nadir  
21 within about 6 months on average.  
22 DR. TESHAYE: Yes, weeks, months.

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1 FEMALE VOICE: So it's more than 10 days?  
2 DR. DYCK: Yes, exactly. Right, exactly.  
3 This whole issue, subacute is one of these nebulous  
4 terms that's very --  
5 DR. FREEMAN: So we want to --  
6 DR. DYCK: -- but if you say chronic, you  
7 get this idea of a very long drawn-out thing, and  
8 it's not that.  
9 DR. BRUEHL: You can say, though, rapidly  
10 developing neuropathy over 2 weeks to 6 months,  
11 something like that.  
12 DR. DYCK: Weeks to months, I think you  
13 could, yes.  
14 DR. FREEMAN: Even ideally, we want to know  
15 that.  
16 DR. DYCK: The problem with the numbers, I  
17 see lots of patients who walk into my office who  
18 are two years into this disease. They say, "Oh,  
19 I'm so atypical." I do a nerve biopsy, and this is  
20 one of the reasons I do a nerve biopsy because it's  
21 still active, and I see microvasculitis.  
22 It is not uncommon for that to go on for a

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1 couple years. Now, not uncommon in my experience.  
2 That may be uncommon in the community, but that's  
3 not so atypical.  
4 DR. BRUEHL: Symptom onset, though, within  
5 6months?  
6 DR. DYCK: Symptom onset usually is quite  
7 rapid, but then it progresses over time.  
8 DR. BRUEHL: I think that would be a point  
9 to make here is that's kind of the pattern that you  
10 would expect to see is rapid progression of  
11 symptoms from normal functioning over a period less  
12 than X time, something like that.  
13 DR. DYCK: It progresses over weeks. I  
14 think on average it hits its worse about 6 months,  
15 but that's average.  
16 DR. FREEMAN: We just think 80 percent. We  
17 aren't interested in the 90 percent cases. The  
18 rest will be variants, so that David Bennett can do  
19 the clinical trial at Oxford. He needs to include  
20 those representative patients.  
21 Can we deal with the usually rapidly  
22 progressing in a subacute fashion and put numbers

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1 on that? I'm assuming we can.  
2 DR. DYCK: No. I think that's typical.  
3 DR. BRUEHL: I agree with you. The  
4 insidious or recurrence, it can be both. It's  
5 pointless to even mention it.  
6 DR. DYCK: No. I --  
7 DR. BRUEHL: But then to mention it here,  
8 you do put it under Dimension 2.  
9 DR. DYCK: But this is the issue, and it's  
10 always this issue about this contradictory sort of  
11 things, and they both can occur. But if you leave  
12 it out completely, you lose the flavor of the  
13 disease, and that's why I think you need to have it  
14 in there.  
15 Yes, Ahmet?  
16 DR. HOKE: Are the insidious ones actually  
17 the same disease as the ones who --  
18 DR. DYCK: Well, I have a paper arguing that  
19 they are. You can argue with me.  
20 No. So my problem was I had these motor  
21 predominant ones that often had a lot of upper limb  
22 involvement. There has been this debate -- and

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1 Vera is a big part of this debate -- of whether  
2 this is or there is not diabetic CIDP. I argued  
3 that if there would be a diabetic CIDP, these  
4 people with a more insidious, more symmetric, more  
5 upper limb predominant neuropathy, a  
6 polygeneralized polyradiculoneuropathy, that should  
7 be diabetic CIDP.  
8 I did nerve biopsies from 20-some of these  
9 patients without pain, and most CIDP doesn't have  
10 much pain. So I thought if there's diabetic CIDP,  
11 this should be diabetic CIDP. We found multifocal  
12 fiber loss, perineural thickening,  
13 neovascularization, microvasculitis. We did not  
14 find segmental demyelination. We did not find  
15 onion bulbs. We found no significant differences  
16 in the pathology.  
17 So from a pathological point of view, I say  
18 they're the same. Clearly, from a clinical point  
19 of view, they're not the same. It depends on, you  
20 know.  
21 DR. FREEMAN: How should we deal with this,  
22 do you think? Do you think we should have two sets

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1 of core diagnostic criteria, painful and painless,  
2 or do you think we should include in your core  
3 diagnostic criteria one set of diagnostic criteria  
4 and, say, maybe painful or painless?  
5 DR. DYCK: I don't have a problem saying  
6 painful, rapidly progressive with an asterisk  
7 saying there are rare cases that don't have pain  
8 and are more insidious.  
9 DR. FREEMAN: Is that okay?  
10 DR. DYCK: I don't have a problem with that.  
11 That's kind of what I tried to do here, just  
12 putting it into that because that is the flavor,  
13 and that's why I did it this way. I was quite  
14 aware that number 3 seems completely contradictory,  
15 but that is the truth is the problem.  
16 DR. PELTIER: Back to your pathophysiology,  
17 Jim, are the insidious/painless cases respond to  
18 Solu Medrol and IVIg in the same way? Because if  
19 they don't, then one could argue are they really  
20 truly the same disorder.  
21 DR. DYCK: That was a retrospective series.  
22 They did seem to go monophasic illness. They did

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1 seem to get better. But again, it's a  
2 retrospective chart review, so it's imperfect data.  
3 DR. SMITH: I'm trying to operationalize 3.  
4 Chronic things always begin -- this is like Yogi  
5 Berra -- at some point, and if they're progressive,  
6 they get worse from that point to when I see them.  
7 As you pointed out, we often -- in fact, the norm  
8 is that we see these patients a year or two years  
9 in.  
10 If the criteria says that there's an onset  
11 with a progression over weeks to months, I'm seeing  
12 them two years later, how do you word it so that  
13 we're not capturing an insidious linear progression  
14 from onset to where I am two years later? How do  
15 we prevent that or differentiate that from the  
16 typical subacute, or does it matter that we do so?  
17 Kind of operationalizing the third criteria.  
18 DR. DYCK: If we do future studies in this,  
19 I would encourage anybody involved -- I'd be very  
20 interested in being involved in that, too -- to get  
21 early cases.  
22 In our study, we required them to come in

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1 within six months of the onset of the most recent  
2 lower limb, and I don't think that was early enough  
3 because I think they all on average already were  
4 hitting their disease nadir. I think that was the  
5 big problem with our study. The problem is, is  
6 that you've got to find a different way of  
7 identifying these patients because essentially,  
8 that's when I was seeing these patients.  
9 DR. FREEMAN: If we go back to the onset  
10 because that's probably what's critical to the  
11 diagnostic criteria, not necessarily when you see  
12 them six months later, but the onset, we're going  
13 to come up with something operational, I think. It  
14 sounds like we are.  
15 DR. BRUEHL: Just out of curiosity, so if  
16 somebody came in two years after it really started  
17 and the criteria says rapid onset of symptoms  
18 within three months, do you think the average  
19 patient, would that stick out in their mind so they  
20 could go, yes, it definitely did?  
21 DR. DYCK: Yes, no. They tell you that  
22 story. So the typical story is I will see them two

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1 years in, and they'll say, two years ago, I  
2 developed terrible pain in my anterior thigh and a  
3 foot drop. Three months later, I got terrible pain  
4 in the thigh. One year ago, I got terrible  
5 weakness in my other thigh, and it started  
6 atrophying. Three months ago, I got foot drop in  
7 my other leg. They tell you this story of this  
8 patchy asymmetrical involvement.  
9 DR. BRUEHL: That seems reasonable to me.  
10 DR. FREEMAN: Nathan, and then Yad.  
11 DR. KOLB: I was thinking that if we think  
12 this is an important distinction, much like we do  
13 migraine with and without aura, we could just point  
14 a time point on it and have them 1.2.2. If we  
15 think that's an important distinction at the  
16 separate time.  
17 DR. FREEMAN: We'll leave that to be sorted  
18 out as this evolves.  
19 Yad?  
20 DR. HARATI: For the inclusion of these  
21 patients, I'm sure that since you're at the  
22 tertiary referral centers, you have seem some

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1 patients who actually were operated on their back.  
2 DR. DYCK: Many.  
3 DR. HARATI: Many of them. How do you deal  
4 with that?  
5 DR. DYCK: Well, so typically, I wouldn't  
6 use that as an exclusion criteria. If they had a  
7 back operation, usually what happens is they come  
8 in with more focal involvement. They have their  
9 operation, and then they get worse in the post-  
10 operative period, and then they develop a more  
11 widespread plexopathy, but that's really quite  
12 common.  
13 DR. FREEMAN: Last couple of things, for a  
14 clinical trial, do you think we need to have the  
15 neurophysiology showing --  
16 DR. DYCK: Absolutely.  
17 DR. FREEMAN: So that's part of the  
18 diagnostic criteria.  
19 DR. DYCK: Yes, right.  
20 DR. FREEMAN: For a clinical trial, I asked  
21 do we need to have the neurophysiology showing that  
22 there is more than one nerve root distribution, and

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1 the answer was absolutely. And then for a clinical  
2 trial, do you think we need to do a lumbar  
3 puncture.  
4 DR. DYCK: I would.  
5 DR. FREEMAN: Does David need to do that?  
6 DR. DYCK: I absolutely see people who have  
7 neurolymphomatosis, who have sarcoidosis, that are  
8 mimickers of this illness.  
9 DR. FREEMAN: David needs to do that.  
10 DR. DYCK: You don't think you need to do  
11 it, David?  
12 DR. HERRMANN: He's smiling.  
13 DR. BENNETT: Actually, I normally do  
14 exactly what he suggests. We do nerve conduction  
15 studies, imaging, and a lumbar puncture, and I  
16 rarely do a biopsy.  
17 DR. DYCK: So I brought the biopsy up. I  
18 don't think you need to do a biopsy, but I just  
19 thought we should have that conversation.  
20 DR. FREEMAN: Gordon?  
21 DR. SMITH: Asymmetry?  
22 DR. FREEMAN: Yes, because I was also

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1 wondering about that. Asymmetry, you say  
2 bilaterally. Do you say bilaterally but  
3 asymmetrically or not?  
4 DR. SMITH: Recognizing that some are  
5 symmetric.  
6 DR. DYCK: But then that's the issue. It's  
7 usually asymmetric. It's not always asymmetric.  
8 DR. FREEMAN: Usually 60 or usually 90?  
9 DR. DYCK: Usually 80-plus.  
10 DR. GIBBONS: So that would move to the  
11 criteria to the diagnostic 2, right?  
12 DR. BRUEHL: If it's just descriptive, yes.  
13 DR. HARATI: Jim, would you require an  
14 imaging with and without contrast because of the  
15 inflammatory process, the spinal AVM, et cetera?  
16 DR. DYCK: Yes, well, no. An AV dura  
17 fistula is another thing that this could be. I  
18 guess I have vascular on there. It's certainly  
19 better. If you're just looking for a structural  
20 thing, maybe that's not needed, but I think you're  
21 going to see tumors and things like that way better  
22 with contrast. It's definitely better.

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1 The other thing is do you require one  
2 imaging or two imaging? In other words, spine  
3 imaging or spine and plexus imaging? Because  
4 again, you can get both.  
5 DR. FREEMAN: I agree. Look, I think one  
6 last thing, cervical, do you think we can say  
7 lumbosacral, cervical, thoracic, all of these  
8 criteria apply? Thoracic is a little tougher. So  
9 it will, as Nathan said, 1, 2, and 3, or do you  
10 think we need to combine all of these together?  
11 DR. DYCK: I would separate.  
12 DR. FREEMAN: You'd do it separate.  
13 DR. DYCK: I think lumbosacral stand alone,  
14 and then you have a diabetic radiculoplexus  
15 neuropathy made up of these other ones.  
16 Jim?  
17 DR. CALLAGHAN: It seems that each of the  
18 main criteria has a caveat: diabetes but maybe not  
19 diabetes, pain but maybe not pain.  
20 DR. DYCK: Yes.  
21 DR. CALLAGHAN: Is this one of those where  
22 maybe we should have like here are the core five or

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1 six, seven features, and if you have greater than  
2 four or five of them -- I don't know what the  
3 cutoff would be -- that that would increase your  
4 level of certainty, knowing that it's not perfect?  
5 DR. DYCK: Well, no. The whole diabetes  
6 issue is another one. We are at a diabetes  
7 consortium meeting. I think when it comes to the  
8 lumbosacral one, there is no question the  
9 diabetes -- I've just shown you good evidence that  
10 diabetes is a major risk factor for developing  
11 that.  
12 For the brachial plexus one, I think it's  
13 much more controversial. In our series, though, as  
14 I say, 50 percent of the ones that have a brachial  
15 plexus have other segments involved, and I think  
16 that really argues it is a little different than  
17 your typical Parsonage-Turner. So I think in that  
18 sense, it's reasonable to classify them that way.  
19 I don't know if it's really the best,  
20 though, just to say 4 of these 7 or whatever  
21 because, for instance, weakness. I think we're  
22 talking about a weakness syndrome here, so I think

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1 everybody has to have weakness. There are probably  
2 mandatory things.  
3 Pain is really typical in this, but there is  
4 this cohort that doesn't have pain. But really,  
5 you're expecting most of them to have pain.  
6 DR. CALLAGHAN: Like POEMS syndrome, POEMS  
7 syndrome has some criteria that are mandatory and  
8 then --  
9 DR. DYCK: Yes.  
10 DR. CALLAGHAN: -- so you could think about  
11 weakness being mandatory.  
12 DR. FREEMAN: Rayaz?  
13 DR. MALIK: Should there be some kind of  
14 system to say pain more than an NRS of 4 or  
15 weakness more than an MRC grade to give it a bit  
16 more solidity? Because otherwise, at the moment  
17 I'm left, how much weakness, how much pain.  
18 DR. DYCK: It is a variable severity  
19 disease. The EMG criteria in a sense, although  
20 it's not measuring weakness per se, to say you have  
21 to have denervation, neurogenic changes in two  
22 different peripheral nerves from two different

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1 lumbosacral roots is getting at that. You have to  
2 have a fairly severe syndrome to show that.  
3 DR. SMITH: This feels to me a bit like the  
4 way you would test is the vignette approach, right?  
5 You're going to throw out a set of criteria that we  
6 have a sense for what they look like, and they're  
7 going to deal with these atypical features. Then  
8 we can easily create typical, atypical, and then  
9 non-entity vignettes to see how they perform.  
10 DR. FREEMAN: I think that's a good one to  
11 put on the list of research studies. I think that  
12 would be great; both.  
13 DR. HERRMANN: I'm thinking ahead to the  
14 trial that you're going to be conducting in this.  
15 Would the trigger be relevant in terms of  
16 eligibility? So you have the subgroup who goes on  
17 extreme exercise, extreme weight loss, et cetera.  
18 Would you want those individuals that have that  
19 very defined trigger in the same trial as the ones  
20 that we see just occurring?  
21 DR. DYCK: I don't know. I have no  
22 reason -- other than that, they seem to be really

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1 very much the same syndrome. In fact, some of  
2 these post-surgical inflammatory neuropathies, I  
3 have a case who had a diabetic lumbosacral  
4 plexopathy happening on its own. Two years later,  
5 he had a CABG. After his CABG, he developed a  
6 little bit of numbness; woke up with a little bit  
7 of numbness over the back of his wrist. Then  
8 progressively over the course of the next three  
9 weeks, he had a plegic upper limb that was  
10 completely allodynic and wouldn't let anybody touch  
11 it.  
12 I did a superficial radial nerve biopsy. He  
13 had vasculitis in that. So he had had a  
14 spontaneous lumbosacral plexopathy, and then he  
15 developed this induced cervical radiculoplexus  
16 neuropathy.  
17 I'm not sure that they are different, but  
18 it's true with all these things that you have to  
19 learn more.  
20 DR. FREEMAN: Any other questions?  
21 (No response.)  
22 DR. FREEMAN: Jim, this was fantastic. You

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1 really made our jobs very, very easy.  
2 Anything else?  
3 (No response.)  
4 DR. FREEMAN: No, good.  
5 What I think we should do now is move back  
6 to the previous presentations, have Eva come up and  
7 do her group's talk, and then finally, James' talk.  
8 But, Jim, thank you very much.  
9 (Applause.)  
10 DR. FELDMAN: I'm going to have Gordon give  
11 it for us.  
12 (Crosstalk.)  
13 Breakout Discussion (continued)  
14 DR. SMITH: This was in some ways the  
15 Toronto criteria redux, and I'll get to, we  
16 basically came up with a very similar framework  
17 with just a couple of differences. The process we  
18 went through was first to think about symptoms and  
19 then signs. We created a list of the symptoms and  
20 signs that we thought were relevant. And just as a  
21 way of organizing these, thought of positive and  
22 sometimes painful symptoms and negative symptoms,

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1 although we don't differentiate these in the  
2 diagnostic criteria and then signs. Then we  
3 organized how these were going to be used into  
4 possible, probable, or confirmed groups. Then had  
5 a discussion about how to use confirmatory testing  
6 for the confirmed.  
7 This is the definition that we arrived at  
8 for positive, and you can see here the symptoms.  
9 So positive and negative aren't really  
10 differentiated in the criteria per se. They're  
11 just for organizing.  
12 Pain, sharp sensation, shocks, burning,  
13 aching, contact sensitivity, pins, needles,  
14 paresthesias, dysesthesias, tingling, numbness, or  
15 other descriptors of loss of sensation. Solomon  
16 talked about the weird feelings people get walking  
17 on stumps, feeling of swelling, and the absence of  
18 swelling, and one might better define these.  
19 Then the signs being vibration abnormalities  
20 with the 128th hertz tuning fork. We had a  
21 discussion about whether to be definitive about  
22 what those criteria would look like timed, on, off,

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1 and these sorts of things. We came down at least  
2 at this point for just abnormal vibration.  
3 Same with pinprick, light touch,  
4 temperature, ankle reflexes. For light touch, it  
5 would be normal or absent and not in a graded  
6 fashion. We actually suggested using cooling,  
7 which is separate from or different from the first  
8 group but thought not to use heat sensation. And  
9 then something I failed to mention is that this  
10 needs to be in an appropriate anatomic pattern, so  
11 a lower extremity, distal, symmetric, a  
12 length-dependent pattern for these.  
13 For possible, it would be either one or more  
14 symptoms or one or more signs, essentially.  
15 Actually, it should be just a symptom or a sign, I  
16 think, as we get to the next one.  
17 We did have a discussion about whether or  
18 not this even was worthwhile. Why have a possible  
19 category? I raised as someone who's a recovering  
20 plantar fasciitis victim, I would be a possible  
21 neuropathy patient if I weren't particularly  
22 eloquent in my description. I blame Noah for my

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1 plantar fasciitis, by the way. I had aching pain  
2 in my feet.  
3 So that's okay in an epidemiologic study.  
4 So if one is in Central Africa doing a prevalence  
5 study of diabetic neuropathy and using just a  
6 survey, then that would be the sort of study where  
7 one might use this approach.  
8 Probable neuropathy was either one symptom  
9 or one sign. So for instance, electric shocks in  
10 the feet with abnormal vibration or more than one  
11 symptom or more than one sign. So if electric  
12 shocks and numbness or abnormal pinprick and  
13 abnormal reflexes, so one symptom, one sign, or  
14 more than one symptom or more than one sign. So  
15 that would be probable.  
16 Then definite was essentially probable with  
17 a confirmatory test. This is where we had some  
18 discussion. I tried my best to lobby for a purely  
19 clinically-driven definite neuropathy, to no avail,  
20 which I can understand why. We then had a  
21 discussion about which tests would be appropriate.  
22 And similar to the first group, we talked about the

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1 utility of quantitative sensory testing and decided  
2 that quantitative sensory testing really is nothing  
3 more than a different way of assessing the same  
4 sign modalities that we're already assessing with  
5 the clinical examination.  
6 I see nodding over here so that's good.  
7 It's always good when Amanda -- I think you agree.  
8 DR. PELTIER: Except I'm going to pick on  
9 you for simplicity's sake. What is really the  
10 operational difference between a paresthesia and a  
11 dysesthesia? I don't even know if I would be able  
12 to quantify that. So I would say use one word or  
13 the other.  
14 DR. SMITH: I actually think I would not use  
15 either word.  
16 DR. PELTIER: That's fine with me.  
17 DR. HERRMANN: I may have this wrong, but  
18 isn't paresthesia spontaneous symptom whereas  
19 dysesthesia is invoked with a --  
20 DR. SMITH: Right, so I think I would  
21 describe these differently.  
22 (Crosstalk.)

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1 DR. TESFAYE: It's painful paresthesia.  
2 DR. SMITH: So paresthesia is unpleasant --  
3 (Crosstalk.)  
4 DR. SMITH: It's an unpleasant paresthesia.  
5 But I think we should capture these in words  
6 that -- we're struggling with this here, that  
7 people who are non-endocrinologists and non-  
8 neurologists would understand.  
9 DR. PELTIER: This is my point is that if  
10 you're a family practice doctor or you're out in  
11 the community -- if you say two or more symptoms,  
12 well, that could be two symptoms, but are they  
13 really that significantly different?  
14 DR. POP-BUSUI: This is for research.  
15 DR. PELTIER: Right, but again --  
16 DR. SMITH: But you can describe these in an  
17 easily understood way, right?  
18 DR. FREEMAN: But you do want to say pain.  
19 That could be electrical shock, burning, aching  
20 because those are all pain variants, I'm assuming.  
21 DR. SMITH: Right. Well, then there's the  
22 other question is we really aren't necessarily

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1 saying there has to be pain.  
2 DR. BRIL: No, but these were put in that  
3 line because some people say the tingling is very  
4 painful, so a dysesthesia, right? But tingling was  
5 repeated because it need not be painful. So it was  
6 done kind of quickly. So there was a distinction  
7 there, pain of all these types or tingling and  
8 going on to the other symptoms.  
9 DR. SMITH: I think we have a separate  
10 taxonomy for painful diabetic neuropathy. So what  
11 I would posit is we really don't need to say  
12 whether or not it's painful in this. We need to  
13 describe the different sensory phenomena, and  
14 clearly, you don't want to have a tingling -- maybe  
15 you don't need tingling and pins and needles. I  
16 don't know. We need to throw something out to  
17 capture that.  
18 I don't have a moderator. Doug?  
19 DR. ZOCHODNE: Doesn't Peter Dyck have a  
20 paper that says in Minnesota that you have to use a  
21 descriptor "prickling"?  
22 (Laughter.)

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1 DR. ZOCHODNE: There is a paper on this for  
2 [inaudible -- off mic].  
3 DR. SMITH: Tongue out of cheek, that's  
4 probably an issue as one thinks to validate  
5 individual symptoms as part of a diagnostic  
6 criteria cross-culturally. I don't know what you  
7 say in the UK.  
8 DR. FREEMAN: Just looking at this, we want  
9 two or more symptoms, and can those two both be  
10 dysesthesias and paresthesias or  
11 dysesthesias -- remember, we can work on this, but  
12 I just want to be sure that pins and needles and  
13 paresthesias are --  
14 (Crosstalk.)  
15 DR. BRIL: How often do you get one without  
16 the --  
17 DR. SMITH: It's an affective component of  
18 it, right? So your paresthesia might be my  
19 dysesthesia because I'm a wimp.  
20 DR. TESFAYE: Pins and needles paresthesia.  
21 DR. SMITH: Yes, so pins and needles --  
22 DR. POP-BUSUI: Pins and needles is the lay

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1 term for paresthesia.  
2 DR. TESFAYE: I think if you say  
3 paresthesias, you don't need tingling in addition.  
4 DR. SMITH: Pick one or the other, yes.  
5 DR. TESFAYE: Pick one, yes.  
6 DR. BRUEHL: In fairness to Jim, I sat in on  
7 this. I did not critique like I did his. I was  
8 kind of withholding judgment, but I agree with some  
9 of the comments that have been made. And one way  
10 to do it would be to have your main criterion be  
11 paresthesias and then parenthetically say such as  
12 and just give a few examples like that where it  
13 doesn't have to be exhaustive.  
14 (Crosstalk.)  
15 DR. PELTIER: I would include itching.  
16 DR. FREEMAN: It seems like we can deal with  
17 pain examples.  
18 (Crosstalk.)  
19 DR. PELTIER: A lot of patients have like  
20 inexplicable in their feet and their lower  
21 extremities and do not realize that it's a  
22 neuropathic symptom.

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1 DR. HARATI: Other symptoms may get better,  
2 but the itching doesn't because they're different  
3 small fibers.  
4 DR. FELDMAN: Gordon, if you go back to the  
5 very first slide we did on probable neuropathy, I  
6 think that what we -- possible. I'm sorry.  
7 "Continue to discuss pain in more refined  
8 definition," and then I just copied and pasted for  
9 the next.  
10 If you remember, we had this discussion or  
11 began to have this discussion as we were talking  
12 about possible, probable, and confirmed. And I do  
13 think we've really started discussing in more  
14 detail confirmed neuropathy, and I think it's  
15 important whatever we decide needs to hold for both  
16 possible and probable.  
17 DR. BRUEHL: For example, one way this could  
18 be worded up here would be pain -- you can have,  
19 let's say, four items, and you say must -- three of  
20 four of these -- if you wanted to go this route,  
21 and you could say pain that is frequently described  
22 as sharp, electric, whatever. You could have a

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1 separate one that's paresthesias. You could  
2 specifically list tingling if you thought it was  
3 key enough, or itching, to have a separate item on  
4 there. Then the numbness or dead feeling, however  
5 that one would be worded.  
6 The way we've structured it here, it's just  
7 like any one of those would qualify, and none is  
8 really primary. My understanding was that's  
9 intentional, correct?  
10 DR. SMITH: I don't think, though, we want  
11 pain as a core feature here. I think the idea is  
12 that we're going describe the sensory phenomena.  
13 There's a separate set of criteria that will deal  
14 with whether or not this qualifies as painful  
15 neuropathy. But here, we can almost be pain  
16 agnostic. Whether or not the pins and needles are  
17 merely paresthetic, dysesthetic is less of an issue  
18 here. It's just that they're paresthesias, that  
19 it's an abnormal positive sensory phenomenon that  
20 in Olmsted County would be prickling. I think  
21 prickling is kind of good. I like that.  
22 DR. GIBBONS: Just one question then. Our

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1 group was really negative on the temperature cool  
2 sensation on the feet.  
3 DR. FELDMAN: Well, David, do you want to  
4 speak up for that?  
5 DR. BENNETT: I think it works very well, a  
6 cool thermal roller. Is there a reason why you  
7 were negative?  
8 DR. PELTIER: Because there's a lot of  
9 patients who have very cold feet that they're  
10 not -- I find it to be less sensitive or less  
11 helpful, and if it's usually positive, the pinprick  
12 is almost always positive, also. So if you're  
13 going to do one, just do the pin.  
14 DR. SMITH: We don't have to do only one.  
15 (Crosstalk.)  
16 DR. BENNETT: I'm not sure I agree. I  
17 didn't have the same experience. It may be  
18 suitably, not clinically.  
19 DR. SMITH: I think thermal -- I think cool  
20 sensation can be helpful. It's not always.  
21 DR. GIBBONS: I guess the question if you're  
22 operationalizing, it is one.

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1 DR. PELTIER: Right.  
2 DR. GIBBONS: And you're saying that cool is  
3 abnormal in someone with cold feet, is that leading  
4 you astray?  
5 (Crosstalk.)  
6 DR. HERRMANN: I think the problem is  
7 testing it reproducibly --  
8 (Crosstalk.)  
9 DR. SINGLETON: The problem is a specific  
10 place.  
11 DR. HERRMANN: -- because the pain, if the  
12 pain isn't from the temperature of the limb, which  
13 pin sensation isn't, and you can't control those  
14 things at the bedside, so I would say if you want  
15 to introduce it, it should be in the form of a  
16 quantitative sensory test as opposed to a bedside  
17 evaluation.  
18 (Crosstalk.)  
19 DR. SINGLETON: -- telling you about the  
20 Mayo setup of brass disks that are used for this  
21 purpose.  
22 DR. FELDMAN: Then they're specifically kept

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1 at --  
2 DR. SINGLETON: Right, in a refrigerator.  
3 DR. BENNETT: That's what I'm talking about,  
4 thermal rollers that are kept at a temperature.  
5 They can work very well.  
6 (Crosstalk.)  
7 DR. GIBBONS: I think you can test it if you  
8 use the right approach.  
9 DR. SMITH: I think you can, too. If you  
10 want to go down this route, then we should start  
11 talking about a tuning fork. I think that this is  
12 a dangerous thing to do because --  
13 (Laughter.)  
14 (Crosstalk.)  
15 DR. SMITH: Yes, I think you can use the  
16 same argument for a reflex hammer. There has to be  
17 Tromner hammer, otherwise, it's not -- yes.  
18 DR. BRUEHL: Gordon, can you jump ahead one  
19 slide just for a second? On the probable, one the  
20 ways you could get it is more than one symptom,  
21 right, or more than one sign.  
22 So when we are starting to talk about

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1 needing more than one in a category, it starts to  
2 make a difference how the items are broken out.  
3 Things that are redundant, listed more than once,  
4 such as sharp and electrical over-weights pain  
5 descriptors, because you could get the diagnosis  
6 just with two of those -- and I'm not sure what the  
7 answer is, but I think some thought needs to be put  
8 into how to lay these out.  
9 So the paresthesia is one, is numbness  
10 separate? How many of them is on the list that you  
11 can choose from?  
12 DR. FELDMAN: I think that was why I guided  
13 everyone to our very first slide. I think at least  
14 our group realized that this was the big weakness  
15 in what we had laid out and that this is what  
16 needed work. But we wanted kind of what Rodica  
17 implied earlier is that we wanted to have more data  
18 in order to do this in, I think, the optimal way.  
19 DR. FREEMAN: It seems to me that the  
20 symptoms are pretty easy. You can just say painful  
21 symptoms, everything in parentheses; non-painful  
22 positive symptoms, another whole bunch of stuff in

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1 parentheses; negative symptoms, numbness, a lot of  
2 stuff in parentheses, including dead in a way. I  
3 think that's relatively easy.  
4 I'm troubled --  
5 DR. SMITH: Roy, can I interject, though?  
6 DR. FREEMAN: Yes.  
7 DR. SMITH: Doesn't that mean that you just  
8 need a positive and a negative symptom?  
9 DR. PELTIER: That's what I would argue.  
10 For probable, you would have positive and a  
11 negative, not just --  
12 DR. SMITH: We opted not to do that, but  
13 what you just described is essentially you have to  
14 have one of these, so either --  
15 (Crosstalk.)  
16 DR. FREEMAN: I like your one, but it could  
17 be one which is either pain or non-pain or  
18 numbness. So one of the two positives and I think  
19 one negative. I think the negatives probably, and  
20 I think that's fine.  
21 DR. SMITH: Two positives, but then you run  
22 into overlapping.

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1 DR. FREEMAN: I think what I'm actually  
2 doing is removing the overlapping because I'm  
3 saying pain, which encompasses everything. Those  
4 are all pain.  
5 DR. SMITH: Yes, pain or non-painful  
6 positive symptoms, so a positive symptom whether  
7 it's painful or not or a negative symptom.  
8 DR. FREEMAN: If you think you can delineate  
9 the negative symptoms in a --  
10 DR. RUSSELL: Gordon, can I just clarify --  
11 DR. SMITH: So that would mean by extension  
12 that a positive and a negative would make you  
13 probable.  
14 DR. RUSSELL: Gordon, can I just clarify  
15 something because we had a terrible problem with  
16 whether you should have symptoms or not symptoms,  
17 and we said you may or may not have them. Are you  
18 saying you have to have symptoms, or could you just  
19 have signs?  
20 DR. SMITH: No.  
21 AUDIENCE: You can just have signs.  
22 (Crosstalk.)

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1 DR. RUSSELL: That's fine. I just wanted to  
2 clarify how you were doing it. Okay. Perfect.  
3 DR. SMITH: For possible, you could have  
4 just a positive or a negative symptom or a sign.  
5 For probable, you would need to have a positive and  
6 negative symptom or multiple two signs, or either a  
7 positive or a negative and one sign. Then for  
8 confirmed --  
9 DR. POP-BUSUI: Why do you really need to  
10 separate positive and negative? We don't need  
11 that.  
12 DR. BRUEHL: We do if pain and  
13 positive -- if you're trying to have pain as  
14 something that might allow somebody to qualify --  
15 DR. POP-BUSUI: But that's different.  
16 That's painful.  
17 DR. SMITH: No, but I think the point is  
18 that these are overlapping, so that's the  
19 challenge.  
20 DR. BRUEHL: The positive sensory could  
21 encompass pain if you wanted to, but you could list  
22 it as separate if you want to have somebody be able

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1 to make it either way. I don't know what the  
2 answer is, but that was the rationale.  
3 DR. FELDMAN: I don't think, Gordon, we said  
4 if you have to have more than -- like a cluster of  
5 symptoms that they had to all be -- they had to be  
6 both a positive symptom and a negative symptom. We  
7 can define it that way, but that's not what we  
8 said.  
9 DR. SMITH: That's not what we said. We've  
10 kind of talked our way into that. We can talk our  
11 way out.  
12 DR. ZIEGLER: Why should numbness be a  
13 negative symptom? I could easily say it's another  
14 positive symptom, so I would skip that dichotomy.  
15 DR. FREEMAN: That's a semantic issue.  
16 (Crosstalk.)  
17 DR. ZIEGLER: I can say that anything the  
18 patient reports to you is positive and anything you  
19 find on your neurological exam is negative. That  
20 would be a straightforward view as well.  
21 (Crosstalk.)  
22 DR. SMITH: The problem with that is then

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1 you --  
2 DR. RUSSELL: So this is based on Jim Dyck's  
3 original definition. So you disagree with that --  
4 DR. SMITH: -- painful symptoms is also  
5 having non-painful symptoms, right?  
6 (Crosstalk.)  
7 DR. SMITH: This is devolving in a  
8 tomato/tomahto sort of thing. So I'm self-  
9 moderating --  
10 MALE VOICE: Just forget the positive and  
11 negative symptoms. Symptoms and signs and  
12 categories.  
13 (Crosstalk.)  
14 DR. SMITH: Well, but then you run back into  
15 the problem here. If you get rid of the positive  
16 and negative, then you have the issue of redundant  
17 or overlapping symptoms in patients --  
18 (Crosstalk.)  
19 DR. CALLAGHAN: Aren't there three symptom  
20 categories; pain, paresthesias, numbness?  
21 (Crosstalk.)  
22 DR. SMITH: But pain and paresthesias are

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1 basically --  
2 DR. GIBBONS: Put them in parentheses with  
3 the burning pain, shooting pain --  
4 DR. SMITH: But once you're at pain, you're  
5 going to have a paresthesia.  
6 (Crosstalk.)  
7 DR. SMITH: Usually you're going to  
8 have -- not necessarily --  
9 (Crosstalk.)  
10 DR. GIBBONS: Could do pain or paresthesias  
11 or one of those two as one category or numbness as  
12 the other.  
13 DR. SMITH: Then how do you do the two  
14 categories or two-symptom domains?  
15 DR. GIBBONS: Symptoms would be this or that  
16 or this, and that would be one as these two, and  
17 then one --  
18 DR. SMITH: Right, so that's where we are  
19 now with --  
20 DR. GIBBONS: But they're just -- the  
21 semantics bother people, positive or negative, so  
22 just put one and two.

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1 DR. BRIL: We didn't say you had to have one  
2 from each domain.  
3 DR. SMITH: No, we didn't, but we --  
4 DR. BRIL: We just said symptoms.  
5 DR. SMITH: This goes to Steve's point about  
6 the overlaps, the fact that these are going to  
7 aggregate together.  
8 DR. BRIL: You've got pain and then  
9 paresthesia and numbness. They are three separate  
10 things. If you've got pain, it can be painful  
11 tingling if you want, but the patient will tell you  
12 that. Others will say I have tingling and no pain.  
13 It doesn't hurt.  
14 I don't quite understand this  
15 dichotomizing --  
16 DR. SMITH: The challenge there, Vera, is  
17 when we come to here, that patient has painful  
18 tingling --  
19 DR. ZIEGLER: It's pain. It's just pain.  
20 That's pain then.  
21 DR. SMITH: Right. But the tingling is the  
22 pain, and so you're saying that they get the two

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1 criteria to --  
2 DR. BRIL: No.  
3 DR. ZIEGLER: No, no, it would be pain.  
4 DR. SMITH: So we're saying the same thing.  
5 (Crosstalk.)  
6 DR. PELTIER: Would it be possible to say a  
7 spontaneous sensation that's not -- so then you  
8 could be anything.  
9 FEMALE VOICE: Then say non-painful  
10 paresthesia.  
11 (Crosstalk.)  
12 DR. SMITH: You would require the person to  
13 have -- either way the patient is going to -- it's  
14 saying the same thing I've been saying. So if it's  
15 non-painful tingling, that by definition means they  
16 don't have pain, thus to be probable, they have to  
17 have one of these, right?  
18 So we're saying the same thing minus  
19 positive and negative so --  
20 DR. FREEMAN: Lose the non-positive,  
21 negative.  
22 DR. SMITH: So kind of neutral.

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1 (Crosstalk.)  
2 DR. HERRMANN: There are a couple of other  
3 symptom categories I think we may be missing. So  
4 truly negative symptoms is the awareness of a lack  
5 of sensation or a loss of sensation, and we sort of  
6 covered that. The patient who tells you when they  
7 put their foot under hot water, they can't feel  
8 that. I don't know where that --  
9 DR. SMITH: I think that would go under the  
10 numbness --  
11 DR. HERRMANN: Define that under the  
12 numbness. Then also balance, there are --  
13 (Crosstalk.)  
14 DR. HERRMANN: -- under the definition  
15 issues around --  
16 DR. SMITH: We brought that up, and I think  
17 the concern we had is that balance problems are  
18 extremely common.  
19 DR. FREEMAN: I've got concerns with the  
20 signs. I think you've got --  
21 DR. SMITH: Sorry. Did you have a symptom  
22 issue, Doug, or a --

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1 DR. ZOCHODNE: [Inaudible – mic] -- Journal  
2 of the Neurological Sciences 2001, Positive Sensory  
3 Symptoms [inaudible – off mic].  
4 (Crosstalk.)  
5 DR. FELDMAN: We published this. That's why  
6 I think that we said -- I really do think this  
7 discussion needs to be tabled until we can look at  
8 what we've all done because there is good data on  
9 this.  
10 DR. FREEMAN: It is unnecessary for me to  
11 remind you, I'm sure, that that was a negative  
12 trial. (Laughter.)  
13 DR. SMITH: I would say any trial that's  
14 accurate is a positive trial.  
15 DR. TESFAYE: I think this is okay for a  
16 start, and we can refine one or two things later.  
17 But effectively, what we came up going through this  
18 exercise previously is that you have positive  
19 symptoms and persistent burning or dull pain, achy  
20 pain; paroxysmal occasionally, electric shock type,  
21 shooting, stabbing, knife-like, these sort of sharp  
22 pains; dysesthesias; painful paresthesias and

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1 tingling; and then the evoked pain, which is  
2 contact hypersensitivity as a positive.  
3 The negative symptoms are numbness, dead  
4 feeling or hypoesthesia and hypoalgesia. Some  
5 patients do say, as was indicated, I can't feel my  
6 feet when I put -- I can't feel that. That is also  
7 a symptom.  
8 I think these encapsulate what we're trying  
9 to do, and we can refine it later. I think  
10 everything that's here is captured.  
11 DR. SMITH: I think we're actually all  
12 saying more or less the same thing in different  
13 ways.  
14 DR. FREEMAN: Five tests, five examination  
15 tests, five signs would be in line with -- having  
16 concern about specificity. Would the guy with  
17 plantar fasciitis have all of those?  
18 DR. SMITH: It depends on how old they are.  
19 DR. FREEMAN: That's where I think we need  
20 to have some granularity. It's hard to  
21 operationalize that temperature --  
22 DR. SMITH: I don't understand how you

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1 operationalize this.  
2 DR. FREEMAN: -- deficits and a light touch.  
3 (Crosstalk.)  
4 DR. SMITH: Roy is worried about  
5 temperature, operationalizing temperature.  
6 DR. FREEMAN: I worry about how to  
7 operationalize temperature, and I worry about five  
8 tests and the likelihood of one being a false  
9 positive.  
10 DR. SMITH: There are concerns over deep  
11 tendon reflexes, and we had discussions over that  
12 and whether or not to include them and how to  
13 assess vibration.  
14 DR. ZIEGLER: I personally think it's fine  
15 because there are scores which include both, the  
16 temperature, and for example, the Neuropathy  
17 Disability Score and others. I think it's a useful  
18 test, cooling, taking the rod. I would keep those  
19 five. Those are the typical bedside tests you can  
20 do.  
21 DR. GIBBONS: But would you then say one or  
22 two signs is the question. How many signs do you

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1 need?  
2 DR. ZIEGLER: Both sides, of course.  
3 DR. GIBBONS: Signs, how many signs?  
4 DR. ZIEGLER: Oh, signs. I think with those  
5 definitions, especially with the possible one, we  
6 are very unspecific because it's very easy in a  
7 healthy person to find one symptom or one sign by  
8 chance. There are people dealing with normative  
9 data that should go through the databases and see  
10 how frequent that is. I would guess you will find  
11 this quite often. So I think the specificity will  
12 be lousy.  
13 DR. FREEMAN: I think we probably want to  
14 get more specific, and that's really the point I'm  
15 making, that maybe we need more than one sign.  
16 DR. SMITH: We do have that now, so we  
17 wanted to be able to capture asymptomatic. So for  
18 probable, either one can have -- so you mean if  
19 there is one symptom --  
20 DR. FREEMAN: Two signs.  
21 DR. SMITH: -- so there always need to be  
22 two signs.

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1 DR. FREEMAN: That would be my sense.  
2 DR. POP-BUSUI: But we can actually test to  
3 see how this type of definition performs in a newly  
4 diagnosed patient population where you can argue  
5 that the likelihood of having the disease, it's  
6 very low because all these tests -- what I'm trying  
7 to say is we can test to see how accurate these  
8 tests perform based on the data that is already  
9 available, because this test has been done in  
10 various patient populations.  
11 DR. ZIEGLER: I think what you have to do is  
12 to look at an appropriate healthy population and  
13 see how it performs there, and from there, you can  
14 embark upon the diabetic population.  
15 I call tell you the opposite; we published  
16 that. We found using the bedside test, we found  
17 very often in newly diagnosed type 2 patients, very  
18 often a possible neuropathy with signs or symptoms.  
19 So it's not that it's infrequent.  
20 DR. POP-BUSUI: I didn't say that.  
21 DR. ZIEGLER: Those are patients under  
22 excellent control, so their A1C is 6.5, and they

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1 are within the first year from diagnosis. It's all  
2 published.  
3 DR. SMITH: So the suggestion is for  
4 probable one symptom and two signs. So is that it,  
5 one or more symptoms and two signs? Or if you have  
6 two symptoms, is one sign acceptable? Is that what  
7 you're suggesting?  
8 DR. HERRMANN: Based on HIV, in the HIV  
9 literature, Dave Simpson and others have looked at  
10 the one sign versus two signs with a confirmatory  
11 test, and the one sign leads to a lot of loss of  
12 specificity. I would encourage sticking with the  
13 one sign for the possible.  
14 I think for the probable, understanding that  
15 you need a confirmed retest for your definite, I  
16 would insist, to Roy's point, on having at least  
17 two signs for the probable.  
18 DR. BRIL: Is that with a symptom? Because  
19 if you don't have a symptom, then you have to have  
20 more than one sign. Here for probable, you have to  
21 have at least one symptom and one sign.  
22 DR. HERRMANN: I would say for probable two

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1 signs whether you have symptoms or not.  
2 Symptomatic neuropathy would be a symptom and two  
3 signs, and asymptomatic would be two signs.  
4 DR. SMITH: So someone who has bilateral  
5 severe burning of their feet, pins and needles,  
6 smells like neuropathy, and the only thing we find  
7 is abnormal pin sensation, that would not be  
8 probable?  
9 DR. HERRMANN: Based on what they've done in  
10 HIV, they've called that [indiscernible].  
11 DR. GIBBONS: I would agree that if you had  
12 plantar fasciitis with achy burning pain in your  
13 feet and you had abnormal temperature, that would  
14 not be probable because you'd still possibly fit  
15 that criteria. You'd still be possible.  
16 DR. SINGLETON: I think you might have  
17 trouble because there's a difference in sensitivity  
18 of the different signs, and I think in general,  
19 small fiber signs are more sensitive. I know Dan's  
20 going to disagree with me about this, too.  
21 But I think especially if you have two signs  
22 and you have only a large fiber predominant

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1 neuropathy, you have decreased vibration and then  
2 nothing else.  
3 DR. BRUEHL: Are you arguing to subclassify  
4 the signs?  
5 DR. SINGLETON: I'd rather be inclusive than  
6 specific in this case.  
7 DR. SMITH: You're going to base your  
8 confirmed --  
9 DR. SINGLETON: On a confirmatory test.  
10 DR. SMITH: There, I have problems because  
11 those confirmatory tests are abnormal in so many  
12 people who don't have signs and symptoms that --  
13 DR. SINGLETON: Were you willing to have  
14 reduced ankle reflexes in an age-appropriate group?  
15 DR. SMITH: We said absent.  
16 DR. SINGLETON: Absent only.  
17 DR. SMITH: Absent only.  
18 DR. SINGLETON: That would help with the  
19 large fiber construct of two signs required if you  
20 were willing to go reduced and not absent.  
21 DR. SMITH: Is this a bargaining -- well, if  
22 we're going to do --

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1 (Laughter.)  
2 DR. SINGLETON: We're making real progress  
3 if we're down to this kind of haggling.  
4 DR. SMITH: Yes, yes.  
5 DR. GIBBONS: Can I maybe just suggest --  
6 DR. SMITH: No, you may not suggest.  
7 DR. GIBBONS: Yes, I will do so anyway. Can  
8 I suggest that maybe we already have these  
9 databases and our own item responses, and table it  
10 and just say do a quick check against our database  
11 to see how that falls out. We already know --  
12 DR. PELTIER: That's what I said.  
13 DR. ZIEGLER: For now you can keep it loose  
14 like the Toronto consensus. There, you don't  
15 mention any number of signs or symptoms.  
16 DR. SMITH: They say sensory --  
17 (Crosstalk.)  
18 DR. SMITH: -- and that's the way it is and  
19 I guess that is a question. Is this different  
20 enough to warrant changing --  
21 DR. FREEMAN: We can't be loose here. This  
22 is --

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1 DR. ZIEGLER: But it's not loose. The  
2 difference is that possible is the same, and  
3 probable will be the same if it stays like this.  
4 DR. FREEMAN: We're moving through degrees  
5 of specificity, so from nonspecific, the possible,  
6 to the probable, more specific.  
7 I take Rob's point about the small fiber  
8 neuropathy. It's a challenge where perhaps  
9 temperature is not as reliable a test, but I think  
10 we've got to move through these phases of possible  
11 to probable with greater specificity.  
12 DR. SMITH: I think what we're going to do  
13 is align the first talk on small fiber neuropathy  
14 into this framework, so I don't think there's going  
15 to be any problem with that.  
16 DR. FREEMAN: I agree, I agree.  
17 DR. SMITH: I think the point is taken. Two  
18 signs as a requirement.  
19 DR. FREEMAN: I think we're good. I can't  
20 wait to see --  
21 DR. SMITH: Back to Vera's point because I'm  
22 confused, you're writing all this down, right?

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1 We're allowing probable neuropathy with just  
2 two signs, which means symptoms are not really  
3 germane to the designation of probable neuropathy.  
4 You'll have symptomatic probable neuropathy and  
5 asymptomatic probable neuropathy is the way we  
6 would construct it.  
7 DR. BRIL: Yes, because you know --  
8 DR. FREEMAN: Does that reflect everybody's  
9 reality?  
10 (Chorus of yeses.)  
11 DR. PELTIER: There are lot of diabetics  
12 running out there who are not going to tell you  
13 anything. They'll have more than [inaudible - off  
14 mic].  
15 DR. TESFAYE: In terms of operation for the  
16 temperature, if somebody has been in the snow and  
17 freezing feet and coming on the table, we need to  
18 specify that it's done in the proper way and that  
19 we need to correct for that. That's important.  
20 DR. SMITH: I think that's true with all of  
21 these. That's why I'm not sure how far you wanted  
22 to get into this, Roy. What's the proper way of

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1 evaluating vibration and what are the age normative  
2 values, and which brand of pins should you use or -  
3 -  
4 DR. FREEMAN: I would say I think this is  
5 going to be a topic for future meetings. I would  
6 say this is not methodology heavy. It's  
7 methodology light, but it's not methodology  
8 neglected.  
9 DR. SMITH: We'll say appropriately  
10 performed by highly trained crackerjack teams,  
11 sensory physiology.  
12 DR. HERRMANN: Position sense is missing  
13 from that list, the original.  
14 DR. SMITH: Yes, position sense, what do you  
15 people think?  
16 FEMALE VOICE: That should be included.  
17 MALE VOICE: I think it's as useful as light  
18 touch.  
19 FEMALE VOICE: Actually, I think it's more  
20 useful than light touch.  
21 DR. TESFAYE: With position sense, they've  
22 found it is very much in advanced disease that you

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1 find it's not sensitive, and therefore, I don't  
2 think it should be included.  
3 DR. SMITH: What's the downside of including  
4 it, I suppose? If it's abnormal, it's other going  
5 to come along. I think that was the --  
6 (Crosstalk.)  
7 DR. BRIL: Also, difficulty walking is a  
8 symptom.  
9 DR. SMITH: It's a negative symptom, or it's  
10 positive if they tell you --  
11 (Crosstalk.)  
12 DR. ZIEGLER: There are several people  
13 sitting in this room who participated in the  
14 Toronto definition, and obviously, this is  
15 different. So the question is whether we should  
16 have a vote as to whether we define this symptoms  
17 and signs or just by signs plus/minus symptoms  
18 because it's a deviation of what has been  
19 published.  
20 (Crosstalk.)  
21 DR. ZIEGLER: I don't think it's slight.  
22 DR. BRUEHL: Within each version of this

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1 because this is going to evolve a lot because we  
2 have another group that's defined it slightly  
3 differently. I think we can circulate via email.  
4 DR. BENNETT: Can I just check? The two  
5 signs, it's got to be different domains. Because  
6 small fiber neuropathy, you're going to have to  
7 have bilateral changes in temperature and bilateral  
8 abnormality in pinprick.  
9 DR. SMITH: Right. So we're going to have  
10 to --  
11 DR. BENNETT: That's a pretty tight  
12 definition.  
13 DR. SMITH: I think we need to map that onto  
14 this. So David's point is for small fiber  
15 neuropathy, does that imply that we have to have  
16 both abnormal pinprick and abnormal temperature?  
17 So it may be that --  
18 DR. BENNETT: Bilaterally, that's asking a  
19 lot.  
20 DR. SMITH: That's captured up here  
21 bilateral and symmetric, but it may be that we're  
22 going to have to modify this a little bit for small

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1 fiber neuropathy.  
2 DR. ZIEGLER: One is enough. One is enough  
3 for small fiber bilaterally because otherwise,  
4 that's really tough, very tough.  
5 DR. SMITH: Yes, I tend to agree.  
6 (Crosstalk.)  
7 DR. BRUEHL: This needs to say bilateral  
8 signs, by the way because that's only referring to  
9 the symptoms. We need to say the same language for  
10 both.  
11 DR. SMITH: We end on accord. We agree.  
12 DR. FREEMAN: Are you going to do definite  
13 or clinically confirmed or whatever you called it?  
14 DR. SMITH: Highly probable, what makes Roy  
15 comfortable; although we're changing this.  
16 DR. BRIL: I think the not needing signs was  
17 because of the small fibers, right, small fiber  
18 neuropathy. We might have the burning pain and yet  
19 not have any deficits, but then you have the  
20 confirmatory test.  
21 DR. SINGLETON: Are you guys willing to  
22 accept hyperalgesia to light touch or to pin like

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1 allodynia? Is that there someplace amongst the  
2 signs?  
3 DR. POP-BUSUI: It's context sensitivity.  
4 We put it into the symptoms.  
5 (Crosstalk.)  
6 DR. SINGLETON: It's very testable as a  
7 sign, right?  
8 DR. GIBBONS: Where does the painless severe  
9 neuropathy fit in?  
10 DR. SMITH: We're not doing severe, and the  
11 other people are doing --  
12 DR. GIBBONS: Not so much severe but --  
13 DR. SMITH: Painless would be --  
14 DR. GIBBONS: -- a confirmed neuropathy, in  
15 other words, painless.  
16 DR. SMITH: Two different signs, two  
17 different signs.  
18 DR. GIBBONS: But it says --  
19 DR. SMITH: We changed it.  
20 DR. GIBBONS: Two and/or, got it. Okay.  
21 DR. SMITH: Stay with us.  
22 DR. ZIEGLER: They also may have painless

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1 symptoms, so paresthesias plus two signs is a  
2 painless neuropathy.  
3 DR. SMITH: But does the painless tree fall  
4 in a forest when you're there or not?  
5 (Laughter.)  
6 DR. SMITH: I think it's time to move on.  
7 We already talked about that. Good.  
8 DR. FREEMAN: Can people survive another  
9 half hour? James, and then we will break.  
10 FEMALE VOICE: Let's get done.  
11 (Crosstalk.)  
12 DR. RUSSELL: The shorter we make this, the  
13 sooner we get to dinner, just as we put it up here.  
14 We kind of made ours pretty simple. The  
15 biggest sticking points were really symptoms, and  
16 the problem was whether or not you really had to  
17 have symptoms or not in defining whether something  
18 was going to be clinically mild, clinically  
19 moderate, or clinically severe. We'll go down here  
20 in a moment to what severe is.  
21 The problem with this was that we kept  
22 getting to the conclusion that while symptoms would

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1 be present most of the time, they may not always be  
2 present. The next problem was really which  
3 symptoms were going to define mild or moderate or  
4 severe, and we had a real problem with this in that  
5 it's very clear that pain may be very severe if  
6 it's clinically mild, but it also may be present,  
7 for example, in patients with moderate severity  
8 neuropathy.  
9 We tried to make this as simple as we could,  
10 and the preclinical one then was that there would  
11 be no symptoms due to neuropathy. The reason why I  
12 say due to neuropathy is because we had the  
13 question, well, if people have some type of sensory  
14 symptom but we don't think it's a neuropathic  
15 sensory symptom, what does that mean? So we said  
16 they have to be symptoms consistent with what we  
17 would think would be neuropathy, and then signs as  
18 well consistent with neuropathy, so no signs.  
19 Then for preclinical then since these are  
20 both negative, you would have to have an  
21 abnormality. We went through what would be the  
22 possible tests one would use in order to determine

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1 the presence of abnormality, and these were ones  
2 that we came up with that at least have pretty good  
3 validation, certainly for somatic symmetrical  
4 polyneuropathy.  
5 With QST, we didn't go into the specific  
6 measures here, but the ones that have been most  
7 validated will be vibration and cold perception.  
8 We took the 95th percentile cutoff level, and  
9 again, you could debate about whether that's as  
10 good as using the 99th.  
11 Then these parts here are more debatable.  
12 So clinically mild, we said that you may or may not  
13 have symptoms of neuropathy, although we do agree  
14 that most people will have symptoms, and they've  
15 been very well defined by Gordon. But you would  
16 have reduced sensory signs consistent with  
17 neuropathy but loss of sensory signs. So this  
18 would separate this from the other groups.  
19 The sensory signs and what may they be, and  
20 we didn't get into a great deal of discussion about  
21 this, so I added this in. The one part that we did  
22 talk quite a bit about was ankle reflexes and

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1 reflexes in general and how you really define this  
2 and what determines whether it's due to the  
3 neuropathy, so I left it out of here.  
4 Certainly, in the talk Gordon gave a little  
5 earlier, one of the things that actually increased  
6 the reproducibility of the testing the second time  
7 the neuropathy expert study was done in Rochester  
8 was simply saying we're not going to use absent  
9 ankle reflexes as defining the presence of  
10 neuropathy. So in other words, if you're over the  
11 age of 60 or 65 and the ankle reflexes are absent  
12 but you can't find other features, then you  
13 wouldn't necessarily call it neuropathy. But that  
14 is debatable.  
15 Cold perception, we've already discussed.  
16 Vibration, I've just simply said this is touch, and  
17 that's because if you are a sensory physiologist,  
18 you will have a lot of debate about which exact  
19 receptors and fibers are affected by things like  
20 the monofilament or other forms of touch. And pin  
21 perception, we've discussed.  
22 Then the next thing is if it's clinically

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1 confirmed, you would have items 1 and 2, and then  
2 you would also have an abnormality of one of these  
3 measures, so quantitative sensory testing, nerve  
4 conductions, intraepidermal nerve fiber density, or  
5 corneal confocal microscopy.  
6 DR. GIBBONS: James, I just want to  
7 interrupt for a question. So looking specifically  
8 at the preclinical and moving to the clinically  
9 mild, for the preclinical, you have no symptoms, no  
10 signs, and your only abnormality is corneal  
11 confocal microscopy.  
12 DR. RUSSELL: Or one of these other  
13 measures.  
14 DR. GIBBONS: Right, but say that was the  
15 only abnormality, it's a test in a different  
16 unrelated tissue bed. We're talking about distal  
17 symmetric. How do you put that together? I'm just  
18 wondering if that's bringing us maybe into the  
19 wrong realm.  
20 DR. RUSSELL: Well, the consensus by  
21 democratic vote was that in preclinical, you would  
22 not have signs and you would not have symptoms. So

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1 you have to define it in some other way.  
2 The question is -- and this is a separate  
3 discussion -- which of these measures would you  
4 really take as your most sensitive measure? We  
5 don't really have time to go into that. That's a  
6 whole other debate.  
7 Would you consider the intraepidermal nerve  
8 fiber density to be the right measure, or would you  
9 consider the nerve conductions to be the right  
10 measure, et cetera? We sidestepped that one.  
11 That's another whole area of discussion.  
12 DR. BRIL: It's debatable, but there's a  
13 growing amount of work that shows that those  
14 parameters are related to intraepidermal nerve  
15 fiber density related to clinical severity and many  
16 other things. It's being used as a surrogate  
17 endpoint. So it's early on, but it is being used.  
18 And you can stratify patients based on corneal  
19 nerve fiber length, which we just did in that study  
20 we published in Neurology this year.  
21 I think that is one possible option, but I  
22 do know there's a lot of work that needs to be done

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1 on that particular one.  
2 DR. PELTIER: I guess I would question, is  
3 there normative data? For somebody who's 75,  
4 what's a normal corneal density that you would --  
5 DR. BRIL: There is normative data for CNFL  
6 and for fiber density and all of that, yes.  
7 DR. PELTIER: If there is, then you could  
8 argue to leave it in.  
9 DR. BRIL: Absolutely, there is normative  
10 data.  
11 Rayaz, you should speak a little bit about  
12 this.  
13 DR. MALIK: Chris, it's getting tiring now  
14 that we have the data, and I don't know, the  
15 neurology community wants to ignore the data. So  
16 we've got two published papers that show very  
17 clearly you use standardized criteria for diabetic  
18 neuropathy, the Toronto criteria, in two different  
19 populations, and you put IENFD up against CCM, and  
20 it performs as well, if not slightly better.  
21 Whoever it is who reviews the papers tends  
22 to ignore that and says, well, let's go back to

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1 physiology, and it's a different nerve, whatever.  
2 DR. BRIL: There's a publication -- and  
3 you've got to forgive me the woman's name, but  
4 she's done all the normatives, male, female,  
5 different decades all through the life. Mitra  
6 Tavakoli. Sorry. She did that --  
7 DR. MALIK: From all of the consortium.  
8 DR. BRIL: -- from all of the consortium.  
9 There's a whole consortium looking at this.  
10 There's a lot of normative data out there, and what  
11 it does is less invasive than a skin punch biopsy,  
12 far less invasive.  
13 DR. HARATI: How specific is it?  
14 DR. MALIK: It's specific.  
15 (Crosstalk.)  
16 DR. HARATI: -- corneal sensory, cocaine  
17 abusers.  
18 DR. BRIL: No. It's as specific as anything  
19 up there. That means it's a sign of neuropathy.  
20 Again, Rayaz, you did CMT, or what did you  
21 do?  
22 DR. MALIK: T1A.

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1 DR. BRIL: CMT and showed loss. But then  
2 loss of intraepidermal nerve fibers is not  
3 specific, either.  
4 DR. RUSSELL: I'd just like to interject  
5 here and say this is a complete separate  
6 discussion, and we've been here nearly four hours  
7 on the first two.  
8 (Laughter.)  
9 DR. RUSSELL: This is about another week of  
10 discussion as to how you define --  
11 DR. BRIL: You deserve an hour.  
12 DR. RUSSELL: -- and which one you're going  
13 to use. I love all your tests, by the way.  
14 They're all great.  
15 (Laughter.)  
16 DR. RUSSELL: Clinically mild, I went  
17 through this, and we said clinically confirmed, you  
18 would have to have these two and then you would  
19 have to have an abnormality in one of these.  
20 Then clinically moderate -- can we move it  
21 up a little bit? Clinically moderate and severe,  
22 clinically moderate, the symptoms I've just

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1 discussed. Here you would have a loss of sensory  
2 signs consistent with neuropathy, so there would be  
3 complete loss, which would then separate this from  
4 mild.  
5 Then clinically confirmed, you would have  
6 this, and then we said that we wanted to really  
7 upgrade this as well so that you'd have to have two  
8 abnormalities of one of these measures here.  
9 Again, I'd like to just defer what those would be  
10 maybe for another session.  
11 DR. SMITH: Can I ask a question?  
12 DR. RUSSELL: Yes.  
13 DR. SMITH: If there's a patient who has no  
14 symptoms, absent vibration of the toes, that's it,  
15 and then has an absent sural and abnormal vibration  
16 on QST, that categorizes them as a clinically --  
17 DR. RUSSELL: There are two separate things  
18 here. There's clinically moderate, which is  
19 defined based on that, and clinically confirmed  
20 would be a separate category.  
21 DR. SMITH: So absent vibration at the toes  
22 is moderately severe neuropathy?

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1 DR. RUSSELL: So based on what we have here,  
2 we have -- so, Gordon, what we have to do is we  
3 have to separate this and this, okay?  
4 DR. SMITH: That's my point is that --  
5 DR. RUSSELL: We could have more -- we could  
6 say here that it has to be loss of more than one  
7 sensory sign. That may be more consistent with  
8 what you presented.  
9 DR. SMITH: And then this doesn't deal with  
10 patients who have, say, reduced pin sensation and  
11 extraordinarily severe neuropathic pain. Because I  
12 worry that for minimally symptomatic or  
13 asymptomatic neuropathy, the majority of patients  
14 are going to be severe, and this is really ordinal.  
15 It's not at all interval, and then patients who  
16 have neuropathic pain, I don't see where they fit  
17 on here.  
18 DR. RUSSELL: The trouble in neuropathic  
19 pain is that it can be very severe in mild and it  
20 can actually be present as well even up to severe.  
21 So we had a lot of debate about how do you take  
22 symptoms and determine severity, and decided, in

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1 fact, that this was quite difficult. So just to  
2 address the symptoms part.  
3 In the severe part we said -- and I've  
4 actually called this non-positive because Rodica  
5 didn't like negative, so I said non-positive  
6 symptoms usually predominate. It's getting into  
7 political correctness now. Again, you might think  
8 about positively taking that out.  
9 Gordon, just addressing your other question  
10 here, so the parameter that determines severe is  
11 that you actually get weakness in addition to loss  
12 of sensory signs of neuropathy. So for moderate,  
13 which is really the one where you have to hang it  
14 between the mild and the severe, you need to decide  
15 how many sensory signs of neuropathy can you  
16 actually lose.  
17 Would moderate be one? Would it be three?  
18 Which specific signs would they be? We said up  
19 here for the preclinical, sensory signs would  
20 include these items here. But this is debatable.  
21 What do people feel? So for moderate, would  
22 people feel comfortable if you lost two signs or

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1 three signs?  
2 DR. PELTIER: I would argue you should have  
3 an either/or. You can have loss of two or more  
4 signs for moderate, and on your abnormalities, I  
5 think they should be like less than the 5th  
6 percentile or something much more significant  
7 because if you just had an IENFD of, say, 5  
8 epidermal fibers and I had a sural of 4, does that  
9 count as two abnormalities?  
10 I think they have to be graded more severely  
11 in the sense that you should be less than the 5th  
12 percentile for age and gender on two of them.  
13 DR. RUSSELL: One thing here is you do run  
14 into problems. So if you take greater than the  
15 97.5 or greater than 99th percentile, you run into  
16 the problem, well -- you could do that for all of  
17 them. You could say that you need to have  
18 abnormalities at a higher percentile level, or you  
19 could simply increase the number of abnormalities.  
20 DR. BRIL: James, if you do that and I'm  
21 looking ahead at severe, that means you're going to  
22 have to do QST nerve conductions and --

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1 DR. RUSSELL: No, no.  
2 DR. BRIL: -- or you mean three abnormal  
3 parameters?  
4 DR. RUSSELL: You'd have to do a combination  
5 here that would give you three, so you wouldn't  
6 have to do necessarily everything.  
7 DR. BRIL: Three out of those four listed?  
8 DR. RUSSELL: Yes.  
9 DR. BRIL: That's a lot. You're asking them  
10 for IENFD or CCF. You have to do --  
11 DR. POP-BUSUI: And QST and NCF.  
12 DR. BRIL: Yes, those two.  
13 DR. RUSSELL: The other way of doing this is  
14 to take this up to the 99th percentile.  
15 (Crosstalk.)  
16 DR. PELTIER: Then the other problem is your  
17 CCF is going to highly correlate with your IENFD,  
18 so you also have to look at which of those tests  
19 correlate. So if they do correlate like you're  
20 saying, then the problem is if you have one  
21 abnormal, you're most likely going to have the  
22 other abnormal. So how does it make it that much

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1 more severe?  
2 (Crosstalk.)  
3 DR. RUSSELL: We had a debate about it.  
4 DR. POP-BUSUI: [Inaudible - off  
5 mic] -- abnormality instead of just saying  
6 abnormality because abnormality is very vague.  
7 DR. RUSSELL: The other --  
8 DR. POP-BUSUI: For moderate and severe, you  
9 should set some criteria that what is moderate.  
10 DR. RUSSELL: The 95th would be abnormal,  
11 but you would make it more abnormal by saying  
12 you're going to go to the 99th or greater. That  
13 would be one option.  
14 MALE VOICE: We could do 95, 97.5, and 99.  
15 DR. TEFAYE: What determines severity, it's  
16 not that you find abnormality using different  
17 modalities of testing but actually having a high  
18 score in one. It could be Toronto. What  
19 determines severity is that the score is very high  
20 in that modality and not detecting neuropathy in  
21 different modalities. That doesn't make it severe.  
22 DR. ZIEGLER: What you could do here is to

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1 define clinically moderate for confirmation, one of  
2 these being abnormal at the 99th percentile, and  
3 for severe, you can take two at 99.  
4 (Crosstalk.)  
5 DR. RUSSELL: We still have Amanda's issue  
6 here and that is --  
7 DR. ZIEGLER: Then you don't need that many  
8 tests. You need only two tests.  
9 DR. RUSSELL: Amanda's issue was if there's  
10 a certain measure you take on this, would you  
11 regard that as being equal to another measure on,  
12 let's say, the intraepidermal nerve fiber density?  
13 DR. ZIEGLER: I don't --  
14 DR. RUSSELL: Isn't that your question? You  
15 said not all things are equal in an individual  
16 case.  
17 DR. PELTIER: I'm just saying that wouldn't  
18 you want to have different measures, so if one is  
19 more of a small fiber, one is more of a large  
20 fiber, wouldn't you want severe abnormalities in  
21 both to make it severe as opposed to just one or  
22 the other? The question I had is, if you had

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1 significant abnormalities on your CCF, then would  
2 you also have significant abnormalities on your  
3 IENFD? And that doesn't necessarily make you that  
4 much more severe is my point.  
5 DR. ZIEGLER: I think you should not over-  
6 estimate the correlation of CCM with nerve -- you  
7 yourself in a landmark study, published that the  
8 correlation of NCV with CCM is something like 0.25,  
9 not more.  
10 DR. PELTIER: No. I'm not talking about --  
11 DR. ZIEGLER: And also, if you --  
12 DR. PELTIER: -- nerve conductions, it's  
13 with the IENFD.  
14 DR. ZIEGLER: Yes, we published in recently  
15 diagnosed patients that the correlation is not  
16 significant. So the correlation is 0.1 in that  
17 particular population. It may be higher, it will  
18 be higher if you take the spectrum of severity and  
19 tell me the correlation coefficient if you have a  
20 population with different severities of neuropathy.  
21 But it will probably not be higher than 0.3 or 0.4  
22 or 0.6.

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1 DR. RUSSELL: Just a second here, one thing  
2 I do want to point out to you, remember that these  
3 patients have to have weakness, okay? So  
4 irrespective of what happens here, they have to  
5 have weakness.  
6 DR. PELTIER: Well, that's my other point is  
7 that how can you have weakness and have no  
8 symptoms? You're going to be symptomatic.  
9 DR. RUSSELL: We had a considerable debate  
10 about this, and the final conclusion was that you  
11 can occasionally have patients who can have quite  
12 severe neuropathy but don't specifically report  
13 symptoms. I don't think it's common, but that was  
14 a discussion.  
15 DR. HERRMANN: Two points. The first thing,  
16 just at a very high level -- and we knew this was  
17 going to be the hardest category, right, of the  
18 three -- is that when you talk about clinically  
19 mild, clinically moderate, or clinically severe, I  
20 think we should distinguish on the one hand, what  
21 we're considering here is just impairment. Because  
22 what we're not considering here is the patient's

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1 perspective.  
2 There are two ways of looking at it. There  
3 is mild, moderate, or severe from the patient's  
4 perspective because the way we're breaking it out,  
5 there may be a very severe impairment that doesn't  
6 translate into what the patient tells us is severe.  
7 But when you look at the impairment and the word  
8 "loss," I think about something like the UENS when  
9 you talk loss, is it loss of pin at the toe, if you  
10 have loss of pin all the way up the leg.  
11 I think just if you're looking at the 95th,  
12 99th percentile for IENF density, I think you also  
13 could look at length-dependent fashion loss that  
14 will help you bring out the --  
15 DR. RUSSELL: Eva, can I just address this  
16 one very quickly?  
17 We actually originally started off and said,  
18 okay, we could define clinical severity by a  
19 clinical scale in which we have percentiles. It  
20 turns out although we have great clinical scales,  
21 we don't have something like a Rasch-built model  
22 where we can easily and translatably say to

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1 everyone, this is what would be the 99th percentile  
2 based on corrections for age, gender, et cetera, et  
3 cetera, et cetera. We have it to some extent but  
4 not perfectly.  
5 The second issue that I want to address with  
6 you is when we had this discussion about what  
7 constitutes mild or moderate and whether this is to  
8 the patient or the physician, it's a very, very  
9 slippery slope, this. Mild pain for me may be  
10 severe for somebody else, et cetera. So this is  
11 part of the problem with defining it that way.  
12 Eva, sorry about that.  
13 DR. FELDMAN: I just wanted to ask you about  
14 your discussion concerning weakness in your group  
15 because I certainly have patients, many, who have  
16 presented to me with frank ulcers who have no  
17 weakness at all, and I consider them to have  
18 clinically severe neuropathy.  
19 I would say that's more common. I certainly  
20 see patients with weakness, but could you reiterate  
21 for the group what the discussion was concerning  
22 weakness? Because I question whether we

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1 should -- you could have plus or minus weakness,  
2 but to have to have weakness to be clinically  
3 severe is something I think may not necessarily be  
4 accurate.

5 DR. RUSSELL: That is actually a very valid  
6 point. What we actually did was we took this  
7 really from previous criteria, particularly the  
8 Dyck criteria, which actually in 2(b) requires  
9 weakness.

10 Now, part of the problem with this is you  
11 can actually skip the whole mild, moderate, and  
12 severe, which is what has been done previously  
13 because they had this same problem. What really  
14 constitutes severe? Instead of that, you grade it  
15 1, 2, 2(a), 2(b), et cetera. But we decided as a  
16 group, we were going to bite the bullets here, and  
17 were going to do mild, moderate, and severe.

18 So yes, that's a very good point. One could  
19 say that you had to have weakness and/or ulcers,  
20 perhaps, making it severe. You could come up with  
21 that as a criteria.

22 DR. FELDMAN: I like that. Something like

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1 that I think would be more appropriate than saying  
2 you have to have frank weakness to be clinically  
3 severe.

4 DR. SMITH: I've got a lot of problems with  
5 this, and part of it's late in the day and my brain  
6 is fried, but what you're creating here is not  
7 mild, moderate, severe. It's less, more, and more  
8 yet. Eva brought up probably the best example.  
9 It's an outcome, so outcomes aren't always patient  
10 reported, but they're functionally significant or  
11 they're meaningful, right?

12 We don't even know the clinical meaning of  
13 nerve conductions, IENFD, and CCM at this point. I  
14 don't know what the clinical meaning of an  
15 individual sign is or the severity of the sign. We  
16 think it's true, and it has some face validity that  
17 the more abnormal signs we have, the more  
18 functional significance that this is going to have  
19 from a patient, including ulceration, gait  
20 abnormalities, neuropathic pain, and so forth.

21 We're haggling over details of these  
22 criteria without an anchoring heuristic. Eva gave

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1 one extreme of that, and I know you were charged  
2 with doing this and it's provocative I would  
3 suggest we ought to go back and think about just  
4 the overall concept of severity.

5 What are we trying to measure? Is it really  
6 just more abnormalities on the scales that we have,  
7 or is something that's meaningful for patients --

8 DR. RUSSELL: Again, I do have to stress,  
9 right, to be clinically severe, you have to have  
10 this, and this is simply to confirm. We're not  
11 saying that this is necessarily the major criteria  
12 for determining severity.

13 I think Eva has a very good point. Remember  
14 here that you have complete loss of sensory signs  
15 of neuropathy, so already everything is pretty bad  
16 from that. We can certainly add the clinical part,  
17 which is fair that you would have ulcers and/or  
18 weakness, but remember, that has to be there, and  
19 this is simply confirmatory.

20 DR. FREEMAN: I'm troubled by ulcers.  
21 Certainly, it's a functional outcome, but it's a  
22 very nonspecific functional outcome. It could be

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1 vascular. It could be due to atrophy. For me,  
2 while I recognize it is a vital functional outcome,  
3 as is amputation, it's not necessarily a measure of  
4 neuropathy. It occurs in patients who have severe  
5 neuropathy, but it also occurs in patients who have  
6 severe vasculopathy. I'm a little troubled by  
7 that.

8 DR. PELTIER: I'm thinking of this and maybe  
9 I don't know if I'm the only thinking of this. I'm  
10 thinking of this in terms of a clinical trial. If  
11 you're going to enroll people in, say, a  
12 neuroprotective agent, you do not want somebody  
13 that you're going to designate as clinically severe  
14 in that trial because the idea is that they have  
15 lost so many nerve fibers that there's not much  
16 left to save. So moving the needle in that patient  
17 population is going to be very hard.

18 I guess to me, that's where I'm coming from  
19 is thinking of maybe not so much from a patient  
20 perspective, but as far as our perspective in the  
21 sense of, okay, where do we think we can move the  
22 needle. If you're giving somebody a treatment

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1 agent, do you want to exclude people in a certain  
2 category? I guess that's where I'm thinking of  
3 this criteria at.  
4 DR. FREEMAN: I take the point about the  
5 severity, but I also want to say I agree with  
6 Amanda. The other point, though, is if some  
7 epidemiologist wants to do a study to look at who  
8 is likely to get an ulcer, this is the group that  
9 you might think that they might want to begin to  
10 look at as part of their cohort or compare them to  
11 clinically moderate and to see who is more  
12 predisposed to ulceration/amputation.  
13 I think we've got to come to this project  
14 with that perspective as well.  
15 DR. RUSSELL: Doug.  
16 DR. ZOCHODNE: I'm not sure how you're going  
17 to fit this in, but to be patient-centric, I think  
18 we're going to have to consider disability;  
19 disabled; unable to work; disabled part of the  
20 time, all of the time; able to walk, not able to  
21 walk. It may not fit with these categories very  
22 well.

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1 DR. FELDMAN: Have you done that in the pain  
2 field? Do you have a lot of quality-of-life  
3 measures? You do, don't you? So that is something  
4 we need to address at some point.  
5 DR. BRUEHL: Yes, but those are not included  
6 in Dimension 1 even in the chronic pain --  
7 DR. FELDMAN: That would be something we're  
8 going to do at a later date.  
9 DR. BRUEHL: Functional consequence.  
10 DR. FELDMAN: That's a later date?  
11 DR. BRUEHL: Yes.  
12 DR. FREEMAN: I think we all agree that the  
13 instruments measuring quality of life in neuropathy  
14 have their imperfections. In dimension, I think  
15 it's 4 or 5, we do look at activities of daily  
16 living. We look at functional, so all of those  
17 will be part of this, but not part of the core  
18 diagnostic criteria.  
19 DR. RUSSELL: Just going back to this --  
20 DR. BRUEHL: I did want to ask a question  
21 because I'm not even clear on this. In the  
22 clinical severity grading like this, is this really

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1 Dimension 1, or is this Dimension 2? Because you  
2 either get the diagnosis or you don't. The  
3 subcategorizations of severity seem to me like a  
4 secondary descriptive issue, which you could use in  
5 clinical trials, but I don't know that it changes  
6 what will go into the Dimension 1 criteria.  
7 DR. FREEMAN: For me, it's a challenging  
8 question as to where this fits in the dimensions.  
9 I'm not sure that it really matters. I think as  
10 far as this is concerned, it's almost the Dimension  
11 1. Dimension 2 is artificial, but what I do think  
12 is that we need to have operationalizable criteria  
13 for the early, for the clinical trial, and for the  
14 late, for the epidemiologists looking for  
15 predisposing factors for ulceration.  
16 DR. RUSSELL: Part of the debate really that  
17 we had as well was should we just simply define  
18 mild since those are the people we would want to  
19 get into clinical trials, and then maybe there  
20 would be another group that would be moderate to  
21 severe. At the end, we decided we would try to  
22 actually follow the order that Roy had presented us

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1 with, that we would have mild, moderate, and  
2 severe.  
3 So this is our attempt to come up with those  
4 three categories, although practically speaking, it  
5 may be that severe is not going to be used that  
6 frequently anyway.  
7 DR. FELDMAN: James, can I ask a  
8 clarification on the at least three abnormal? Are  
9 we saying, though, we have to do three of those  
10 four tests in order to be clinically severe?  
11 DR. RUSSELL: It's thought to be an  
12 abnormality --  
13 DR. FELDMAN: I know we were discussing it -  
14 -  
15 DR. RUSSELL: It's thought to be an  
16 abnormality. So I guess --  
17 DR. FELDMAN: Or is it --  
18 DR. RUSSELL: -- if the vibration perception  
19 threshold and the cold perception threshold, that  
20 would be two abnormalities. And then one could  
21 define in the nerve conduction studies which  
22 measures you thought were the most important. So

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1 would they be the sural sensory amplitude? Would  
2 they be the peroneal conduction velocity? For the  
3 intraepidermal nerve fiber density, you could say  
4 would you count distal and proximal as being the  
5 measure. Would you perhaps use subdermal fiber  
6 densities as well as epidermal?  
7 These are the questions one might ask. As I  
8 say, there's --  
9 DR. FELDMAN: I'm wondering if we're --  
10 DR. RUSSELL: -- a lot of discussion about  
11 exactly how you're going to define that.  
12 DR. FELDMAN: I guess I would just throw  
13 this out, and I know we've discussed this already.  
14 But thinking about, for example, what Teresa Jones  
15 said this morning and what's permeated our  
16 discussion somewhat during the day is we are  
17 hopeful to use these trials in clinical research,  
18 epidemiological research, and even drug  
19 interventions. And to say that one must do three  
20 of these in any of those research scenarios seems  
21 somewhat cumbersome and maybe repetitive. Maybe at  
22 some point, this could be opened up for more

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1 discussion because I think that is actually  
2 probably unnecessary.  
3 DR. RUSSELL: As a start here, could I just  
4 suggest that maybe what we do is for the mild, we  
5 say there's one abnormality greater than the 95th.  
6 The moderate, we say is two abnormalities greater  
7 than the 95th. The third, we say there's two  
8 abnormalities greater than the 99th percentile.  
9 DR. SMITH: But do we know that having an  
10 abnormal skin biopsy and abnormal nerve conduction  
11 studies or for that matter, abnormalities of all  
12 four conveys greater severity? So for instance --  
13 DR. RUSSELL: Gordon, you're missing my  
14 point.  
15 DR. SMITH: -- we frequently see patients  
16 with preclinical neuropathy who have abnormal skin  
17 biopsies, abnormal nerve conduction studies, and  
18 abnormal CCM. I question whether or not this is  
19 really a matter of severity. It's just more. It's  
20 a certitude issue.  
21 DR. FELDMAN: I agree with you, Gordon.  
22 DR. RUSSELL: Let me stress again you have

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1 to have this. This has to be present, and this is  
2 just to confirm. This by itself is not determining  
3 severity. This is actually determining severity.  
4 DR. BRIL: Can I clarify what you said? Did  
5 you mean vibration and quantitative thermal  
6 thresholds would be two abnormalities out of that  
7 list?  
8 DR. RUSSELL: I'm saying you could consider  
9 that.  
10 DR. BRIL: So it wouldn't be that you'd have  
11 to do all four. You could do two and get four --  
12 MALE VOICE: Nobody's going to do --  
13 DR. BRIL: I know what you're saying.  
14 DR. SMITH: It doesn't mean it's not severe.  
15 I think we're arguing over something that isn't on  
16 the same axis. It's a certainty issue. It's not a  
17 severity issue, and it goes to -- foot ulceration,  
18 Amanda's point is really good. Those, I  
19 understand. I'm just not sure I understand --  
20 DR. FELDMAN: I don't.  
21 DR. RUSSELL: So one of the options here is  
22 to just take out the clinically confirmed part

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1 altogether and simply go with these measurements  
2 here.  
3 DR. FREEMAN: Gordon, I just want to say  
4 that I'm not sure that the two of you are  
5 disagreeing. Because Gordon is talking about  
6 increasing the probability that the patient has a  
7 neuropathy by having a test, and I think you're  
8 saying the same thing, that you're increasing the  
9 probability by using the clinically confirmed.  
10 That really is what the clinically confirmed means.  
11 The question, I think, is to what extent  
12 does having three or two or one of those  
13 abnormalities increase the probability. That's how  
14 I would delineate this discussion.  
15 I'm very interested in people's views,  
16 whether thermal threshold, having both  
17 intraepidermal nerve fiber density decreases, and  
18 thermal sensory threshold increases are one in the  
19 same, whether they are totally concordant, whether  
20 having two is the same as having one, whether it  
21 really increases the probability. I don't know the  
22 answer to that, and that's something that there are

1 data that exist. So that's the one thing.  
2 The other is if we are going to take it out  
3 of the confirmation increasing the probability  
4 realm, then it's Amanda's thesis going from the  
5 95th to the 99th percentile because there, I think,  
6 you're looking at severity. We can also then  
7 discuss whether severity actually increases the  
8 probability. So that's how I'm seeing this  
9 discussion, but I don't know if we're going to  
10 resolve it tonight.

11 DR. FELDMAN: I think that's a nice summary,  
12 actually.

13 DR. GIBBONS: Can I advocate that maybe we  
14 table this for now? I think everybody is, in fact,  
15 getting -- we're starting to rehash our arguments,  
16 and I think everyone's getting a little fatigued  
17 with the discussion. Maybe we should take an hour  
18 break. We can meet at dinner, further hash things  
19 out, but take a break for now or just to reset.

20 (Crosstalk.)

21 DR. FELDMAN: Chris, could we talk about the  
22 consortium this evening then, have a working dinner

1 because I have to leave.

2 DR. FREEMAN: That's fine, to set out the  
3 tables. I asked them to do that. I don't know how  
4 well they can do that.

5 How many people want to attend the  
6 consortium working dinner? How many do not want  
7 to -- rather say who doesn't want to discuss  
8 neuropathy?

9 (Laughter.)

10 Adjournment

11 DR. FREEMAN: I think probably we should  
12 eat.

13 DR. BRUEHL: Can I make one note? We were  
14 talking earlier about the distribution of documents  
15 earlier. If anyone of you are interested in a  
16 detailing of what I presented in my talk today,  
17 including the examples, out on the table out there,  
18 they have copies of the Journal of Pain issue. I  
19 think it's the last or the next-to-last article in  
20 there. You can just grab one.

21 (Whereupon, at 6:01 p.m., the meeting was  
22 adjourned.)

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