

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

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1 scores every 3 months, so it just happened to be a  
2 very convenient way to measure a change in glucose  
3 control.  
4 As you magnify or increase your change in  
5 glucose control, your risk of neuropathy  
6 development goes up, so this is the absolute risk  
7 of developing neuropathy. And you can see, by the  
8 time you exceed a 6-point change in hemoglobin A1c  
9 over 3 months, you have a nearly 100 percent chance  
10 of developing the neuropathy. And the  
11 distribution, again, increases over time.  
12 Red is really burning pain. The gray are  
13 people who have variable amounts of pain. And it's  
14 really a selective small fiber presentations. This  
15 is the classic distribution that I'm seeing in my  
16 own clinical patients.  
17 In terms of the data we had to generate  
18 this, looking at a group of individuals referred in  
19 for diabetic neuropathy, looking at change in  
20 glycemic control and the relationship to the  
21 development of this neuropathy.  
22 Basically, those who had a hemoglobin A1c

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1 change or 2 points or more in the last 3 months, we  
2 looked at those selectively and found that 104 of  
3 those actually met criteria for treatment-induced  
4 neuropathy; so in other words, they had a sudden  
5 change in glucose control, resulting in a dramatic  
6 increase in neuropathic pain in a link-dependent  
7 fashion with some associated autonomic features.  
8 This again took us to the distribution of  
9 the pain and the severity, and this is really what  
10 it looked like. So if your hemoglobin A1c drops a  
11 modest amount, these are pain scores. These are  
12 hemoglobin A1c scores. So if you're dropping on  
13 the 2 to 4 range, basically, your pain score would  
14 go up to about 6. This is on the Likert scale, a 0  
15 to 10 scale.  
16 There's no pain prior to this. There's a  
17 time lock development of pain, and it's typically  
18 presented with burning pain in the feet, the  
19 classic neuropathic pain that we think about. But  
20 if you had a larger change in hemoglobin A1c, the  
21 distribution was larger and the pain score was  
22 actually greater.

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1 Then finally, if you had a very significant  
2 change, these are people who had essentially  
3 hemoglobin A1c changes of about 6 points or more in  
4 3 months, a very large distribution of pain, very  
5 high pain scores. So this is for the distribution  
6 and the representation.  
7 DR. ZOCHODNE: Chris, those diagrams, that's  
8 not sensory loss, right?  
9 DR. GIBBONS: So this is distribution of  
10 pain. And sensory loss actually would be  
11 associated with this in small fiber, so pain and  
12 temperature. Thermal sensitivity would typically  
13 be lost in most cases in the red situation. It  
14 does depend on the timing of your assessment. So  
15 if you have a very rapid change and you catch it  
16 early, you may still have hyperalgesia, some  
17 hypersensitivity. If you wait a series of months,  
18 they actually are pretty profoundly denervated. So  
19 if you're doing biopsies of the sites that are red,  
20 essentially there are no nerve fibers.  
21 DR. ZOCHODNE: The pain, though, the  
22 intensity of the pain is related to its

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1 geographical distribution like you've shown or is  
2 it more intense in the afflicted areas?  
3 DR. GIBBONS: Yes. And it's a little tough  
4 to tease that out because the pain is extremely  
5 intense. It seems to be intense. The intensity is  
6 worse and the distribution is worse. So it does  
7 seem that this is painful, but it hurts, it's  
8 really uncomfortable, but it's mostly at night.  
9 That's the typical neuropathic pain  
10 distribution and presentation. It is a little bit  
11 more than one might expect, but by the time you get  
12 to here, these are people who essentially are  
13 almost walking around in clothing like this because  
14 anything touching them is extraordinarily  
15 uncomfortable. They're restless. They can't touch  
16 anything.  
17 So it's a pretty severe kind of descriptor,  
18 and most of these people on multi-modal pain  
19 therapy are still uncomfortable.  
20 DR. WRIGHT: I'm sorry. Did you say they  
21 had a decrease in their INF?  
22 DR. GIBBONS: Yes. So it depends on the

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1 timing. We did a serial on some of these patients,  
2 and there's a fairly rapid decline in neurofiber  
3 density for about 2 months. And then if you wait  
4 out -- and I'll talk about this a little bit more  
5 later in terms of the natural history -- then  
6 there's an improvement in some patients over time  
7 later, but it does seem to tie in.  
8 DR. WRIGHT: Did you see that widespread  
9 picture you've seen with the higher decrease also  
10 in those with lower or is it always like we  
11 described here?  
12 DR. GIBBONS: So it seems to be link  
13 dependent, but the magnitude goes, as your larger  
14 change here, you tend to be moving up in terms of  
15 the distribution.  
16 DR. WRIGHT: But my question is, have you  
17 seen patients who had that widespread pattern with  
18 the lower decrease in A1c? Do you see that?  
19 DR. GIBBONS: So you do get variability in  
20 terms of who presents with what.  
21 DR. WRIGHT: So that's possible, that's  
22 possible.

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1 DR. GIBBONS: It is possible. I'm  
2 suspicious about whether it's simply a measurement  
3 issue. In other words, maybe they dropped before  
4 we measured the A1c and then they dropped again,  
5 and we didn't. So I think there are many potential  
6 errors in measurement here, but that distribution.  
7 Rayaz and then --  
8 DR. MALIK: Is this a prospective study?  
9 DR. GIBBONS: No. This was prospectively  
10 following people who were referred in from my  
11 clinic, but it was basically also a retrospective  
12 review of what had happened prior.  
13 DR. TESFAY: Did some of these patients  
14 develop proliferative retinopathy or changes in  
15 their --  
16 DR. GIBBONS: They all did. They all did.  
17 Yes, yes.  
18 DR. POP-BUSUI: Did you say that this is in  
19 3 months, this decrease in A1c?  
20 DR. GIBBONS: So this is within 3 months,  
21 yes.  
22 DR. POP-BUSUI: How many patients did you

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1 see with that decrease of 7 points?  
2 DR. GIBBONS: So this was about 35.  
3 DR. POP-BUSUI: Is it depending on treatment  
4 or regardless of what type of agents have been used  
5 to decrease the A1c at such magnitude?  
6 DR. GIBBONS: So I actually have a slide on  
7 that, so we'll talk through that as well.  
8 DR. ZOCHODNE: Did you biopsy the arm?  
9 DR. GIBBONS: So I did in some patients. So  
10 this is the distribution. The pain in this case  
11 was fairly clearly tied to where the small fiber  
12 damage was occurring, so I did biopsies at  
13 different sites to try and understand if this was  
14 in fact tied to the problem, and it did seem to be  
15 fairly clearly tied.  
16 DR. HARATI: I just wanted to be clear what  
17 number you used. You said 168 patients and 104 of  
18 them developed this. That's a very large number.  
19 MALE VOICE: That's biased.  
20 DR. POP-BUSUI: That is referral bias  
21 because you get to see them.  
22 DR. GIBBONS: It is absolutely referral

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1 bias. It's absolutely referral bias. And that was  
2 why I started that with my bias slide.  
3 DR. HARATI: These patients, 104, had no  
4 indication of any pain or neuropathy before that?  
5 In other words, the term that they used as  
6 treatment induced, I want to be sure that is the  
7 correct term and is not treatment aggravated.  
8 DR. GIBBONS: Correct. So there are two  
9 aspects to that question that I think you have to  
10 think about. So these were people who didn't have  
11 any neuropathic pain to speak of beforehand with a  
12 few exceptions. There were some people who had  
13 some general distal burning pain that was very  
14 mild. It was not of a degree that they had cared  
15 to bother seeing a neurologist or even their  
16 endocrinologist to any degree. They did say, in  
17 hindsight, yeah, my feet had burned a little bit in  
18 the past, never really bothered me.  
19 But the presentation was essentially very  
20 rapid onset of this picture, so something changed  
21 dramatically, and I'll get to the specifics of what  
22 that meant in this population.

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1 Rob?  
2 DR. SINGLETON: Yes. That mostly answered  
3 my question.  
4 DR. GIBBONS: I think most of the questions  
5 in there, I think, hopefully will get answered as  
6 we go through some additional slides.  
7 It's not just pain. There are a lot of  
8 autonomic features that occur, so if you do  
9 autonomic testing on these individuals, they do  
10 tend to show some fairly subtle but significant  
11 changes in parasympathetic function. But they also  
12 have actually frequent syncope or orthostatic  
13 intolerance.  
14 So they're not complaining about it because  
15 the pain is the primary concern in their  
16 presentation, but the risk of syncope actually goes  
17 up through the roof. And considering many of these  
18 are younger people, syncope is not something that  
19 we would expect to see.  
20 There's a lot of gastric symptoms as well  
21 that suggests some relationship to gastroparesis,  
22 but we didn't have gastric-emptying studies, so I

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1 can't really comment on that. Certainly, some  
2 sweating abnormalities occur or erectile  
3 dysfunction, but retinopathy actually was a very  
4 significant increase in risk as well as there was  
5 also substantial change in renal function, in this  
6 case just measured by microalbuminuria, but there  
7 were other measures as well.  
8 So the concept is that it is more than just  
9 neuropathy. It's a diffuse microvascular process,  
10 and it seems to be all time locked together.  
11 Everybody had retinal images done every 6 months,  
12 and so we know 6 months earlier, they didn't have  
13 any retinopathy. Six months later, they all  
14 actually had proliferative retinopathy, so it was a  
15 pretty substantial change in retinal imaging.  
16 DR. POP-BUSUI: The change was from no  
17 retinopathy to proliferative retinopathy?  
18 DR. GIBBONS: Yes. So there were a few  
19 people who had mild non-proliferative or very early  
20 stage, but essentially, anybody in this group moved  
21 to proliferative within 6 months. This group down  
22 here, some people went from mild to moderate or to

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1 severe non-proliferative, so they moved up the  
2 scale, but this group almost universally moved to  
3 proliferative retinopathy.  
4 DR. SMITH: I just had a question about the  
5 cohort. So is this really a preferred cohort or  
6 did you mine the database, pull out people who had  
7 A1c changes, and evaluate to see who had  
8 neuropathy?  
9 DR. GIBBONS: These were all the people who  
10 were just referred in for diabetic neuropathy.  
11 That was the cohort. It was all comers. And then  
12 of that cohort, I looked at those who didn't have a  
13 change in hemoglobin A1c versus those who did of a  
14 significant degree.  
15 Thirty-two of this group did have a sudden  
16 increase in pain for, as far as I could tell, no  
17 apparent reason. It wasn't nearly the magnitude of  
18 the rest. So there did seem to be some spontaneous  
19 pains that could occur that were significant, but  
20 not to this degree. And so clearly, the magnitude  
21 shifted to the pain with that.  
22 DR. SINGLETON: Chris, have you done the

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1 data mining exercise?  
2 DR. GIBBONS: No. I mean, I have, but not  
3 in a way that I can present data at this point. I  
4 don't have results at this stage.  
5 DR. HERRMANN: You presented diagrams that  
6 suggest that phenomenology is perfectly symmetric.  
7 Can it ever be asymmetric, the pain presentation?  
8 Is that a red flag if it is?  
9 DR. GIBBONS: So it's an interesting  
10 question, and I'll talk about the differential  
11 diagnoses. So Jim Dyck and I have had a lot of  
12 discussion about this and the question is, is this  
13 some sort of variant of --  
14 DR. HERRMANN: [Inaudible – off mic].  
15 DR. GIBBONS: Exactly. And we don't know.  
16 It's an interesting question. I don't think I have  
17 seen any non-symmetric presentation. These have  
18 been very symmetric. But again, I'm wondering if  
19 I'm categorizing the non-symmetric differently  
20 based on this. So again, that's an inherent bias  
21 in this question.  
22 DR. HERRMANN: The reason I asked is we just

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1 had a patient, a woman who had a very rapid  
2 correction in her hemoglobin A1c that a colleague  
3 of mine saw. And all she really had was to come in  
4 with acute burning pain in one lower extremity that  
5 was clearly not a monoradiculopathy or  
6 mononeuropathy.  
7 There was no weakness associated with it, so  
8 we wondered is this a form first of what Jim spoke  
9 to yesterday, but of course, weakness is the  
10 hallmark there; had a little bit of weight loss,  
11 but not a lot. And so that put her somewhere  
12 between this and what Jim spoke to. And we do see  
13 those patients once in a while.  
14 DR. GIBBONS: So there's probably a bigger  
15 picture out here that we don't yet have a handle  
16 on.  
17 DR. ZIEGLER: So the cases we've seen were  
18 all symmetric, actually, so I think this is  
19 typical. And we also observed those cases, which  
20 therefore those patients that get stigmatized  
21 because they report widespread pain. And of  
22 course, a diabetologist wouldn't be expecting a

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1 distal symmetric polyneuropathy and would not trust  
2 him. And therefore, they refer to psychiatrists  
3 and so on.  
4 DR. GIBBONS: This distribution is  
5 interesting. I actually thought these were  
6 ganglionopathy patients when I first started seeing  
7 them because many of them were talking about pain  
8 in the scalp as well; I mean, it was really  
9 diffused. And it was really only when I mapped out  
10 the variance in this that I recognized that some  
11 were clearly link dependent, and it was in this  
12 case much more widespread. So it did seem to be a  
13 link-dependent process, but just quite profound.  
14 DR. SMITH: Chris, is there nerve biopsy  
15 data?  
16 DR. GIBBONS: I do not have nerve biopsy. I  
17 only have skin biopsy data.  
18 DR. TESFAYE: Actually, many years ago, we  
19 did serial nerve photography in these patients, and  
20 we found that they developed new vessels on the  
21 surface of the nerve, on exposure of the nerve, and  
22 also they had lots of RCVN shunts [ph], which is

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1 really a completely disordered picture on the  
2 surface of the nerve.  
3 So I think the main hemodynamic factors may  
4 have a role either as a consequence of the pain or  
5 maybe causing the pain. So it's very interesting.  
6 DR. GIBBONS: Yes. And the paper that you  
7 had on that describes well what I think is going on  
8 retinally as well, diffuse proliferation of  
9 vasculature. And it's widespread, so it seems to  
10 be both vaso vasorum as well as looking through  
11 retinal/renal as well. So it's an interesting  
12 diffuse microvascular process.  
13 So this comes to some of what I'm trying to  
14 suggest as core diagnostic criteria and what we're  
15 thinking about describing this at least. The  
16 diagnostic criteria -- and we'll talk about some  
17 more specific details, but it's really a small  
18 fiber sensory or autonomic neuropathy. Some  
19 potential controversy of this is there are some  
20 motor cases that have been reported, but it's  
21 interesting. I've only seen motor involvement in  
22 recurrent cases of this particular problem, so

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1 people who have actually had a substantial change  
2 in hemoglobin A1c developed a classic picture.  
3 At some point in the future, often several  
4 years later, they have returned to severe  
5 hyperglycemia and then have another episode where  
6 they bring it down rapidly, and then they develop  
7 motor involvement. So it's sort of a caveat, but I  
8 don't think it changes necessarily the diagnostic  
9 criteria.  
10 I had looked at this. I had used this,  
11 again, hemoglobin A1c change of 2 points in 3  
12 months, again, with my endocrinology colleagues.  
13 They are much better at looking at glycemic control  
14 dynamically, and I think that is an option to  
15 consider. I don't have good data on what that  
16 means. In other words, if I use a glucose monitor  
17 on a daily basis, what would I expect as the  
18 change?  
19 Also, simultaneously, what is the magnitude  
20 and does that matter? If I start at 15 and go to  
21 12, is that the same as 11 to 8? I don't know.  
22 The data again suggests that there probably is a

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1 difference, but I don't have enough numbers across  
2 that distribution to answer that, so that's still a  
3 controversy.  
4 I looked at pain on a Likert scale of more  
5 than 3 points change within that same time frame,  
6 in this case developing over 2 weeks of physician  
7 severity to seek medical attention. So this was a  
8 significant change within 2 weeks of a period of  
9 glycemic control change.  
10 This question here is, does this need to be  
11 expanded, contracted, that's an unclear question in  
12 that this pain and/or autonomic dysfunction  
13 actually occurs within 8 weeks, so this classic  
14 picture of distribution is within 8 weeks, and  
15 similarly, do we need to expand or contract the  
16 time frame?  
17 DR. BREUHL: What are you thinking of when  
18 you say, like in the third point here, autonomic  
19 dysfunction? What would you expect to see reported  
20 or what would you observe?  
21 DR. GIBBONS: In terms of autonomic  
22 dysfunction, this is where it's a challenge because

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1 most patients won't necessarily have had autonomic  
2 function first. So they won't necessarily have  
3 testing that we can see a change to, so it might  
4 not be relevant there. However, what they might  
5 have is, on orthostatic vital signs at bedside,  
6 they might have orthostatic hypotension, and that's  
7 something that could be measured and documented  
8 that wouldn't have been previously expected.  
9 DR. POP-BUSUI: Chris, I have a couple of  
10 questions. Is there any gender difference in the  
11 risk of developing this treatment induced?  
12 DR. GIBBONS: There is.  
13 DR. POP-BUSUI: I was wondering, for  
14 clinical practice, it would be extremely relevant  
15 if, with your data, we could design or actually  
16 define the phenotype of people who are at risk of  
17 developing these type of complications because it  
18 can guide treatment regarding glucose control.  
19 DR. GIBBONS: Yes. So as we go through the  
20 diagnostic criteria, I get into demographic  
21 distribution issues as well as other medical  
22 comorbidities, so I think we'll work into some of

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1 those questions.  
2 DR. ZIEGLER: Do you have an approximate  
3 percentage how many develop autonomic dysfunction?  
4 DR. GIBBONS: So in terms of the magnitude,  
5 nearly, I would say, 85 percent developed autonomic  
6 dysfunction, but it was often mild. We did do  
7 autonomic testing on them, so we could detect that,  
8 but again, most of these were in fact subclinical.  
9 Things like erectile dysfunction were prominent in  
10 men, but again, it's one of those where it's a  
11 little challenge. They're in significant pain.  
12 They're often now getting pain medications. It  
13 gets a little bit complicated.  
14 DR. ZIEGLER: But you even described  
15 gastroparesis, correct?  
16 DR. GIBBONS: But again, not with gastric  
17 emptying, symptoms of or suggestive of. So yes,  
18 there were many subtle things that were leading us  
19 in that direction. The hard findings on that side  
20 are harder to pick up except for the orthostatic  
21 hypotension.  
22 DR. FREEMAN: Just to focus it a

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1 little -- and we can just flesh this out in detail  
2 later, probably when I think of the menu, when I  
3 think of same migraine with aura kind of picture,  
4 you're going to need to say autonomic dysfunction,  
5 2 of 5, 3 of 5 of the following symptoms.  
6 DR. GIBBONS: Yes, and I'm adding some  
7 additional on that. David?  
8 DR. HERRMANN: So clearly, the precursor is  
9 a drop in the change of glycemic control, but in  
10 the setting of bariatric surgery, can you have a  
11 hybrid situation where hemoglobin A1c goes down,  
12 but not to the extent that you're talking about,  
13 but then you've got all the acute weight loss and  
14 the vomiting?  
15 DR. GIBBONS: So it's now been reported.  
16 Actually, an Australian group published -- they  
17 didn't realize they published the same thing, but  
18 they published the same thing after bariatric  
19 surgery. I reached out to them, and the timing was  
20 the same in terms of the glycemic control, and they  
21 were much more in the subtle presentation.  
22 So it does occur in that situation, and

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1 there are other factors that you worry about,  
2 nutritionally, et cetera, so that makes a little  
3 bit more of a challenge. I've also seen it in a  
4 couple of variances, both bariatric surgery.  
5 Pregnancy clinic is another concern. Women with  
6 diabetes who are suddenly pregnant want to take  
7 better control of the baby's health and suddenly  
8 make a change. And we'll get into some of the  
9 demographic and psychosocial issues with that.  
10 DR. HERRMANN: You want an asterisk or  
11 something in your criteria about some of these  
12 typical scenarios. I just throw that in there.  
13 DR. GIBBONS: Yes. And I think that comes  
14 in, in core 2 as the variables in that.  
15 DR. TESFAYE: Is core 2 coming?  
16 DR. GIBBONS: Yes. So I'm going to  
17 hopefully get all those. James?  
18 DR. RUSSELL: So are you going to  
19 specifically state which autonomic signs you will  
20 be able to demonstrate by the bedside? Because  
21 there are people that aren't going to be able to do  
22 autonomic testing.

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1 DR. GIBBONS: So I'll try and be specific.  
2 DR. RUSSELL: So probably one or two, you  
3 can say are really specific.  
4 DR. GIBBONS: Yes. I'll try and be very  
5 specific on that as we go through.  
6 DR. SMITH: So the way this is worded now,  
7 if I understand, your category or autonomic  
8 dysfunction, which implies that there's slated  
9 autonomic presentation. Is that true?  
10 DR. GIBBONS: No. I think that's true, and  
11 I do want to talk about that a little bit. Some of  
12 the patients present with a much more autonomic  
13 flavor to it. They have a little bit of pain, but  
14 they're actually profound orthostatic hypotensions.  
15 There is some variance in terms of how severe it  
16 can be. Those are much less common, maybe 5 to 10  
17 percent of the group as a total, but they're also  
18 the hardest, I think, to pick up. But there is a  
19 spectrum of this, so you have pure pain and then  
20 you have almost pure autonomic with a spectrum in  
21 between.  
22 DR. TESFAYE: I would agree with that.

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1 DR. SMITH: If you were doing a trial, would  
2 you include both in the trial or does there need to  
3 be separate categories?  
4 MALE VOICE: Microphone.  
5 DR. SMITH: I'm sorry. My question is  
6 asking whether or not those that are autonomic  
7 predominant need to be viewed as a different class  
8 and the reason being would you want both in a  
9 clinical trial?  
10 DR. GIBBONS: Right. So I think the concept  
11 is, we have some insult, which we think there may  
12 be some microvascular process going on diffusely as  
13 to why it's selecting one territory more so than  
14 another. It's not clear that there's a reason. We  
15 can maybe have an AB in there, autonomic or sensory  
16 predominant. I don't know mechanically from a  
17 trial at this point whether it would make any  
18 difference. That's very limited data.  
19 DR. TESFAYE: I would agree with that  
20 because the patients that we described, a series,  
21 we found autonomic dysfunction, which can be  
22 actually extremely severe. One patient, we had to

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1 nurse for 6 weeks flat because as soon as she just  
2 lifted her head, her blood pressure just went into  
3 her boots. So there's a big spectrum, but it is  
4 part of the syndrome.  
5 DR. BRUEHL: I think overall, this looks  
6 really good with some additional specifics to  
7 operationalize some of those terms. I do think  
8 subtype is an option, which would be kind of  
9 optional. People can classify if they want to, but  
10 it wouldn't be required for the diagnosis.  
11 The other thing -- this is very minor -- is  
12 I would avoid the use of the word Likert scale  
13 because technically that has negative and positive  
14 valence, so I would just call it a pain rating  
15 scale.  
16 DR. GIBBONS: Excellent point  
17 DR. BENNETT: I think you really need to set  
18 thresholds. I mean, I think, in some ways, what's  
19 probably more relevant is type of pain, where the  
20 pain is, quality.  
21 DR. GIBBONS: Yes. It's an interesting  
22 question.



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1 DR. BENNETT: It's so subjective.  
2 DR. GIBBONS: Yes. It's very subjective  
3 and, if we don't have some quantitative descriptor  
4 or something, will we be catching anybody who's got  
5 routine diabetic neuropathy that at some point  
6 starts? I don't know. That's an interesting  
7 question.  
8 DR. BENNETT: Maybe the change in the  
9 distribution is more helpful.  
10 DR. GIBBONS: Yes.  
11 DR. BENNETT: I mean, many patients get  
12 exacerbations. We see them all the time in their  
13 pain severity. It might be more relevant to say  
14 the evolution of the distribution of the pain, and  
15 the fact that it gets worse rather than setting a  
16 straight threshold of 3.  
17 DR. GIBBONS: Pain that's sufficient to seek  
18 medical attention or something along those lines.  
19 DR. TESFAYE: To use the word "neuropathic."  
20 DR. GIBBONS: Thank you, yes, neuropathic,  
21 absolutely.  
22 So these were some proposed diagnostic

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1 criteria that I changed a little bit based on some  
2 of the questions in that. And this was an acute  
3 small fiber or autonomic neuropathy that progressed  
4 to involve myelinated sensory -- sorry, this should  
5 have been sensory or autonomic fibers, a decrease  
6 in hemoglobin A1c of greater than 2 points over 3  
7 months. And I think the red part is again  
8 something that might need to be debated or an  
9 equivalent decrease in daily blood glucose  
10 monitoring levels in the setting of at least 6  
11 months of sustained hyperglycemia.  
12 There is this piece to it. Again, there has  
13 to be a period of hyperglycemia. I don't know what  
14 that is, how long is required, but I would say at  
15 least 6 months is probably necessary. This isn't  
16 the random fluctuation that you see. There has to  
17 be a period, and we just don't know what that  
18 period is that makes people susceptible.  
19 We sort of just talked about the question of  
20 both the Likert scale and the point, so maybe that  
21 will be modified a little bit there. And then the  
22 pain and/or autonomic dysfunction occurs within 8

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1 weeks of glycemic change. And I would say the  
2 measurable thing that we're trying to get to here  
3 would probably be orthostatic hypertension at  
4 bedside, and maybe that would be the way to  
5 categorize that.  
6 DR. FREEMAN: Could you come up with a menu?  
7 I think the major point would actually be to have  
8 symptoms, 1 or more, 2 or more, 3 or more protocol  
9 on that of the following symptoms and/or signs,  
10 orthostatic hypertension, the point made, most  
11 people aren't going to be great varied.  
12 So if you were to choose symptoms, what  
13 would you choose?  
14 DR. GIBBONS: Symptoms would be pain.  
15 DR. FREEMAN: Autonomic symptoms.  
16 DR. GIBBONS: Autonomic symptoms, that would  
17 be first with the static intolerance, then it would  
18 be gastric. For men, it would be erectile  
19 dysfunction, but gastric-related systems, and then  
20 finally sweating, change in sweating patterns.  
21 DR. FREEMAN: On the same, sensitivity and  
22 specificity, how many of your menu?

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1 DR. GIBBONS: I would probably say, if we're  
2 including autonomic, it has to be at least 2 of the  
3 4.  
4 DR. FREEMAN: Two of 4 signs and symptoms, 2  
5 of the following.  
6 DR. SMITH: Chris, you could evaluate this  
7 in your cohort, right?  
8 DR. GIBBONS: Yes.  
9 DR. SMITH: You have all of these data.  
10 You've got a group of people who had acute  
11 fluctuations in the severity of their neuropathic  
12 pain who didn't have 10. So you can create  
13 whatever Chinese menu that you want, and then  
14 validate it in the data set that you already have.  
15 DR. GIBBONS: You actually can get it  
16 evaluated prospectively in an ongoing process that  
17 we're working on.  
18 DR. FREEMAN: You have your gold standard.  
19 And then do you have the other, and don't have what  
20 you think --  
21 DR. GIBBONS: Again, I have that whole  
22 cohort that I looked at, the 742 that didn't

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1 develop this. It could use that as a comparator.  
2 Yes. So that's actually a quick way to look back  
3 and check.  
4 DR. SMITH: You could even use your  
5 retrospective data set as sort of a developmental  
6 data set and then validate it prospectively, so  
7 refine it.  
8 DR. SINGLETON: It isn't acute, though, is  
9 it?  
10 DR. GIBBONS: I'm sorry?  
11 DR. SINGLETON: It's not acute. It's not  
12 within a week or two.  
13 DR. PELTIER: It's pretty acute.  
14 DR. GIBBONS: So it's within 2 weeks, but it  
15 maximally general hits within 8 weeks.  
16 DR. SINGLETON: Yeah. I think acute's a  
17 bit --  
18 DR. GIBBONS: Subacute? But we'll use  
19 numbers, 2 to 8 weeks.  
20 DR. TESFAYE: Chris, I think on the gastric  
21 side of things, over the years, I've never come  
22 across any patient who says he knows of post-

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1 prandial fullness or any gastric symptoms. And I  
2 think unless you have robust data again, you need  
3 to mine it and look that this is a clear indicator  
4 of gastroparesis. I would be uncomfortable to put  
5 it. That's number one.  
6 Number two, it's at least 6 months of  
7 sustained hypoglycemia, and again, there are  
8 patients who, even with type 1 diabetes diagnosed,  
9 glycemic control improved rapidly. And again, I'm  
10 not sure whether putting 6 months is necessary.  
11 DR. GIBBONS: I did put the asterisk there  
12 because I knew this was a tricky one,  
13 particularly -- and we'll get to the demographics.  
14 But those with type 2 that are undiagnosed, we just  
15 have no --  
16 DR. TESFAYE: We have no indication of what  
17 happens.  
18 DR. GIBBONS: Yes.  
19 DR. POP-BUSUI: Why don't we look at the  
20 demographics a little bit before we make a final  
21 decision? Because I think that's important.  
22 DR. GIBBONS: So maybe I'll jump forward so

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1 everybody has a --  
2 DR. MALIK: Chris, there is a very rare  
3 entity, hypoglycemic neuropathy. So is there a  
4 subtype within this group that you've got that have  
5 a history of severe hypoglycemia for example?  
6 DR. GIBBONS: It's an interesting question.  
7 So this group has by and large all been severe  
8 hyperglycemia for a long period of time, until this  
9 episode occurs. They don't have true hypoglycemia  
10 during these -- I do have good records on  
11 this -- although the concept of relative  
12 hypoglycemia compared to where they were before I  
13 think is absolutely an important concept to debate.  
14 And that I think is where there is a big issue.  
15 DR. TESFAYE: But hypoglycemic neuropathy  
16 doesn't present in this manner. Hypoglycemic  
17 neuropathy is usually focal, and I think this  
18 entity is completely different.  
19 DR. GIBBONS: It's a little different, yes.  
20 DR. ZIEGLER: But the question is whether  
21 you have records of documented hypoglycemia,  
22 symptomatic, because those may experience

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1 hypoglycemia at 100 glucose and try to find a  
2 relationship between the pain development and the  
3 other manifestations. Whether there is a  
4 relationship to the frequency or hypoglycemia, for  
5 example, would be interesting.  
6 So all of symptomatic hypoglycemia in that  
7 context would be very interesting because the DCCT  
8 has shown the transient deterioration of  
9 retinopathy, which was related to hypoglycemia in  
10 the initial lowering of glucose.  
11 So it would be interesting to learn the role  
12 of hypoglycemia in that context as well.  
13 DR. POP-BUSUI: But it was not so severe. I  
14 mean, we didn't see proliferative in such a short  
15 term, but I agree completely it was after the first  
16 year that deterioration was clearly there.  
17 DR. GIBBONS: But again, the numbers were  
18 really only a change of about 2 points, so they  
19 were on the lower side.  
20 So Amanda's been waiting patiently.  
21 DR. POP-BUSUI: Your patients have not only  
22 type 1, right? Or they are all type 1?

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1 DR. GIBBONS: No, they're mixed, and we'll  
2 get into that.  
3 DR. POP-BUSUI: Right, right.  
4 DR. PELTIER: You ever see it without pain?  
5 Because it's almost always with pain.  
6 DR. GIBBONS: Yes. I think even the  
7 autonomic predominant have some pain.  
8 DR. PELTIER: Right. So I would argue the  
9 pain should be a core feature that you should have  
10 to make the diagnosis.  
11 DR. GIBBONS: Yes. I think it will be core.  
12 And the question is, do you have an autonomic,  
13 predominant, or -- yes. So it should be, yes,  
14 subtypes --  
15 DR. PELTIER: Subtypes, sensory only.  
16 DR. GIBBONS: -- but all in one overall.  
17 Right.  
18 DR. BRUEHL: If I could make a  
19 general -- because this will apply to other people  
20 as well. So if anybody has proposed criteria and a  
21 data set that encompasses many of the components in  
22 the criteria, the thing to do is, just in a

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1 simplistic way, is break your groups using cut  
2 points like you've proposed here, like single  
3 items, like the pain 3 or greater versus not, and  
4 look at frequencies. Because if you do that cut  
5 point and only half the people in the group you're  
6 interested in are showing that greater than 3, then  
7 you clearly are going to have to adjust it.  
8 So you want to set those thresholds to where  
9 most of the group you're interested in are going to  
10 have values in that range, and then you can go on  
11 next to lumping together multiple things. Like  
12 Roy's point about the autonomic features if you've  
13 got 4 of them, is look at how many have 0, 1, 2, 3,  
14 4 of those, and look at the percentages when  
15 they're clustered like that. So you can kind of  
16 empirically iteratively go back and re-jigger  
17 things so it looks more like what you're trying to  
18 capture.  
19 DR. GIBBONS: What I'm getting to here.  
20 Gordon?  
21 DR. SMITH: This is a question for you and  
22 Steve. So as I understand it, you have a data set

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1 that encompasses a group of patients with  
2 neuropathy who have had no change and minimal  
3 change, and then hyperglycemia. You have a group  
4 that have had acute changes with minimal change in  
5 hyperglycemia, and then you have the TIND group and  
6 a group of people who have had a large change in  
7 their glycemic control without developing TIND.  
8 Couldn't you just take the data and give it  
9 to Steve's computer that is going to see if these  
10 different groups aggregate out? I mean, one would  
11 predict that it'll be very easy for his  
12 supercomputer to recognize the TIND phenotype.  
13 DR. BRUEHL: Yes. In theory, you should be  
14 able to do that, yes.  
15 DR. SMITH: Now, you could just take an  
16 unbiased, hand it off to whatever algorithm you  
17 use.  
18 DR. BRUEHL: That won't get rid of the issue  
19 of exactly what the cut points should be for  
20 clinical diagnostic purposes, but it would at least  
21 document the existence of a clear subgroup, and it  
22 would be able to phenotype them so that you'd have

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1 a good idea of what features really do differ well.  
2 DR. SMITH: It would give you the individual  
3 domains that you would then go back and look at to  
4 determine the cutoff value  
5 DR. BRUEHL: Exactly.  
6 DR. TESFAYE: In our series, we found that  
7 most of these patients had resolution of their  
8 symptoms within 18 months, most of them. In your  
9 series, this is a key sort of distinguisher of this  
10 condition from chronic sensory motor neuropathy,  
11 and should this feature as a core diagnostic  
12 criteria?  
13 DR. GIBBONS: Yes. That's an excellent  
14 question. I think particularly as we're thinking  
15 about this group going into an enrollment, the  
16 possibility for these people to improve exists.  
17 I'll get into a little bit about why that may or  
18 may not work, because it turns out it's a little  
19 trickier than I had hoped, unfortunately.  
20 So in terms of limitations on this, we  
21 worked through many of these things already, so  
22 we'll skip over this slide because I think we've

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1 just rehashed this. I wanted to talk about the  
2 differential diagnosis a little bit. Again, I put  
3 this up just because of this question of an overlap  
4 and phenotype clinically. These are totally  
5 different, so this isn't a diagnostic, but from  
6 pathophysiology, you have to wonder about these  
7 relations.  
8       Again, this is the link-dependent small  
9 fiber neuropathy that occurs or predominantly small  
10 fiber neuropathy is just time that these are people  
11 developing it anyway. That's always a question  
12 that comes up, some sort of acute process, whether  
13 it's drug or toxin related, and then the  
14 possibility of an inflammatory or infectious acute  
15 neuropathy. Again, they seem fairly remote, but  
16 they're definitely on the differential.  
17       So I moved this to tabular form to try to  
18 get at some of these details. And I think we've  
19 talked about this and already reviewed some of the  
20 details as to why this might or might not work out.  
21       One question, though, is how would we  
22 quantify this exam, and I think it fits best to the

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1 UENS in terms of distribution of small fiber  
2 neuropathy. However, I wonder if that actually  
3 doesn't grab enough territory to magnify that, but  
4 maybe that's something we can think through later.  
5 But that was just a question because this component  
6 doesn't fit as highlighted yesterday on the NIS-LL  
7 scale. It just doesn't fit with a particular  
8 problem.  
9       I highlighted these points here. Pain is,  
10 again, link dependent but may appear as a whole  
11 body in the more severe cases. This part clearly  
12 needs to discuss or remove, and then no other  
13 diagnosis that better explains the neuropathy.  
14       Common features in demographics.  
15       DR. FREEMAN: I think we are working through  
16 this. Can we go back to this a little? If we  
17 think of the flow-through criteria, first it's  
18 going to be pain score, so starting at the  
19 symptoms, the first would be the appearance. What  
20 are we going to call it? Subacute or give you a  
21 time frame of pain. Then symptoms, you're going to  
22 give your menu of autonomic features, the Gordon

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1 approach or from your clinical experience.  
2       Then I suppose you're going to quantify the  
3 pain. I'm seeing 4. That probably is going to go  
4 back. You're going to describe the pain.  
5       DR. GIBBONS: This probably will then move  
6 into -- yes.  
7       DR. FREEMAN: Yes, so 3 and 4 will be  
8 combined.  
9       DR. GIBBONS: Have a menu both for pain in  
10 terms of severity distribution and then an  
11 autonomic severity distribution.  
12       DR. FREEMAN: I mean timing to severity.  
13       DR. GIBBONS: Yes.  
14       DR. FREEMAN: You led that small fiber  
15 group. You probably could on your exam combine  
16 conclusions you came to, we will come to later in  
17 the day with respect to the examination, and then  
18 the background. I think that would probably work.  
19       What do others think about that?  
20       DR. GIBBONS: Dan?  
21       DR. ZIEGLER: I agree with Solomon. I would  
22 skip the 6 months.

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1       DR. GIBBONS: No, I agree, so this will be  
2 revised based on that because that's the consensus  
3 here, I think.  
4       DR. FREEMAN: We'll go through all of the  
5 comments that were made.  
6       DR. GIBBONS: Yes. So thankfully we have a  
7 stenographer in the back who's saving us.  
8       DR. BRUEHL: You don't want to include  
9 anything in the criteria also that might limit your  
10 ability to make the diagnosis just because of  
11 absence of information.  
12       DR. GIBBONS: Great point.  
13       DR. TESFAYE: Presumably, the patients in  
14 large fiber tests, most of them were normal, but in  
15 some, there was some --  
16       DR. GIBBONS: Yes. And I'll address that as  
17 we move into this. Gordon?  
18       DR. SMITH: So my predictable question, I  
19 suppose, do you need or will you require a  
20 confirmatory test? So if you go back on the slide,  
21 you talked about neurophysiologic, neuropathologic,  
22 do you think you need something like that?

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1 DR. GIBBONS: I don't think you do. Do you  
2 guys think you need it?  
3 DR. ZIEGLER: In practice, you don't need  
4 that.  
5 DR. GIBBONS: Right. I don't think you need  
6 a confirmatory test.  
7 DR. BENNETT: So providing you've got  
8 examination findings.  
9 DR. ZIEGLER: Right, a simple neurological  
10 examination, which may or may not be normal.  
11 DR. GORDON: They're preclinical. I'm just  
12 kidding.  
13 (Laughter.)  
14 DR. SINGLETON: Do you think any blood work  
15 is necessary to exclude other conditions?  
16 DR. GIBBONS: I do, yes. So I think as we  
17 go through the differential diagnosis, on the  
18 clinical side, I think you need to make sure there  
19 isn't another neuropathy that would better explain  
20 this. So in terms of most cases, they'll generally  
21 have had basic blood work suggesting that there an  
22 acute process. You want to make sure obviously

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1 major B12 issues aren't present, but again, this  
2 isn't a dorsal column problem. So for the most  
3 part, it's really going to be linked history to the  
4 physical exam.  
5 DR. BRUEHL: I think the standard thing at  
6 the end of this would be to make just a general  
7 comment about there aren't other conditions,  
8 diagnosable conditions, that can explain the  
9 pattern of symptoms and not get into how you would  
10 determine that necessarily, because it's just too  
11 many possibilities.  
12 DR. SINGLETON: It'd probably be limited,  
13 actually, the number of other conditions then.  
14 DR. GIBBONS: Yes, no. It's going to be  
15 quite limited, and unless somebody was given  
16 chemotherapy, hopefully that comes out in the  
17 history or something along those lines.  
18 DR. HARATI: Or post-bariatric, that's  
19 becoming very common.  
20 DR. GIBBONS: I think that may be this, but  
21 that's a separate issue. David, did you have --  
22 DR. BENNETT: They all have abnormal

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1 examinations?  
2 DR. GIBBONS: Yes.  
3 DR. BENNETT: So you need the  
4 interchangeable thing, which is if the examination  
5 was normal, a confirmatory small fiber test may  
6 substitute.  
7 DR. GIBBONS: Although I think that has to  
8 probably be clarified, because it can be very  
9 easily missed, because it's all small fiber.  
10 DR. BENNETT: That's my concern, yes.  
11 DR. GIBBONS: So there is loss, either  
12 hyperalgesia or loss of pin, or temperature  
13 sensitivity. However, if it's really diffused, you  
14 can't see a gradient and that's where you can get  
15 fooled.  
16 DR. BENNETT: So maybe the role for the  
17 tests will be where the examination is normal, you  
18 could still make a diagnosis on the basis of  
19 reduced epidermal nerve fiber count.  
20 DR. GIBBONS: That's an interesting point,  
21 excellent point. And other confirmatory things,  
22 particularly for those more severe cases, I think

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1 will be retinal changes as well. So that will be  
2 some other potential supplemental testing.  
3 DR. ZIEGLER: So how frequent is this with  
4 oral medication?  
5 DR. GIBBONS: So in terms of this  
6 distribution, the group, the cohort I presented, 79  
7 were type 1 diabetes; the rest were type 2. So in  
8 terms of those with type 1, everybody was on  
9 insulin, obviously; those with type 2. We  
10 essentially 16 on oral medications, and I think the  
11 remaining 10 were on oral plus insulin, and then 2  
12 were diet control. So there were actually 2 people  
13 who just restricted their diet, dropped their  
14 hemoglobin A1c from like 12 to 7 in 3 months just  
15 on diet.  
16 Yeah, so it does exactly very bad efforts  
17 and good intentions.  
18 DR. POP-BUSUI: The proportion of women was,  
19 what, 70 percent, I remember from your paper,  
20 right?  
21 DR. GIBBONS: The women, definitely more  
22 frequent, particularly in the type 1, so it's about

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1 80 percent women. And I'll talk a little bit more  
2 about this because I think it's a major  
3 pathophysiologic psychosocial issue that we'll get  
4 into.  
5 DR. PELTIER: Social, yes.  
6 DR. POP-BUSUI: Yes. And then I had seen  
7 that there were a lot of eating disorders in these  
8 people.  
9 DR. GIBBONS: A huge amount of eating  
10 disorders, so that I think comes in core 3 because  
11 of other comorbid illness, so that will be  
12 something I talk about. But in terms of this  
13 distribution of type 2s, it's far less common as a  
14 proportion of the population.  
15 The common features, we've gone through this  
16 I think fairly quickly. Hot burning, stabbing,  
17 lancinating pain, the classic descriptions. Other  
18 complications, autonomic, we talked about this, the  
19 retinal and renal.  
20 Epidemiology, again, this is a question  
21 where it's pretty limited against single center,  
22 and this makes it a little bit more complicated.

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1 But it was 11 percent of the population referred in  
2 just for general diabetic neuropathy. Again, it's  
3 hard to extrapolate that to the rest of the  
4 population. Certainly, Joslin's is a unique group  
5 of patients there, so uniquely dynamic changing  
6 glucose is possible. I think they're more than  
7 other places.  
8 DR. PELTIER: We see it, too.  
9 DR. GIBBONS: So it is out there, and  
10 clearly people see it, but I think the numbers are  
11 a little bit more unknown.  
12 DR. PELTIER: In Tennessee, we call it the  
13 "Come to Jesus" talk.  
14 (Laughter.)  
15 DR. FREEMAN: Can you comment on any sense  
16 of prevalence?  
17 DR. TESFAYE: I don't know. I think I  
18 reviewed your paper, Annals of Neurology and all  
19 the papers. Eleven percent I think is because of  
20 referral biases.  
21 DR. GIBBONS: I agree.  
22 DR. TESFAYE: It's quite exceptionally rare,

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1 but I think people need to have their brain tuned  
2 not to dismiss these patients, because I've had a  
3 few patients who have been referred because they  
4 did nerve conduction studies, which are normal, and  
5 these patients have severe small fiber neuropathic  
6 pain, which was not appreciated, and I think  
7 probably not as much as 11 percent.  
8 DR. GIBBONS: One of the things that I  
9 conducted in terms of this patient population is I  
10 actually did a study of how frequently the  
11 physicians who referred the patients in recognized  
12 the problem, and there was a clear relationship  
13 because the prominent the symptoms, the classic  
14 picture, the more likely they were to recognize  
15 this.  
16 However, as soon as it was more of a distal  
17 symmetric kind of really feet only, nobody  
18 recognized it. And if it was autonomic  
19 predominant, they did not recognize it. They  
20 didn't think of that in this disorder. So the  
21 relationship to the referrals were definitely  
22 inversely reported to the classic presentation.

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1 DR. ZIEGLER: If it's widespread, the  
2 physician would say that it's not due to diabetes.  
3 This is what I have frequently heard from the  
4 patients coming from psychiatrists and so on.  
5 DR. GIBBONS: It's definitely missed if too  
6 secure.  
7 DR. ZIEGLER: I think it's pretty rare.  
8 It's very rare, I would say, because if you ask 20  
9 diabetologists about it, maybe one would know it.  
10 So it cannot be very frequent in that sense.  
11 DR. GIBBONS: Yes, although I have asked  
12 that same question of the diabetologists who  
13 referred these patients, and they've said they've  
14 never seen it even though they refer these  
15 patients. So we get into that same thing.  
16 Ahmet?  
17 DR. HOKE: What's the time lag between these  
18 patients who actually have that drop in their  
19 hemoglobin A1c and when they were referred to you?  
20 I mean, did you see these patients early on in  
21 their course?  
22 DR. GIBBONS: I saw them early, yes. So

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1 luckily, I really got the word out. If you have an  
2 acute change in pain, make sure they get in to see  
3 me quickly, e-mail me, call me. I really try to  
4 get them in as fast as possible just to answer  
5 that.

6 DR. HOKE: I know patients don't have that  
7 rapid decline in their hemoglobin A1c. I may have  
8 seen maybe 1 or 2 patients in 20 years, and David  
9 was saying the same thing. It's rare.

10 DR. GIBBONS: Yes. It's challenging  
11 because, if you're not getting A1cs regularly, you  
12 don't know when it happened, so you can certainly  
13 miss this relatively easily.

14 DR. RUSSELL: So Chris, I think if you run  
15 an autonomic lab, they're actually far more  
16 frequent. I think that's the criteria that  
17 determines how often you see them.

18 DR. GIBBONS: Although, yes, these weren't  
19 referred to autonomic, though. These were referred  
20 to general diabetic neuropathy clinical.

21 DR. RUSSELL: It's less than what I see in  
22 autonomic labs.

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1 DR. ZIEGLER: Do you have any statement on  
2 the reversibility? Because I think it's important.  
3 Yes.

4 DR. GIBBONS: Yes. So I do as natural  
5 history. That's a couple slides ahead here.  
6 So other lifespan considerations, we talk  
7 about a question of whether this could occur in  
8 pediatric populations, certainly in type 1  
9 diabetes, absolutely, this is I think a big issue.  
10 Possibly in type 2. We're seeing unfortunately a  
11 lot of type 2 diabetes in the pediatric population  
12 as well. I've never seen a case, but I think  
13 unfortunately it's inevitable.

14 I think it's really a change in A1c that's  
15 driving a lot of this. But in the more severe  
16 cases, there is definitely a risk of both morbidity  
17 and mortality. The larger the magnitude change,  
18 the more profound the problem is. And many of  
19 these people do progress to both visual loss, renal  
20 failure, amputations, et cetera, and I'll talk  
21 about why. But that can definitely occur in terms  
22 of lifespan considerations.

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1 This gets to this important issue that  
2 Rodica was hinting at with the account of medical  
3 and psychiatric comorbidities. So in terms of this  
4 population, eating disorders are extremely common.  
5 The issue primarily for the severe hyperglycemia is  
6 diabulimia, where essentially you're withholding  
7 insulin in order to lose weight.

8 So as a population, these are typically  
9 women who discover if they don't take their insulin  
10 or take it very infrequently, they can eat what  
11 they want and lose weight. So they run very severe  
12 hyperglycemia, but they've learned to kind of  
13 maintain at that level. Something typically  
14 happens, some intervention, as Amanda calls it, the  
15 coming-to-Jesus talk. That's what they do in  
16 Tennessee, but essentially it's an intervention  
17 that typically occurs for some reason with family  
18 and with medical providers, where there's a sudden  
19 specific change in behavior, and this basically  
20 predisposes to the rapid changes in glycemic  
21 control that can occur. So it's definitely seen in  
22 the eating disorders population and the pediatric

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1 type 1 population in particular.

2 Other common comorbidities, particularly in  
3 the type 2 population, hypertension,  
4 hyperlipidemia, tobacco use. I would say there's a  
5 history of medical denial. These are the people  
6 who have been fine for 10 years, haven't seen a  
7 physician. They do have a number of problems.  
8 They finally come in. They have undiagnosed  
9 diabetes amongst other things, so that tends to be  
10 the type 2 population that we see unlike the type  
11 1, which is different. I think these should  
12 probably be segregated by type 1 and type 2 in this  
13 discussion.

14 Going on to concepts of neurobiological,  
15 psychosocial risk factors, protective factors, just  
16 looking at the neurobiological aspects, known  
17 mechanisms of disease. I think this is an issue,  
18 and we're trying to get at what is the mechanism.  
19 There are a couple things we've thought about with  
20 relative hypoglycemia causing mitochondrial  
21 dysfunction, seminal transport failure.

22 DR. TESFAYE: Microvascular dysfunction

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1 possibly.

2 DR. GIBBONS: Yes, precipitating, all these

3 things ultimately leading to microvascular

4 dysfunction, and then inflammatory mediators where

5 hypoglycemia causes massive cytokine and

6 hyperalgesia, potentially microvascular change,

7 these are theories and there's some degree of

8 evidence, but again, nothing, I think, has clearly

9 drawn the line across.

10 DR. ZOCHODNE: That's a tough one, Solomon.

11 I mean, how would you explain loss of terminals and

12 selectively in small fibers in a nerve trunk from a

13 microvascular cause? I mean, it just doesn't fly.

14 DR. TESFAYE: Recently, in fact, when we go

15 back in the paper, what we found recently is we did

16 a skin biopsy in patients with chronic painful

17 diabetic neuropathy, and we found old stuff, which

18 Rayaz and I published 30 years ago. Actually,

19 there is an abundance of proliferation of

20 microvessels in the dermis of these patients on

21 skin biopsy, stained using von Willebrand factor.

22 There's also several papers that we

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1 published many years ago in those with painful

2 neuropathy. There seems to be increased shunting

3 on the surface of the nerve. Is it a consequence?

4 I don't know. What is the metabolism that's

5 driving this? I don't know. But these patients

6 develop proliferative changes in their eyes, and

7 there is association with microalbuminuria. And a

8 similar process could be taking place on the

9 surface of the nerve, rendering the nerve maybe

10 ischemic or hypoxic, leading to pain.

11 I don't know what the mechanism is, but

12 clear observation, there are vascular changes in

13 these patients. In all the patients that we did,

14 we exposed the nerve, and there was proliferation

15 of blood vessels on the surface.

16 What's driving this? What are the

17 mechanisms behind this? We don't know.

18 DR. HOKE: I guess even just a relative

19 reduction in glucose levels in the nerve could lead

20 to the degeneration. In vitro, when you culture

21 neurons, you're culturing them at relatively high

22 glucose levels, 25 millimolar. And if you drop

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1 that to quote/unquote, "normal" glucose levels,

2 7 millimolars, a lot of times the axons will

3 degenerate, without doing anything else.

4 So probably that rapid, I mean, sarcomas,

5 the neurons kind of got used to living at those

6 high glucose levels --

7 DR. GIBBONS: Relative hypoglycemic state.

8 DR. HOKE: -- then when you take it away,

9 they undergo --

10 DR. GIBBONS: That's relative hypoglycemia.

11 DR. HOKE: Exactly.

12 DR. ZIEGLER: I thin in these early studies,

13 Gary Whelan actually described some kind of

14 sprouting of those nerves as well.

15 DR. GIBBONS: Yes, exactly. Gordon?

16 DR. SMITH: Has anybody attempted to model

17 this in an animal system?

18 DR. GIBBONS: Nigel has.

19 DR. WRIGHT: In processing right now, I

20 think this would be really amenable to anti-NGF

21 antibodies. I would suspect that there's probably

22 proliferation of NGF. You're getting an increased

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1 response. The nerve degeneration is interesting,

2 but it may be secondary because it's a change.

3 You've got this incredible increase in pain

4 sensitivity. I think C fibers are very modifiable

5 in terms of changing and trying to adapt with the

6 central nervous system, but I think this would be

7 really interesting to model that, and I bet it

8 would be sensitive to anti-NGF antibodies.

9 DR. GIBBONS: Yes. So I know Nigel Calcutt

10 had been working on that. And he's been working on

11 it for a while, and I haven't seen much out of it.

12 So I think one of the big issues modeling this is

13 that the animals all die, so it's a challenge. And

14 maybe the model he was using --

15 DR. WRIGHT: Is it because of hypoglycemia?

16 DR. GIBBONS: Yes. So the issue for the

17 question of having a sustained period of

18 hyperglycemia long enough, then you control, I

19 don't know. I think there's an issue in terms of

20 lifespan in terms of the effects.

21 DR. WRIGHT: You just have to monitor their

22 glucose better.



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1 DR. GIBBONS: Yes. Vera?  
2 DR. BRIL: I'm not sure if the transient  
3 autonomic dysfunction is due to the hyperglycemia  
4 or is it separate from the pain? We had a case  
5 years ago, and we published it, a 15-year-old girl  
6 with type 1 for 11 years, sent to me from a very  
7 excellent endocrinologist at the Hospital for Sick  
8 Children. And she developed bladder failure, I  
9 mean, retention that required catheterization and  
10 gastric symptoms that required a medical provider.  
11 She had an A1c of 7 percent. She hadn't changed  
12 recently. She hadn't sustained hyperglycemia. She  
13 didn't have other comorbidities, and she improved  
14 after 2 or 3 months.  
15 Still, this is the mystery case for me. I  
16 have no idea what happened to her and why she had  
17 this. But I'm not sure that transient autonomic  
18 failure or dysfunction is always related to  
19 hyperglycemia or rapid correction of hyperglycemia.  
20 DR. GIBBONS: Yes. What I'm thinking that  
21 necessarily it's always by any means. It's a  
22 question of the time-locked basis of this.

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1 So I'm being told I have to move on, so  
2 we'll try and quickly dip through this, and then  
3 have time I think for more questions afterwards, so  
4 we're getting close.  
5 So the psychosocial and other risk factors,  
6 so I highlighted most of these. There are clearly  
7 psychosocial risk factors both leading to prolonged  
8 hyperglycemia and some psychological event that  
9 triggers the newfound glycemic control,  
10 particularly in those with type 1 diabetes.  
11 I think this is a key area of research  
12 opportunity because there's clearly a population at  
13 risk that we can target. We know who these eating  
14 disorder groups are. They are a massive number of  
15 people that are at risk there, so that's, I think,  
16 a targetable population.  
17 I think this question of multifactorial  
18 interventions could be used to consider this in  
19 terms of preventing recurrence as well because once  
20 these people get this, there actually is a  
21 significant proportion that do this again. So they  
22 have more than one episode, and then go on to have

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1 more severe complications, including motor, renal  
2 failure, amputations, et cetera. So this is, I  
3 think, a big risk population that we could target  
4 from a research perspective.  
5 Protective factors, there are many things  
6 that are unknown. There are a lot of, I think,  
7 theoretical approaches, whether it's mitochondrial  
8 health, that it could be considered. The big open  
9 target here is slower glycemic change. We  
10 hypothesize that if we do this more slowly, they  
11 won't develop this. We don't actually know this  
12 for sure, but this is, I think, a clearly testable  
13 hypothesis, and that's the hope. It's a challenge  
14 because these are the people who it's sort of an  
15 all or nothing phenomenon in terms of the glycemic  
16 control, so this is probably going to be very  
17 difficult, but this would be the question; in a  
18 prospective trial, if we changed the rate, could we  
19 prevent it?  
20 Other concepts of anti-inflammatory  
21 interventions or blending of cytokine release might  
22 be also possibilities.

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1 Consequences. There is diffuse  
2 microvascular involvement. The pain is quite  
3 severe, often requiring polypharmacy. Again,  
4 autonomic dysfunction we've talked about, the renal  
5 and retinal issues. Long-term complications can  
6 again progress if they have more than one episode.  
7 So in terms of overall conclusions, again,  
8 there's a lot of limitations to this data. There  
9 are a lot of I think pluses that really don't at  
10 this point have any validated questionnaires that  
11 we would selectively use, although we have a number  
12 of good things we can suggest.  
13 I've looked at both of these. The UENS is  
14 clearly a much more dynamic range for this, which  
15 questioned whether it needed to be expanded in some  
16 way, and then we talked about the diagnostic  
17 criteria.  
18 Conclusions. I think key aspects of this  
19 for future research, strategies to further identify  
20 those at risk, so target that population. Altering  
21 radioglycemic change is preventive. And then  
22 preventable therapies, mitochondrial, anti-

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1 inflammatory, cytokine release modifiers, this  
2 would be really interesting. Then salvage  
3 therapies. Once people develop this, is there  
4 anything we can do acutely to prevent it? Again,  
5 the approach they've taken in the lumbosacral  
6 radiculoplexus neuropathies; can we pulse, hit  
7 something hard quickly to prevent or more rapidly  
8 recover?  
9 So I'll stop at that point because I want to  
10 make sure we stay on time.  
11 (Applause.)  
12 Q & A and Panel Discussion  
13 DR. FREEMAN: So we'll move on to Rob's  
14 talk. At this point, [inaudible – off mic] – the  
15 switch were meant to be on the Chris, Jim talk, and  
16 don't have anything to say.  
17 Eva, not here. Ahmet, anything that you  
18 want to [inaudible – off mic].  
19 So where are we? So the rest was Jim,  
20 Chris, Ahmet.  
21 Rayaz, any additional comments?  
22 DR. MALIK: I guess is there any way of

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1 interrogating the big clinical trial data, sets  
2 like ACCORD, PADT, DCCT perhaps? Is there  
3 something in there that you can potentially get  
4 access to, to try and find out how common this  
5 problem really is?  
6 DR. GIBBONS: There is signal data that's  
7 available in there. In DCCT, they talk about the  
8 early and worsening retinopathy. But again, those  
9 are the people -- there were still relatively small  
10 changes in A1c, so it wasn't the magnitude of the  
11 problem that I'm talking about.  
12 I think there is signal data available. And  
13 particularly for bariatric surgeries as well, that  
14 is, I think, a great and ripe opportunity.  
15 DR. MALIK: If you look at VADT, I think it  
16 reported, actually, they did -- an ACCORD as well.  
17 They had a list of autonomic symptoms, for example.  
18 So they're obviously recording them at time points,  
19 and I'm sure all of the trials were doing it in  
20 some way, perhaps not pain scores, but certainly  
21 autonomic symptoms were recorded.  
22 DR. POP-BUSUI: Autonomic symptoms were not

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1 recorded in ACCORD.  
2 DR. MALIK: VADT was. I think it was one of  
3 them that had --  
4 DR. POP-BUSUI: VADT had some, but I don't  
5 know whether the magnitude of A1c reduction was so  
6 big -- even in VADT, it was from 8.9 to 7.  
7 DR. MALIK: Yes, but that's the mean.  
8 That's the average.  
9 DR. POP-BUSUI: Right.  
10 DR. MALIK: Within that population, if  
11 you've got a trial of 10,000 people, you're going  
12 to have individuals.  
13 DR. POP-BUSUI: There is a question also  
14 whether the two entities may be separate. Is this  
15 the same type of painful induced neuropathy in type  
16 1 versus type 2? Because I think that a phenotype  
17 of patients is actually very, very different just  
18 looking at some of these demographics.  
19 DR. GIBBONS: The clinical phenotype and  
20 comorbidities are definitely different. The  
21 clinical picture in terms of pain actually is the  
22 same, and that's where it's very interesting.

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1 DR. FREEMAN: Amanda, the other panelists,  
2 anything else to say?  
3 DR. PELTIER: The other thing I was going to  
4 comment on is whether or not we should look more  
5 into the nutritional component more carefully,  
6 because if you have a group that's in type 2 that  
7 are going from obese to significant weight loss and  
8 then the reverse happens in type 1, where you have  
9 someone who is essentially underweight or not  
10 eating well, and then presumably is going to gain  
11 weight significantly or have this rapid shift, that  
12 might be something you might want to take into  
13 account as a pre-disposing factor.  
14 DR. POP-BUSUI: No. I don't think that you  
15 can expect so much weight gain in 3 months just  
16 with this improvement of glucose control.  
17 DR. PELTIER: No. They won't.  
18 DR. POP-BUSUI: But the point with the  
19 bariatric is actually quite --  
20 DR. PELTIER: Right. Is there some other  
21 nutritional component with that shift?  
22 DR. POP-BUSUI: It's very possible that

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1 these people who had an eating disorder had a  
2 baseline nutritional dysfunction that could have  
3 just been just triggered by this acute change in  
4 glucose levels.  
5 DR. FREEMAN: Last quick word from Dan?  
6 DR. ZIEGLER: We're still missing the aspect  
7 of reversibility, because this is the first -- I  
8 tell the patient, I reassure them that this will go  
9 away. And I think this should be one criterion and  
10 clearly differentiation to the chronic DSPN.  
11 DR. GIBBONS: So we did have a recent  
12 publication on the reversibility of this. And so  
13 you're absolutely right. The classic group that we  
14 saw, the majority of those with type 1 got better  
15 in 18 to 24 months, but not completely. They  
16 didn't go back to baseline, but they definitely got  
17 better in all aspects.  
18 However, that was pre-disposed to a stable  
19 glycemic control for the entire duration. Those  
20 who had significant fluctuations again up or didn't  
21 quite have better control to this degree actually  
22 got substantially worse. And those with type 2

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1 diabetes had no improvement. That was unfortunate.  
2 So it was only type 1s that showed recovery.  
3 DR. FREEMAN: So I think we've done a really  
4 good job with these tight package disorders, germs,  
5 diabetic radiculoplexopathy, and this one. Let's  
6 move on with similar success to Rob.  
7 Presentation – Robinson Singleton  
8 DR. SINGLETON: Thank you, Roy and Chris.  
9 That was the point I was going to make, that we're  
10 moving from incredibly well definable disease to a  
11 giant baggy sort of vague entity that defies easy  
12 definition, so I think that is really the challenge  
13 for us.  
14 I just want to tell you about the overall  
15 concepts that I want to engage you with here.  
16 First, that metabolic syndrome is a complex  
17 spectrum disorder with a continuum of injury to  
18 nerve and risk for that injury. Metabolic syndrome  
19 features, especially obesity and dyslipidemia,  
20 contribute to the pathogenesis of neuropathy. And  
21 as I've said, the different features of metabolic  
22 syndrome contribute probably different degrees of

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1 risk.  
2 I'm taking an extremely reductionist  
3 position with regard to the taxonomy of this  
4 disorder because I think that, basically, the  
5 neuropathy of pre-diabetes, of metabolic syndrome,  
6 is the neuropathy of diabetes, and the diagnostic  
7 criteria from a phenotypic evaluation for the most  
8 part are the same.  
9 So the discussion that we had yesterday  
10 about what defines neuropathy in these patients,  
11 really, we've had that discussion. I think we did  
12 a good job of that yesterday. It's really not so  
13 much about what defines the neuropathy as what are  
14 the attributes, what are the contributors to that  
15 neuropathy.  
16 I think there's good data basically that  
17 features a metabolic syndrome, that contributes  
18 something to the pathogenesis of peripheral  
19 neuropathy.  
20 So why should we have this be its own entity  
21 if it's going to be so vague? I think the most  
22 important argument from me is that the risk pool

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1 for patients who may have a contribution of this  
2 type to their neuropathy is huge. Thirty-five  
3 percent of the U.S. population has metabolic  
4 syndrome and some even larger percentage are obese.  
5 Recognizing this disease early means that we have a  
6 chance to offer effective treatment, and if we  
7 point out that neuropathy can be something that  
8 happens in this setting, that brings more patients  
9 to effective metabolic control.  
10 But more specifically to the entity, I think  
11 recognizing that per-diabetic neuropathy as a  
12 disease entity allows practitioners in general  
13 practice to consider this diagnosis. It's  
14 foundational for examining the consequences of the  
15 disorder in terms of progression, and it encourages  
16 study of the pathogenic mechanisms. If we don't  
17 define this disorder, we don't have a chance to  
18 study it effectively.  
19 I think it's important to set this in the  
20 context of this spectrum of metabolic disorder, and  
21 I think I'm going to come around to talking about,  
22 again, how almost certainly genetics, the complex

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1 multivocal genetics, to some degree will be shown  
2 to define the risk for this. Why is it that some  
3 patients develop neuropathy in the pre-diabetic  
4 period and others do not? I'd say that at least  
5 some of that is determined by your genetic make-up.  
6 For a long time, I've thought Homer Simpson  
7 is the perfect example of this. He's got a donut  
8 in one hand and probably a beer in the other. And  
9 these overweight patients develop a neuropathy that  
10 is sensory predominant, symmetrical, distal, often  
11 painful, sometimes has autonomic involvement, and  
12 essentially, it is undifferentiated from the  
13 disease of patients with early diabetic neuropathy.  
14 And I would argue that nearly any feature of  
15 diabetic neuropathy can be seen in the pre-diabetic  
16 setting, with perhaps the exception of Chris's  
17 disorder. If you haven't been treated, you are not  
18 going to have treatment-induced polyneuropathy.  
19 There's a problem with nomenclature. Just  
20 getting off the ground, what are we going to call  
21 this disorder? And we've used a number of terms.  
22 Pre-diabetic neuropathy ties this to diabetes, but

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1 I think it doesn't recognize the contribution of  
2 other features of metabolic syndrome.  
3 We've talked about impaired glucose  
4 tolerance neuropathy, which is really the same pre-  
5 diabetic neuropathy. Gordon has used and others  
6 have used cryptogenic sensory polyneuropathy as  
7 really almost a winking choice. We mean metabolic  
8 syndrome neuropathy, but we don't want to say so  
9 because we worry that our critics will complain  
10 about the idea that somehow it's tied to this vague  
11 metabolic syndrome.  
12 I think we should consider calling this what  
13 it is. It's polyneuropathy in the setting of  
14 metabolic syndrome, and I am going to use that term  
15 at least for this lecture here, but we could debate  
16 whether we want to stick our neck out by making  
17 that point.  
18 DR. FREEMAN: Before you move on, [inaudible  
19 – off mic].  
20 DR. SINGLETON: I think we're going to get  
21 there. I think some of them are in the audience.  
22 I just want to say that I'm going to talk about the

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1 data, about the evidence for polyneuropathy and  
2 metabolic syndrome. And this data, the better it's  
3 done, in some ways the shakier it gets. But what I  
4 want to say is that neuropathy is a multi-  
5 contribution disease for many patients, and we see  
6 this across the spectrum of metabolic syndrome. So  
7 it's not only true in patients with metabolic  
8 syndrome, but in patients with diabetes, that we go  
9 out looking for their B12 deficiency and their  
10 gammopathy in addition, and those things contribute  
11 together.  
12 So I want to come away from that idea of  
13 saying not that we can necessarily say that  
14 metabolic syndrome features provide only cause for  
15 neuropathy. I think that's probably not true in  
16 most patients, but that instead metabolic syndrome  
17 contributes something, something important to the  
18 development of injury to these peripheral nerves.  
19 I was going to say that as I go through  
20 this, I apologize if I either haven't talked about  
21 the important work that you've contributed or if  
22 I've mangled important work that you have

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1 contributed to this disorder.  
2 Basically, this is the main thrust of this.  
3 Epidemiology suggests this association, as we'll  
4 talk about. Animal models recapitulate the  
5 features of pre-diabetic or metabolic syndrome  
6 neuropathy. There have been studies looking at the  
7 biology of nerve injury in the pre-diabetic  
8 setting. And there's been a lot of research that  
9 looks at the biology and has developed a plausible  
10 pathogenic mechanism, especially for fat and  
11 obesity to cause injury to peripheral nerve.  
12 So this is maybe a whole bunch of studies  
13 that look at patients with otherwise idiopathic  
14 neuropathy and find an excess of features of  
15 metabolic syndrome or pre-diabetes in those  
16 patients compared to controls.  
17 Dr. Visser at University of Utrecht has done  
18 this, but so have lots of other people, including  
19 us. There is, in addition to that data,  
20 data -- and this is the only time I'm going to  
21 try -- I'm going to try and stay away from  
22 diabetes, but just to talk a little bit about the

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1 situation in which you have diabetes, but metabolic  
2 syndrome features within diabetes contributes  
3 something to the development of neuropathy.  
4 I think Solomon's study, the EURODIAB study,  
5 which took patients with type 1 diabetes who did  
6 not have neuropathy at baseline and then followed  
7 them for a surprisingly long time, for 7 years on  
8 average, found that these features of metabolic  
9 syndrome were risk factors for the development of  
10 incident neuropathy, even in type 1 patients. We  
11 had a discussion yesterday from Gordon about how  
12 type 1 and type 2 diabetes are different diseases,  
13 yet even in type 1 diabetes, these metabolic  
14 syndrome features play an important role in the  
15 development of neuropathy.  
16 We've done a less good in many ways study  
17 where we've taken patients with type 2 diabetes and  
18 followed them for a long time to see what happens  
19 to them, and to see if they have neuropathy at  
20 baseline, and what are the features that are  
21 associated with it. I think if there's a strength  
22 of our study, it's that if we're focused on

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1 neuropathy, we're focused on the features of  
2 neuropathy in a much more intensive fashion than  
3 the Tesfaye study. But here, we found a very  
4 strikingly similar result, which is that this is  
5 prevalence, not risk factors -- not incident  
6 neuropathy. But we can see that metabolic syndrome  
7 is associated with an increased prevalence of  
8 neuropathy in patients with diabetes compared to  
9 those who don't have other features of metabolic  
10 syndrome.  
11 Then treatment studies in which there's been  
12 multimodal attempts to try and control all the  
13 features of metabolic syndrome and not just  
14 hyperglycemia have shown that there can be a  
15 reduction in the overall risk profile for those  
16 patients. This is not so much about neuropathy as  
17 it is about showing that you get better control of  
18 all the features, the consequences of diabetes, if  
19 you treat not just hyperglycemia, but other  
20 features of metabolic syndrome.  
21 So turning to the obverse of this, which Dan  
22 pointed out yesterday, we want to look not at

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1 patients who have neuropathy with the inherent  
2 referral bias, but instead look at patients who  
3 have the underlying condition and then see how many  
4 of those patients have neuropathy.  
5 Here, the data is certainly weaker. This  
6 study Dr. Ziegler did shows an increasing  
7 prevalence in his case control population, both of  
8 neuropathy as defined by the MNSI and also of  
9 neuropathic pain. And then a study by Vera Brill  
10 and Dr. Perkins' group is a larger study looking at  
11 patients at great risk for progression to type 2  
12 diabetes, and they found, again using the MNSI as a  
13 questionnaire and using a neuroesthesiometer to  
14 measure vibration, an excess of injury and reports  
15 of neuropathic features in patients who are in the  
16 pre-diabetic state.  
17 The biggest, least biased study that I think  
18 is out there is Brian Callaghan's study, which he  
19 has searched the records of the Health ABC study  
20 participants and basically looked at this in a  
21 really pure epidemiologic exercise.  
22 What you can see is that there is clearly an

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1 excess of prevalence in the diabetic group, but not  
2 really in the pre-diabetic group. In fact, if you  
3 look here, if you don't have other metabolic  
4 syndromes somehow in this group, it's protective.  
5 If you just have hyperglycemia, you are better than  
6 average in terms of your risk for neuropathy. And  
7 what he found, though, overall in looking at all  
8 this data is that each feature of metabolic  
9 syndrome adds about 1.1 percent to your overall  
10 prevalence, your risk for the development of  
11 peripheral neuropathy and that, amongst the  
12 different metabolic syndrome features, waist  
13 circumference and dyslipidemia in the form of low  
14 HDL had the greatest association with the secondary  
15 measures that they did of diabetic sensory  
16 polyneuropathy.  
17 We know a lot -- and this is where the  
18 mangling comes in. I'm not going to really go very  
19 much into this, but we know about dyslipidemia and  
20 fat as pro-inflammatory, biologically, hormonally  
21 active tissue that has a real influence on the  
22 pathogenesis in terms of injury to peripheral

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1 nerve. As central adiposity increases, adipocytes  
2 grow larger. They produce and release free fatty  
3 acids that accelerate the cycle of insulin  
4 resistance. They break up, causes of inflammatory  
5 injury. And they also release pro-inflammatory and  
6 reduce their release of anti-inflammatory or  
7 vasoprotective cytokines.

8 This again is super simplistic. The slide  
9 points out the contributions of obesity and  
10 dyslipidemia to other mechanisms that we already  
11 know about in the pathogenesis of peripheral  
12 neuropathy.

13 DR. ZOCHODNE: So Rob, there should be an  
14 arrow directly from insulin resistance to neurons  
15 and axons as well, I think.

16 DR. SINGLETON: I wanted to say this slide  
17 is rather dated. I think there are many more  
18 arrows on this slide and factors that are not even  
19 mentioned here. But I think it just makes the  
20 overall point that there are a number of places  
21 where dyslipidemia and obesity have inputs to the  
22 known pathogenic features.

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1 Now, just to turn again to this, can we see  
2 the consequences of individual features of  
3 metabolic syndrome on risk for neuropathy? We've  
4 done a little bit of this work in a very basic sort  
5 of way. In this study, where we looked at  
6 bariatric patients who didn't have diabetes and  
7 measured -- the ultimate goal here, that's not  
8 completed, to look at their regenerative capacity  
9 using capsaicin axotomy before and after bariatric  
10 surgery. But in the baseline period, we found that  
11 non-diabetic patients who are scheduled for  
12 bariatric surgery are more likely than controls to  
13 have an abnormal UENS or MNSI, and that there's a  
14 statistically significant correlation between body  
15 mass index and these features of neuropathy.

16 Separately from this, really now rich  
17 literature from animal studies have shown that, in  
18 rodents, people like Doug Wright, who provided this  
19 slide to me, who I'm going to now mangle's slide,  
20 these can serve as experimental systems that very  
21 easily reproduce the conditions of pre-diabetic  
22 neuropathy.

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1 So if you give mice the Homer Simpson diet  
2 of pizza and beer, you generate an increase in  
3 weight that exceeds what you expect. You see  
4 insulin resistance and hyperglycemia as a  
5 consequence. But in the period before diabetes  
6 develops, these small rodent patients already  
7 develop clear behavioral abnormalities that are  
8 neuropathic. I think, as Doug has put on this  
9 slide, the important thing is that this is not just  
10 a peripheral nerve problem -- that's what we're  
11 here to talk about -- but this affects central  
12 nervous system biology as well.

13 I'm going to go to this slide, just a  
14 different system in Black6 mice -- this is Eva's  
15 group now -- has shown that if you give a high-fat  
16 diet, same thing, you can reproduce pre-diabetes in  
17 the metabolic syndrome in these mice, that they  
18 have measurable abnormalities of peripheral nerve  
19 function. Then, if you reverse the diet for these  
20 mice or if you go back one slide, if you run these  
21 mice on a wheel, alive with exercise, they'll  
22 either not develop this, they'll be resistant to

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1 the development of this pre-diabetic metabolic  
2 syndrome neuropathy or that you can reverse it.

3 So in animal models, it seems like, with a  
4 little bit of effort, it's been easy to prove this  
5 happens. It happens across multiple strains of  
6 mice in multiple conditions.

7 We've taken humans and done the same thing.  
8 This is an ancient study now done in 2005, but we  
9 gathered a bunch of patients at three sites with  
10 impaired glucose tolerance who also had a  
11 neuropathy. Three-quarters of them fully met  
12 criteria for metabolic syndrome, and we gave them a  
13 not-very-well deployed regimen of counseling to  
14 basically follow the diabetes prevention program,  
15 goals of weight loss and exercise.

16 In that study, we found that there was a  
17 dramatic improvement from pre-diabetic to less than  
18 pre-diabetic, better than pre-diabetic glucose, a  
19 reduction in weight for these patients. And in  
20 that setting, there was an improvement in the  
21 number of nerve fibers that reached the skin, the  
22 intraepidermal nerve fiber density for these

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1 patients.

2 We've also used this capsaicin axotomy. So

3 just to describe briefly, we place capsaicin on the

4 skin for 48 hours. That causes the nerve fibers on

5 the skin to die back from the epidermal into the

6 dermal layer. And then by doing serial skin

7 biopsies, we can count the number of their fibers

8 that were there before the patch was placed, or

9 there after to show that we denervated, and then to

10 watch over time as those nerve fibers grow back in.

11 And with that, we can calculate a regeneration rate

12 for the skin.

13 So this lets us treat humans a lot like

14 rodents, really an experimental model for looking

15 at regenerative capacity. And in this, we've taken

16 patients who have pre-diabetes, but who don't have

17 neuropathy, subjected them to a baseline

18 renevation bout, then giving them 6 months of

19 intensive diet and exercise, and repeated that

20 renevation bout in this last 3 months of that

21 period.

22 What we've seen is that doing this, we can

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1 have an impact on the regeneration rate, the number

2 of fibers that regenerate, the fraction of fibers

3 that regenerate at 30 days, and also in the rate of

4 that regeneration.

5 So here, in patients who don't yet have

6 diabetes, we can nonetheless demonstrate a defect

7 in the biology of these nerve fibers that's

8 reparable by improving their metabolism or

9 sometimes just by exercising.

10 Yes?

11 DR. ZOCHODNE: So Rob, just out of interest,

12 I'm wondering if you ever looked at the actual

13 trajectories of the original fibers, the ones that

14 disappeared with capsaicin and the ones that came

15 back. We just had this observation coming out that

16 when they die from capsaicin, it's interesting that

17 they really project back again in their original

18 trajectories, same cells.

19 DR. SINGLETON: It's really hard to see the

20 same fibers. Michael Polydefkis did nested

21 biopsies, so first 3 millimeter punch biopsy, and

22 then, like, a 5- or a 6-millimeter punch biopsy,

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1 where they try and look at the surround around the

2 place where the punch happened in order to try and

3 even look at the same fiber so much as to just see

4 the surrounding local environment.

5 I don't know how I would look at the exact

6 same fibers twice in this setting. Maybe that's

7 not even what you're asking.

8 DR. ZOCHODNE: That's true. You're right.

9 DR. SMITH: Have to do a blister presumably,

10 right, because if you do a punch, you're going to

11 be regenerating into a scar. Do a blister and

12 image it.

13 DR. SINGLETON: So with all of that, as I

14 sat here yesterday, I tried to produce some sort of

15 model for this. And this is super simplistic and

16 limited by my primitive Illustrator skills, but I

17 think it gets at some of the things that I think

18 are operative.

19 So if we imagine this progressive thing in

20 which severity gets worse as time goes by and

21 metabolic progressive injury occurs, we can define

22 points on this that are normal, and pre-diabetic,

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1 and diabetic using impaired glucose tolerance or

2 A1c.

3 Over that period, different aspects of this

4 are operant and contributing to the neuropathy that

5 we might discover. Like, if you're way out over

6 here, if we look at all comers with idiopathic

7 neuropathy, we're going to find probably that a

8 fair number of them have some genetic influence on

9 their disease. And that genetic influence

10 continues throughout this period. We don't know

11 exactly how that risk contributes, but it's still

12 there.

13 We just got finished saying, and other

14 people have said, that the influence of

15 hyperglycemia on risk and on the manifestations of

16 neuropathy grows over time as you move from the

17 pre-diabetic to the diabetic state. I could just

18 as easily labeled this -- I said time to

19 progression on the X-axis, but really this could

20 be, we'd say, from small to large fiber. Dan's not

21 listening to me. It's like skipping by from mild

22 to moderate, from reversible to irreversible, from

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1 metabolic to axonal. So as we move up this, we  
2 replace small fiber metabolic tip of the axon  
3 mitochondrial injury with microvascular injury that  
4 is less reversible.  
5       So whether it's caused by hyperglycemia or  
6 whether it just is corresponding with the increase  
7 in hyperglycemia, nonetheless, we move from a  
8 reversible to an irreversible process in this.  
9       The contribution of metabolic syndrome of  
10 other features like obesity and dyslipidemia  
11 continues through this period, but as we move from  
12 the pre-diabetic to diabetic state, as  
13 hyperglycemia becomes more operant, the  
14 contribution of this from these different aspects  
15 of metabolic syndrome grows to be more  
16 hyperglycemic and less the other features, perhaps.  
17 But at the same time, a chance that when we look at  
18 a patient with early diabetes who has neuropathy,  
19 diabetes as the primary contributor grows larger;  
20 whereas if we're further down the scale, the chance  
21 that the cause of your neuropathy is just these  
22 items of metabolic syndrome and not something else

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1 is less.  
2       We're always going to have this other  
3 potential risk contributors for neuropathy, either  
4 things that we know about like a B12 deficiency or  
5 things that we don't yet know about, that we  
6 haven't defined. And that stays maybe more or less  
7 the same. It's just that as we move further up  
8 where diabetes becomes a bigger contributor, other  
9 becomes a less important contributor by comparison.  
10       So I say that as we move up the scale or  
11 down the scale from diabetes to pre-diabetes, it's  
12 not that these things don't play an important role;  
13 it's just that it's harder to be sure that they are  
14 the primary contributor, and that has obvious  
15 implications for our taxonomy exercise.  
16       So that's a ton of talk, and we didn't even  
17 talk about taxonomy at all, which is kind of my  
18 whole goal here, because when we talk about the  
19 diagnostic criteria, first of all, there really are  
20 not authority of current diagnostic criteria, so  
21 we're free to choose what we like.  
22       My recommendation is that it is exactly the

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1 symptoms and exam findings of neuropathy and  
2 confirmatory testing as we promulgated yesterday,  
3 as we talked about for diabetic neuropathy. This  
4 is the same entity in a less severe form. We can  
5 talk about which metabolic syndrome criteria we  
6 should use to define by this. And we would say  
7 that this is in a disease that's not better  
8 described to another neuropathic disorder, but with  
9 the recognition that, in this disorder, the  
10 etiology is almost certainly multifactorial.  
11       These seem like the two most likely ATPIII  
12 criteria that we would consider. The metabolic  
13 syndrome criteria, ATPIII, is agnostic with regard  
14 to the metabolic syndrome. So any three of these  
15 makes the diagnosis, whereas the World Health  
16 Organization pre-supposes that diabetes is the most  
17 important. And probably even though ATPIII is  
18 more, I'd say, commonly used, in some ways the  
19 World Health Organization, because they recognize  
20 the primacy of hyperglycemia, might be a more apt  
21 choice for the definitional choice in our taxonomy.  
22       Then I just want to finish with these

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1 controversies.  
2       DR. BRUEHL: Excuse me. Before going into  
3 the controversies, can you go back to the actual  
4 criteria?  
5       DR. SINGLETON: Here?  
6       DR. BRUEHL: Yes.  
7       DR. SINGLETON: So my quarter slide?  
8       DR. BRUEHL: Yes. I just wanted to mention  
9 something just because it got me thinking about  
10 this. So what seems to be different about this  
11 condition compared to the other ones we're talking  
12 about is this is potentially preventative. The  
13 analogy to me seems to be like this expansion of  
14 recommendation to use statins to try to reduce  
15 cardiac risk in people who maybe have a less  
16 likelihood of developing it, but they want to  
17 capture as many people as possible and prevent as  
18 much as possible.  
19       So I think the criteria you come up with  
20 here, unlike some of the other conditions, might  
21 want to overweight sensitivity to make sure you  
22 catch these people because of the possibility of



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1 prevention. And I guess I would wonder, when you  
2 say symptoms and exam findings of neuropathy plus  
3 confirmatory testing, that sounds like a pretty  
4 high bar, and I wonder if maybe referencing back to  
5 what we came up with yesterday for the possible  
6 diabetic neuropathy might make more sense before  
7 they have to meet the full criteria.  
8 Does that make sense?  
9 DR. SINGLETON: Yes, no. I think what gets  
10 worse is not the neuropathy necessarily, but the  
11 risk factors for your neuropathy get worse over  
12 this spectrum of disease. Some patients are more  
13 susceptible to those risk factors than others.  
14 This comes back to Gordon's point that,  
15 really, what is it that we're adding by adding a  
16 confirmatory test? We're adding some surety to  
17 this, but is that really a benefit, especially as  
18 you've said, in the setting where the goal is to  
19 help practitioners to recognize this entity, and  
20 patients to recognize this entity, and to take  
21 action for it.  
22 DR. HERRMANN: On the diagnostic criteria,

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1 just two thoughts. The first is, not to get too  
2 specific about the systems, and the exam, and the  
3 confirmatory test, but do you think the range of  
4 neuropathy phenotype of metabolic syndrome equals  
5 the range of neuropathy phenotype of distal  
6 symmetric polyneuropathy? So in other words, are  
7 there exclusionary caveats?  
8 In some of the early literature, from you,  
9 Gordon, and others, pain was a big feature,  
10 painless less so, and large fiber dysfunction was  
11 much less common. But of course, how much large  
12 fiber dysfunction would be exclusionary. Does this  
13 have to be a small fiber or pre-dominantly small  
14 fiber phenotype? I'd ask that one question. And  
15 then the other point gets to terminology.  
16 I think what you've shown here, and what the  
17 literature seems to show, but I may be incorrect,  
18 is as a neurologist, when I hear the term pre-  
19 diabetes -- I understand the pre-diabetic milieu  
20 with metabolic syndrome and all that, but when I  
21 hear the term "pre-diabetes," I still think in  
22 terms of impaired fasting glucose or IGT. And the

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1 evidence you show is that if you just have that  
2 impaired fasting glucose and IGT, that alone absent  
3 some other features of the metabolic syndrome, is  
4 not clear that that is enough glucose dysmetabolism  
5 to be etiologically linked to the syndrome.  
6 So maybe not using the word "pre-diabetic  
7 neuropathy," saying that it's rather using  
8 metabolic syndrome. And if you want to use pre-  
9 diabetes, just say the pre-diabetic milieu, because  
10 if you just use pre-diabetic neuropathy, then I  
11 think it could lead to a lot of overdiagnosis and  
12 not thinking about other possibilities; I don't  
13 know; I just throw those two elements.  
14 DR. SINGLETON: Yes. I think just to touch  
15 on a lot of the things you just said, some of them  
16 are on this slide. We've said for a long time that  
17 pre-diabetes, hyperglycemia in that pre-diabetic  
18 state is just a marker for metabolic syndrome. So  
19 it's really the metabolic syndrome and not the  
20 hyperglycemia itself that may be the driver,  
21 especially for small fiber nerve injury.  
22 I think one of the controversies -- not

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1 controversies, but one of the things we should  
2 discuss is should we either give more weight to  
3 some metabolic syndrome criteria than others in our  
4 diagnostic criteria. Should we call out specific  
5 metabolic syndrome features like obesity? Can  
6 obesity itself be cause for neuropathy? I think  
7 there's not enough data yet to suggest that, but  
8 you see where I'm going with this.  
9 Then back to your point, is there a severity  
10 of neuropathy that's too severe to be this  
11 disorder? I think there is. When we had this  
12 discussion yesterday about what constitutes severe  
13 neuropathy from a standpoint of our taxonomy, I say  
14 anyone who falls into that category in the pre-  
15 diabetic metabolic syndrome period is either super  
16 unlucky with their genetics or has an identifiable  
17 other disease that we should be looking hard for.  
18 So down here at the bottom, because the  
19 diagnostic assurance of this is less than for  
20 diabetic neuropathy, is it incumbent on  
21 practitioners and us to look harder for alternate  
22 causes of neuropathy in the pre-diabetic period

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1 than we do in the diabetic period? And if so, what  
2 more should we do?  
3 I think one thing I can imagine is that in  
4 the coming world of \$50 whole genome genetic  
5 testing, we do a genetic panel for every one of  
6 these patients. We look for known monogenetic  
7 causes of neuropathy to look for pharm  
8 [indiscernible] that put people at greater risk.  
9 And that's not what I mean at the very bottom here,  
10 which we should, I think, as part of our  
11 consortium, mount some sort of phenotype/genotype,  
12 sort of registry, in order to look for multi-  
13 genetic influences in a more systematic way.  
14 Yes, Gordon?  
15 DR. SMITH: Yes. The challenge here is  
16 attribution of pathophysiology. In Alabama, which  
17 is, I'd like to say, my new favorite state --  
18 (Laughter.)  
19 DR. GORDON: -- half of people there are  
20 obese and have metabolic syndrome. So we expect  
21 that 50 percent of anyone we pull off the street,  
22 whether or not they have neuropathy, are going to

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1 have metabolic syndrome.  
2 So the attribution of cause in C-SPAN, which  
3 is Rick Barron's term -- and actually, the reason  
4 I've used it is because we could create a fancy  
5 name for a trial called TOPSPIN that had nothing to  
6 do with hiding from metabolic syndrome. And in  
7 fact, the DSMB-IV forced us to add metabolic  
8 syndrome to the trial's name. It's really an  
9 amalgam of different risks, so there's the whole  
10 voltage-gated sodium channel narrative where there  
11 are conflicting data from different groups about  
12 the roles of these and if not causing small fiber-  
13 predominant C-SPAN, at least driving risk of C-  
14 SPAN.  
15 I think the likelihood that we're going to  
16 find monogenetic causes in idiopathic neuropathy is  
17 relatively low. I mean, there's good data using  
18 next-generation panels or whole exome for a  
19 neuropathy phenotype and the yield, and in a  
20 setting where you expect a high yield is still  
21 something like 17 or 18 percent.  
22 But I think it's really the boundary of risk

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1 versus causality, and I think the relevance of this  
2 axis of chaos, which I think is more chaotic than  
3 the others, is one that we're living through right  
4 now, trying to organize or organizing a trial for  
5 this in some sort of coherent way because it's  
6 inevitable that there are going to be messy  
7 boundaries around this.  
8 Then I question the primacy of pre-diabetes  
9 and think either the syndrome or obesity is the way  
10 to go if one had to pick.  
11 DR. FREEMAN: To me, I think there may be  
12 three issues that I'd like us to flesh out, and  
13 Dan's going to do this once I finish. The first  
14 is, what are we going to call this? And the second  
15 is are we going to -- and whatever we call it is  
16 going to depend on the second point -- are we going  
17 to say that this is neuropathy associated with, or  
18 due to, or in the setting of, or are we going to  
19 say that, at this point, we don't know, but these  
20 are the criteria were we to do a study where you  
21 two submit an NIH grant; this is what I'm going to  
22 study; these potential factors of obesity,

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1 hyperlipidemia, and you break them down.  
2 Then I think it would be good, the point  
3 David Herrmann made, to be somewhat restricted,  
4 because I think there's no doubt that the extremes,  
5 the severe neuropathy, is not part of this picture  
6 such as it exists.  
7 Somehow or other -- and I was thinking  
8 somewhat similarly to Gordon -- there are 35  
9 million Homer -- Homer Simpson, is he?  
10 DR. SINGLETON: Homer Simpsons, yes.  
11 DR. FREEMAN: -- yes, in the country, yes.  
12 And there's a lot of peripheral neuropathy as well.  
13 DR. ZIEGLER: I think it would be very, very  
14 premature to call this a metabolic syndrome  
15 neuropathy as long as we don't know which  
16 components contribute to that kind of neuropathy.  
17 So all I can say is that, from the epidemiological  
18 standpoint, factors like obesity and dyslipidemia,  
19 these are the two factors you're talking about, has  
20 there ever been any epidemiological studies showing  
21 that, really, in that population base, in those  
22 patients who are obese compared to lean patients,

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1 the prevalence of polyneuropathies is increased?  
2 The same for high triglycerides and low HDL, I'm  
3 not aware of any appropriate studies.  
4       What I'm aware of is -- and we contributed  
5 to this -- that there's an increased prevalence in  
6 pre-diabetes of polyneuropathy, except from Peter  
7 Dyck's data, which you didn't show, but we have to  
8 acknowledge that that group did not find a higher  
9 prevalence.  
10       What we see is clearly that especially if  
11 you have the combined abnormality, IGT and IFG, the  
12 prevalence is as high as in newly detected diabetes  
13 or even diabetes, meaning that it looks like the  
14 hyperglycemia or even these great swings of  
15 hyperglycemia would contribute to the development  
16 of neuropathy in people who are prone to this,  
17 maybe genetic factors also contributing or  
18 whatever.  
19       Has this ever been convincingly shown for  
20 dyslipidemia, for hypertension, or for obesity? I  
21 think before we call this metabolic syndrome  
22 neuropathy, this needs to be done. Which component

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1 is contributing?  
2       For example, we could say there is an age-  
3 induced neuropathy because age is a clear risk  
4 factor of polyneuropathy. Why don't we do that?  
5 Is there an age neuropathy? Has this been  
6 mentioned in our discussions? I'm not aware of  
7 that. So as long as I don't know this, these are  
8 risk factors associated with polyneuropathy, and  
9 that's basically it, unless we have any other  
10 convincing data.  
11       But this is interesting, and I will go back  
12 to our current database and we will have a look at  
13 that, I think, and maybe we will find something.  
14 So far, we were mostly interested in the glucose,  
15 and it looks like the glucose is important in  
16 causing -- of course, this fits to the continuum  
17 from pre-diabetes to diabetes, so there is a sound  
18 pathophysiological basis for that. I'm not sure  
19 whether the pathophysiological basis is really  
20 there for the other components. And if you speak  
21 about hypertension as an important component of the  
22 metabolic syndrome, and now given the lower cutoffs

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1 now, which have been proposed, many people have, so  
2 is there a hypertensive neuropathy? I'm not sure  
3 about it. So I think we need some more clear-cut  
4 view on the individual components of the metabolic  
5 syndrome.  
6       DR. SINGLETON: I kind of liked Roy's  
7 statement of neuropathy associated with metabolic  
8 syndrome, which is kind of agnostic. It doesn't  
9 say we think it's caused by, we think it's  
10 associated with. I think that's a fairer  
11 statement. And I think it's agnostic with regard  
12 to which components are the most powerful.  
13       I totally agree with you, Dan, that we need  
14 a good study. Well, we have studies that have had  
15 excellent epidemiology on the metabolic syndrome  
16 side, but not good phenotyping on the neuropathy  
17 side, so someone needs to combine those two pieces.  
18       I think, if we did that, we would find what  
19 you've said and what Peter Dyck has said, that if  
20 we look carefully, we would discover large fiber  
21 neuropathy, asymptomatic large fiber neuropathy in  
22 a greater proportion of patients than we expect.

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1       DR. PELTIER: I think that you do have some  
2 epidemiologic data if you look to the DCCT studies.  
3 So if you look at factors other than glucose, what  
4 pulls out of the DCCT study as far as risk factors  
5 for neuropathy? Hypertension, high targeted  
6 cholesterol, obesity, smoking obviously, so all  
7 those factors --  
8       DR. TESFAYE: Insulin administration.  
9       DR. PELTIER: -- of metabolic syndrome are  
10 present in the DCCT study as additional risk  
11 factors for neuropathy. So I don't think it's that  
12 far to jump to say that those factors are  
13 associated in these patients with less  
14 hyperglycemia.  
15       DR. SINGLETON: I'm sorry. Vera is next.  
16       DR. BRIL: Thank you. I was just going to  
17 say that, even in people without impaired glucose  
18 tolerance, even within the normal range of A1c, you  
19 can see increasing burden abnormalities on nerve  
20 activity and neuropathy within the normal range,  
21 which leads me to think that we set the bar for  
22 diabetes too high and that the A1c should be even

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1 lower.  
2 This might then undermine some of this  
3 because many of your patients may well be in the  
4 normal range but still in the upper normal range of  
5 A1cs without having abnormalities. So if you can  
6 stratify already within the normal A1c range, your  
7 burden of neuropathy, then maybe we have to do with  
8 diabetes what's being done with hypertension.  
9 DR. RUSSELL: So Robin, in partial answer to  
10 Dan's question here and perhaps to tell you a  
11 little bit about the metabolic syndrome and  
12 autonomic neuropathy, we have the data here. And  
13 the two things that actually drive autonomic  
14 neuropathy in metabolic syndrome -- this is using  
15 the ATPIII criteria, the same one you used -- the  
16 highest is with the diastolic blood pressure and  
17 the second is cholesterol, total cholesterol.  
18 So in fact, to tell you how dismal glucose  
19 is, fasting glucose has an odds ratio of 0.7, the  
20 2-hour glucose 0.7, and vicosylated hemoglobin,  
21 1.8. So basically the glucose part of it really is  
22 irrelevant.

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1 DR. SINGLETON: How many patients are in  
2 that?  
3 DR. BRIL: This is about 140, I think.  
4 DR. POP-BUSUI: [Inaudible – off mic] --  
5 and autonomic function, and glucose, and it was  
6 related to impaired glucose tolerance and IGT.  
7 DR. SINGLETON: Did they look at autonomic  
8 function? Was that a cardiac autonomic function?  
9 DR. POP-BUSUI: Yes. They looked at the  
10 EKGs.  
11 DR. SINGLETON: B to B?  
12 DR. POP-BUSUI: Yes, some measures.  
13 Obviously, there was not so comprehensively -- I  
14 know that, right now, they are looking particularly  
15 at the neuropathy data, so they are doing the  
16 analysis to see.  
17 DR. SINGLETON: It's unfortunate. We tried  
18 to convince large studies to include more  
19 sophisticated measures of neuropathy a long time  
20 ago, and they didn't do it. And so now we have,  
21 like I said, fantastic metabolic syndrome, detailed  
22 metabolic syndrome, epidemiological data, and a lot

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1 of information about other features that people  
2 previously identified, like retinal disease, but  
3 lousy phenotypic data about peripheral neuropathy.  
4 DR. ZIEGLER: I think we should be careful  
5 here. We shouldn't lump together peripheral  
6 neuropathy and heart rate or I believe cardiac  
7 autonomic because if you take hypertension, for  
8 example, the role of hypertension may be very much  
9 different in autonomic dysfunction versus  
10 peripheral neuropathy. We know that hypertension  
11 may lead to reduced parasympathetic sensitivity and so  
12 on, and it also may reduce heart rate variability  
13 leading to cardiac autonomic dysfunction. And this  
14 may not be the same mechanisms or this may not be  
15 involved in peripheral neuropathy at all. So we  
16 should separate this.  
17 But nonetheless, we clearly showed that,  
18 even more clearly for autonomic dysfunction, there  
19 is a clear gradient with an increasing degree of  
20 glucose intolerance. So in that dose, again, we've  
21 combined IGT/IFG, had virtually similar prevalence  
22 of abnormalities in heart rate variability as those

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1 recently diagnosed with diabetes and not much lower  
2 compared to the known diabetes population.  
3 So again here, even more clearly because  
4 this is an objective measurement, this is really  
5 more straightforward than the crude MNSI we're  
6 using for peripheral neuropathy. So this convinces  
7 me much more about the role of subtle glucose  
8 swings in the induction of the neuropathic process,  
9 in this case in autonomic nerves.  
10 DR. TESFAYE: But if it was just  
11 glucose -- I mean, it's Dan's finding --  
12 DR. ZIEGLER: I'm not saying it's just the  
13 glucose.  
14 DR. TESFAYE: -- hang on -- IFG and IGT  
15 having a higher prevalence of peripheral neuropathy  
16 than newly diagnosed diabetes. If it is just a  
17 glucose issue, why would this group have a higher  
18 rate? I think there is an interaction in  
19 hypertension to vascular risk factors that Amanda  
20 mentioned just a few minutes ago, are interacting.  
21 There is inflammation. And you recently showed  
22 that inflammation in type 2 diabetes may be a risk

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1 factor for neuropathy.  
2 I mean, anecdotally -- and this is not my  
3 area of expertise -- but patients that are obese  
4 and who have high blood pressure, high cholesterol,  
5 and are bordering towards diabetes, have a high  
6 prevalence of neuropathy than an equivalent group  
7 of patients who do not have these risk factors. Am  
8 I right or wrong?  
9 DR. ZIEGLER: I don't think there is enough  
10 data to support that notion. There is enough data  
11 regarding glucose, but not for the other  
12 components. And that's what I was asking for, to  
13 show convincingly that those individual components  
14 are not only risk factors for neuropathy, but are  
15 really, really involved causatively.  
16 DR. SINGLETON: I think, Dan, inclusively  
17 convincing data about that may be hard to come by  
18 because this is a multifactorial entity. So I  
19 think it would be a mistake for us to -- I think if  
20 as a group, we think that there is, I don't know,  
21 better evidence than not, that these features play  
22 some contributory role, I think it would be wise

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1 for us to claim that territory by saying something  
2 about metabolic syndrome in the title, for  
3 instance.  
4 I again come back to Roy's suggestion that  
5 this is metabolic syndrome-associated  
6 polyneuropathy. Recognizing that there is still  
7 work to be done here, I think part of the goal  
8 should be to encourage that work, and we do that by  
9 claiming that association.  
10 DR. SMITH: It facilitates the work, and I  
11 think one person's risk factor is another person's  
12 cause, isn't it? I think there's a spectrum there,  
13 and I agree with the concerns you express, and I  
14 think there's opportunity for better epidemiology,  
15 yet there's a variety of data ranging from animal  
16 models to epidemiology.  
17 Rob referenced the study we're doing in  
18 bariatric surgery. I can tell you that about  
19 amongst 100 bariatric surgery candidates who don't  
20 have diabetes, there's a very high prevalence of  
21 subtle findings of neuropathy. They have low  
22 intraepidermal nerve fiber density. And when we

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1 look at nerve regenerative capacity in people who  
2 undergo bariatric surgery, it's equally reduced  
3 compared to what Michael has reported in controls  
4 between diabetic and non-diabetic.  
5 In the study that Rob pointed out, in  
6 regenerative capacity improvement after exercise,  
7 half of those patients didn't have diabetes; half  
8 did. So I think there's an amalgam of evidence  
9 that suggests that there's at least a risk  
10 relationship. And I think the reason it's time to  
11 create criteria around it -- and this is in my own  
12 personal interest -- is we're designing a trial  
13 around this. Now we've designed a trial, and we've  
14 just kind of made up our criteria. I think our  
15 understanding of this is not only going to be  
16 facilitated by good epidemiology, but essentially  
17 risk factor modification studies. And in order to  
18 do those, we need to have some taxonomy to guide us  
19 so that the next trial and the next trial after  
20 that are organized in a similar fashion.  
21 DR. FREEMAN: That's exactly the point I  
22 wanted to make. I think this has been a terrific

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1 discussion, but I want to now bring us back to the  
2 mission, which is to give -- when you guys write  
3 your grants and when others do that or when some  
4 pharma wants to study this as the earliest diabetic  
5 neuropathy, if that exists, that we can say these  
6 are the criteria that we suggest.  
7 So I'm going to propose -- and I want to get  
8 some feedback on this -- that somehow or other, you  
9 incorporate in the name the association; two, that  
10 we say quite clearly that the evidence at this  
11 point does not support causality, but supports  
12 association.  
13 I'm thinking of every manuscript as having a  
14 background, and the background to this one is  
15 really important, and that in the background, you  
16 actually lay out the evidence such as it exists for  
17 causality, higher probability.  
18 DR. SINGLETON: You can see I spent 80  
19 percent of my time talking about this. Yes.  
20 DR. FREEMAN: I know, and I think that's the  
21 background. And then I think you need to define  
22 the criteria that you think and this group felt it

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1 was appropriate to use these criteria for the  
2 metabolic syndrome, but we also suggest, if that's  
3 what we do suggest, that these features can be  
4 alone or in combination and cutoffs for  
5 hypolipidemia, for hypotension, for obesity.  
6 So that's the one we're looking at, the  
7 setting, and then secondarily, this is the  
8 neuropathy. And I think we need to come up with  
9 something prescriptive taken from yesterday's talk  
10 and what we will discuss this afternoon, what we  
11 think is the neuropathy that is typically  
12 associated with this, but the variants that exist.  
13 So I wonder if we can just discuss this very  
14 briefly -- and I'm going to call, as I did last  
15 time; we won't have the panel, but I'll call on  
16 panelists at the end -- what disagreement is there  
17 with this thesis.  
18 DR. SINGLETON: Rayaz, do you have  
19 something?  
20 DR. MALIK: So Roy, I think it is important  
21 that we don't try to invent new criteria for  
22 cutoffs because I think the message that we want to

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1 send out to people is that some components of  
2 metabolic syndrome, as is recognized by the medical  
3 fraternity, is linked. Because if we start  
4 creating new, I think that will muddy the waters.  
5 DR. SINGLETON: I agree with that. Yes.  
6 Would you go with ATPIII? Would you go with World  
7 Health Organization? Do you have a preference?  
8 DR. MALIK: Probably ATPIII, I think, is  
9 better because it's more weighted away from the  
10 glucose, because I think WHO is very much weighted  
11 to the glucose. And I think one of the issues with  
12 that is that the original cutoffs were based on  
13 retinopathy as opposed to neuropathy, which I think  
14 occurs probably earlier. So ATPIII, I think, would  
15 be better.  
16 DR. SINGLETON: I am certainly happy with  
17 that idea, that we would be more agnostic in the  
18 way ATPIII is agnostic about those features.  
19 DR. RUSSELL: The other criteria is the  
20 International Diabetes Federation. Does anyone  
21 have any strong views for or against that?  
22 (Crosstalk.)

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1 DR. RUSSELL: Very good.  
2 DR. MALIK: So I guess IDF is more  
3 international and takes into account ethnicity as  
4 well. So that's the only other thing that we need  
5 to be aware of, if you're going to talk across the  
6 world, because their cutoffs for waist  
7 circumference are different for different ethnicity  
8 groups.  
9 DR. POP-BUSUI: [Inaudible – off mic].  
10 DR. MALIK: Are they? Okay. That's fine.  
11 DR. SMITH: Is it necessary to select a  
12 criteria? Because I'm just thinking, what happens  
13 when the ATPIV comes out? Are we going to have to  
14 get back together?  
15 MALE VOICE: Say what we're using for now  
16 and then we --  
17 DR. SMITH: Yes, yes, no. I get it. But  
18 I'm just throwing out the idea as to how important  
19 is it to tie ourselves to one.  
20 DR. SINGLETON: I just worry, if we didn't,  
21 then people would immediately say, which one.  
22 DR. POP-BUSUI: But I still think that this

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1 is going to be also a fluid definition because, as  
2 long as we accumulate --  
3 DR. SINGLETON: That's my concern.  
4 DR. POP-BUSUI: -- more evidence, whether  
5 one or other of these risk factors may be weighing  
6 more towards the risk, then we might change it.  
7 But for the moment, we do not have.  
8 DR. FREEMAN: That's why I suggested the  
9 possibility of looking at the individual factors,  
10 and I proposed cutoffs, because these may differ.  
11 I do think we should put a stake in the ground and  
12 say this is what we think at this point in time  
13 because obviously things are going to change. The  
14 hemoglobin A1cs that we just said previously will  
15 change. But I think we need to put our stake in  
16 the ground, but I think of course we'll change.  
17 DR. POP-BUSUI: Because the risk for  
18 complication is not only for neuropathy at much  
19 lower level than retinopathy. It's also for  
20 cardiovascular disease and we know that, at least  
21 at this continuum, starting actually as early as  
22 5 percent A1c.

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1 DR. HERRMANN: I think you had termed this,  
2 but I think it might have to be -- for the  
3 disorders we've spoken about, implicit has been,  
4 although we haven't listed them, the exclusionary  
5 criteria. But for this one in particular, in terms  
6 of being granular about defining the metabolic  
7 syndrome criteria and the neuropathy phenotype, I  
8 think particularly as investigators will be using  
9 this for research studies, you may want to list out  
10 in more granular detail what the exclusionary  
11 criteria are, including things like foot  
12 deformities. Just at least think about that, so  
13 that you increase the likelihood that what you're  
14 dealing with is a metabolic syndrome associated  
15 neuropathy.  
16 DR. SINGLETON: I think that's something we  
17 can imagine of severity of neuropathy, in which we  
18 think it's very unlikely that you have this as the  
19 sole cause. I think that's the kind of statement I  
20 would make about it.  
21 DR. HERRMANN: Then other laboratory tests,  
22 yes.

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1 DR. BENNETT: In terms of other tests,  
2 though, having an interest in genetics, I would  
3 just keep genetics out of it because you have  
4 exactly the same issue with attribution, and many  
5 of the variants that were described as pathogenic  
6 are probably risk variants. So I think you're just  
7 muddying the water further if you bring genetics  
8 into it.  
9 DR. SINGLETON: You're probably right. I  
10 bring it up because I think that it plays an  
11 important role here, and it's something we should  
12 study.  
13 DR. BENNETT: It's a great issue for  
14 research.  
15 DR. SINGLETON: Yes.  
16 DR. BENNETT: But I think it's really going  
17 to muddy the issue with diagnostic criteria at this  
18 stage.  
19 DR. FREEMAN: So what I'd like to do is  
20 [inaudible – off mic] -- I think this is far more  
21 effective.  
22 DR. SINGLETON: It's a bigger panel.

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1 DR. FREEMAN: So just [inaudible – off mic].  
2 DR. WRIGHT: Rob, it's an opportunity to  
3 include activity as a factor. I feel like this  
4 would be a missed opportunity if that's not  
5 addressed as well. I think the animal research is  
6 really going to provide great evidence that  
7 activity, inherent activity, is a big modifier.  
8 DR. SINGLETON: But you'd say, like, in the  
9 setting of decreased activity, this is more likely,  
10 something like that.  
11 DR. WRIGHT: Prevalence would be high.  
12 DR. SINGLETON: The taxonomy so far isn't  
13 really addressing the treatment so much as the  
14 diagnostic criterion, so I think that would be very  
15 reasonable to say that's a pre-supposing, pre-  
16 disposing factor, behavioral factor at the very  
17 least.  
18 DR. SMITH: In domain 3, right?  
19 DR. ZOCHODNE: So Rob, this isn't a chair-  
20 type question, but did you say you measured insulin  
21 levels and had been looking at those as a marker of  
22 insulin resistance?

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1 DR. SINGLETON: No, not really. I mean, in  
2 what study? I guess that's the question.  
3 DR. ZOCHODNE: I think it would be pretty  
4 interesting.  
5 DR. SINGLETON: We are doing it now -- we  
6 have done it in our bariatric surgery cohort, and  
7 we've done it in ADAPT. We're doing it in ADAPT.  
8 We haven't said we're doing it in TOPSPIN, right?  
9 DR. SMITH: We are.  
10 DR. SINGLETON: We are doing insulin levels?  
11 DR. SMITH: Yes  
12 DR. SINGLETON: Excellent.  
13 DR. SMITH: Yes.  
14 DR. FREEMAN: [Inaudible – off mic].  
15 DR. ZIEGLER: I said it all. I just would  
16 add that I would never use the term "metabolic  
17 syndrome" in a patient report, so all I would do is  
18 to name the individual components and see whether  
19 those risk factors are present or not of the  
20 diagnoses.  
21 DR. FREEMAN: Good. So now is the time  
22 [inaudible – off mic].

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1 (Applause.)  
2 DR. FREEMAN: [Inaudible – off mic].  
3 (Whereupon, at 10:13 a.m., a brief recess  
4 was taken.)  
5 DR. FREEMAN: We're ready to begin. This  
6 has been very productive. We're almost back on  
7 schedule. Some housekeeping issues. Sign in if  
8 you haven't signed in. Check out if you haven't  
9 checked out. Departures, consider sharing taxis to  
10 the airport. I do want to be clear that everybody  
11 understands the reimbursement, and that you will  
12 receive a stipend, and no receipts, no, you're on  
13 your own. That works out obviously very well  
14 organizationally and should work out for most  
15 people.  
16 Then finally, emphasized by the  
17 stenographer, again, so that everybody knows, every  
18 word that you mutter is being taken down by the  
19 stenographer unless you don't talk into the  
20 microphone. She can only hear if you talk into the  
21 microphone.  
22 So if you have something to say that you

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1 don't want taken don't, don't talk in the  
2 microphone; otherwise the microphone.  
3 Vera, I think you're up.  
4 So I just want to mention I hear one or two  
5 people may be leaving earlier. The afternoon  
6 session actually is quite important because we  
7 flesh out anything, define the research agenda,  
8 talk about next steps, and discuss the manuscripts.  
9 And maybe we should do the manuscript discussion  
10 once Vera finishes because that's such a critical  
11 point.  
12 Presentation – Vera Bril  
13 DR BRIL: Good morning, and being the, what  
14 is it, penultimate talk -- r I don't know, the last  
15 talk, the final talk -- it's not going to be too  
16 long. And I found this, I have to tell you, very  
17 difficult to do. It sounds so simple, reminds me  
18 of my fellowship exams.  
19 In those days, we had four long-answer  
20 questions, each worth 25 marks. And we had to have  
21 80 percent or we'd fail. And one of the hardest  
22 questions for me to answer was, how do you treat

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1 stroke in a 48-year-old man? And I could have done  
2 that like that in my first year, but by the time I  
3 finished, it was hard. And here too, is kind of  
4 hard, but let me get on with it.  
5 Those are disclosures. I've come from this  
6 clinic. And let's talk about mononeuropathies, and  
7 I'm very embarrassed to say this to this audience,  
8 but I just thought I'd throw it up there.  
9 Acute or the result of compressive or  
10 entrapment from distortion within a canal or  
11 something like that or repetitive external  
12 pressure, you have motor findings and muscle  
13 supplied by the nerve distal to the lesion.  
14 Sensory findings are less reliable, and you confirm  
15 the mononeuropathy nature by nerve conductions and  
16 EMG, really simple, straightforward. In the  
17 differential diagnosis of the different forms of  
18 focal diabetic neuropathies are median, ulnar,  
19 radial, and peroneal, and we always think the  
20 patients with diabetes are pre-disposed to these  
21 things.  
22 So let's talk about the peroneal nerve -- I

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1 hope you can see it; I see the print is a little  
2 small -- because I thought this would be the  
3 easiest, fastest, and least difficult to do, and  
4 one with the fewest papers.  
5 So we don't know the prevalence in the  
6 general population or the incidence. I don't know  
7 any of that epidemiological data for peroneal  
8 neuropathies. I couldn't even tell you in my own  
9 clinic how frequently I see it; I don't track it,  
10 never mind in diabetes patients, but just in  
11 general patients.  
12 It can be caused by trauma to the knee or  
13 hip, and there are so many traumatic injuries,  
14 compression at the knee if you're kneeling or  
15 surgery, if in Japan you're sitting with legs  
16 crossed. So they won't even do peroneal nerve  
17 conductions in neuropathy studies in Japan because  
18 there's so many that are abnormal; and intrinsic  
19 lesions from cysts or ganglia.  
20 These are all there, fairly common. It's  
21 not rare to see a peroneal neuropathy. But looking  
22 at those in diabetes, there are two small case



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1 series, one from 1952 with Garland and one from  
2 Stamboulis in 2005. The co-existence of peroneal  
3 nerve palsy, those who had diabetes, in the most  
4 recent study was at about 30 percent of patients  
5 with peroneal nerve palsy.  
6 So this was a retrospective review, and  
7 that's as good as the evidence gets, of 642  
8 patients seen in that lab between 1994 and 1999,  
9 and 7 of 23 who had peroneal nerve palsies also had  
10 diabetes. So that's pretty weak evidence if you  
11 think about it, one lab, retrospective review.  
12 Often, these get better. They're  
13 spontaneous. They get better in diabetes or non-  
14 diabetes. If they don't get better, you usually  
15 send them to surgery for exploration and to look,  
16 or you image and you look for different things like  
17 cysts and ganglia. The management is pretty  
18 straightforward.  
19 I forgot about the decompressive surgery  
20 group, the surgeons who are cutting the nerves at  
21 the ankles -- I mean cutting the entrapment sites  
22 at the ankles. And we should exactly think about

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1 it a bit, I thought, so I'm throwing it up here.  
2 So what about entrapment of the deep  
3 peroneal nerve at the ankle? It can present as  
4 pain on the dorsum of the foot and sensory deficits  
5 in the web area between toes 1 and 2, so like a  
6 mononeuropathy. And there have been observational  
7 studies on releasing the peroneal nerve at the  
8 ankle as a treatment for diabetic neuropathy.  
9 Of course, they don't just release the  
10 peroneal nerve. They release the posterior tibial  
11 nerve, and the peroneal nerve, and I think there's  
12 another. There's about three nerves on each foot  
13 that they release. And the studies are based on  
14 Tinel signs sites of potential entrapment, a  
15 surgeon tapping on the nerve, getting a Tinel sign.  
16 They don't do nerve conductions. And in the  
17 studies where they have done this, they operate on  
18 one foot and use the contralateral foot as their  
19 control.  
20 I put this out because it's being done.  
21 There is even a surgeon now in northern Ontario who  
22 is doing this. The literature reviews of these

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1 procedures by the American Academy in 2006 and a  
2 more recent review by Tannemaat in 2016 said that  
3 there was no definitive proof.  
4 I put it here because, if you're thinking  
5 about lower limb peripheral nerve entrapments, we  
6 have to be aware of an entire population of  
7 physicians who believe this exists and that they  
8 can treat painful diabetic neuropathy particularly  
9 by surgery. That's what I want to say about the  
10 peroneal nerve.  
11 Would anyone like to comment at this point  
12 or should I wait until after Roy?  
13 DR. GIBBONS: So I just want to throw in a  
14 comment. Thank you for raising this. This is so  
15 critical because you're right. We're sort of a  
16 little bit of head in the sand saying we know it  
17 doesn't really exist as a truth. But I think the  
18 question of belief by the physicians is critical  
19 because I'm not entirely sure they even believe it.  
20 Some of them are evangelical about it.  
21 But this is a cash business. I have seen it  
22 multiple times now in airlines on the in-seat

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1 magazine advertisement now in this, compressive  
2 neuropathy surgery. It's a cash business. They do  
3 extremely well doing this. And they think maybe  
4 their patients get better, but they're happy to do  
5 them for them.  
6 DR. HARATI: But do the patients get better?  
7 DR. BRIL: Let me just answer this for a  
8 second. In painful diabetic neuropathy studies, we  
9 know the placebo response rate is a good 40  
10 percent. So I think if someone presented with  
11 isolated pain on the dorsum of their foot and  
12 numbness in the web space, perhaps they have an  
13 entrapment. Perhaps they would benefit from  
14 release. So it's not impossible.  
15 Tarsal tunnel syndrome, in my experience, in  
16 non-diabetes patients, is exceedingly rare. I  
17 don't know why, but it is exceedingly rare. And  
18 the patients I've sent for release haven't had very  
19 good outcomes for some reason. But we need to  
20 think about this.  
21 DR. GIBBONS: So the local  
22 advertisements -- and Roy, you may have seen this

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1 as well -- in our own newspapers, they advertise as  
2 85 to 95 percent success rate in the newspaper. I  
3 have never seen a patient get better ever.  
4 DR. HARATI: Patients report to the surgeons  
5 that they are better, but the improvement doesn't  
6 last long enough, so when they come and see us, we  
7 don't see any improvement.  
8 DR. RUSSELL: Vera, there is a rigorous  
9 Cochrane review of this that was sent with the  
10 first by Chowdhry [ph], that actually looks at all  
11 the research done, including all the papers  
12 published by surgeons. And actually, most of that  
13 is based on pretty broad sensory testing. So that  
14 may form a basis for your decision.  
15 Now, I know the surgeons are trying to  
16 create a rebuttal to that Cochrane review, but so  
17 far, I haven't seen a meaningful response from  
18 them.  
19 DR. BRIL: I wonder if that's the second.  
20 Doug?  
21 DR. ZOCHODNE: There is this weird clinical  
22 trial that's been completed that they're really

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1 touting. I don't know if you mentioned this  
2 already, but we're going to have to look really  
3 carefully at that and see what they did. But  
4 they're congratulating themselves on solving the  
5 problem of diabetic neuropathy.  
6 DR. BRIL: Any other? Sorry.  
7 DR. HERRMANN: Yes. I think conceptually,  
8 there's a difference if you have a mononeuropathy  
9 that you believe to be compressive and you do  
10 studies on decompressing that as opposed to the  
11 Dellon procedure, where they do multiple  
12 decompression to treat underlying distal symmetric  
13 polyneuropathy.  
14 DR. ZOCHODNE: That's what the trial is on.  
15 DR. BRIL: In their view, that's not  
16 polyneuropathy; it's multiple compressions in the  
17 foot. So just a different view, way of looking at  
18 the same disease.  
19 DR. FREEMAN: Do you think, Vera, that you  
20 can come up with firm diagnostic criteria for those  
21 patients who we think genuinely have, let's just  
22 pick, anterior tarsal tunnel syndrome? And that

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1 will include both symptoms, clinical exam, and  
2 neurophysiological criteria. And I know these  
3 exist and the AANEM has those.  
4 DR. BRIL: They exist. No, I do think,  
5 though, yes.  
6 DR. FREEMAN: The same thing for peroneal  
7 neuropathy -- and do you have those?  
8 DR. BRIL: I didn't bring them with me.  
9 DR. FREEMAN: You didn't bring those, but  
10 that would be the aim. And there's no need to  
11 reinvent the wheel because I know the AANEM has  
12 done that, and in the Preston book, I think it's  
13 covered very nicely. But that's what we want.  
14 DR. BRIL: So there would be a role for  
15 prospective studies in this, looking forward.  
16 DR. FREEMAN: Absolutely. And that's the  
17 goal --  
18 DR. BRIL: There are none.  
19 DR. FREEMAN: -- really to do exactly that,  
20 to provide the framework for future studies for  
21 these kinds of conditions.  
22 DR. MALIK: So Vera, I had reviewed recently

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1 a study that was randomized as it can be, but they  
2 had matching groups from the Netherlands that  
3 showed no benefit. So I'm aware of one.  
4 DR. BRIL: Beautiful, yes. Has it appeared  
5 already or reviewed it?  
6 DR. MALIK: I'm not sure. It's about three  
7 months ago that I reviewed it.  
8 DR. BRIL: Right. I didn't see it, but  
9 maybe it's out.  
10 So the ulnar nerve, we know, is compressed  
11 at the retro epicondylar groove and at the  
12 aponeurotic arcade that joins the two heads of the  
13 flexor carpi ulnaris, or at the arcade of Struthers  
14 more proximally, or more distally, where it exits  
15 the flexor carpi ulnaris.  
16 We know that repeated trauma at the  
17 retro epicondylar groove, or pressure in surgery if  
18 the arm's immobilized, or if there's an accessory  
19 anconeus muscle, or spontaneous hemorrhage, or  
20 gout, or low BMI, losing weight, all pre-disposed  
21 to the development of ulnar mononeuropathy.  
22 Mondelli wrote in 2005 of a standardized yearly

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1 incidence of 20.9 per 100,000.  
2 DR. FREEMAN: In diabetic patients?  
3 DR. BRIL: No. This is in the general. So  
4 now, we look at the Stamboulis study, this  
5 retrospective study from 1994 to 1999 of 642  
6 patients. Forty-one of their subjects had ulnar  
7 nerve palsy and also had diabetes, so it's about 12  
8 percent. In another study where I haven't put the  
9 author down, 6 percent of patients with ulnar nerve  
10 at the elbow had diabetes. And in another small  
11 study by Murata in 2003, a retrospective study of  
12 31 patients, 19 percent who had ulnar nerve at the  
13 wrist had diabetes.  
14 So it is controversial whether diabetes is a  
15 risk factor for ulnar nerve so far in this  
16 background. But Rota in 2014 looked at 64  
17 consecutive diabetes patients, and he diagnosed  
18 ulnar nerve at the elbow, ulnar neuropathy by these  
19 criteria, one of these, decreased sensory nerve  
20 velocity and SNAP of the ulnar nerve, slowing of  
21 ulnar motor conduction, and so on.  
22 So he set out the criteria by which he

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1 diagnosed an ulnar nerve at the elbow, and he found  
2 this in 34 percent of patients. And this was with  
3 recording from the ADM in '16 or from the FDI in  
4 '14 and from both in '08. And 82 percent of those  
5 who had ulnar nerve at the elbow also had diffuse  
6 polyneuropathy. Only 6 percent of the patients had  
7 sensory symptoms in an ulnar nerve distribution or  
8 had signs.  
9 So then we come to the question -- and this  
10 will come again when I talk about carpal tunnel in  
11 what we did -- is this just part and parcel of the  
12 diffuse polyneuropathy since most of them have it  
13 rather than an ulnar neuropathy? Should we be  
14 diagnosing these mononeuropathies with the clinical  
15 symptoms and signs?  
16 I would tend to favor that. I'll tell you  
17 why when I get to the end of median nerve. But  
18 these are abnormalities of electrophysiological  
19 function related to an anatomical course of the  
20 nerve, I think, that makes them more prone to this  
21 in this patient with diffuse neuropathy.  
22 So this is what I would say for ulnar nerve.

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1 And again, there was that consecutive study, and  
2 this is the only one, but no other prospective  
3 studies. He did the ulnar nerve at the wrist as  
4 well, and these are the criteria he set out. And  
5 he found 11 percent had ulnar nerve at the wrist,  
6 100 percent had polyneuropathy, and only 6 percent  
7 again had this change.  
8 So Jang also in 2014 looked at 105 diabetes  
9 patients without clinical ulnar neuropathy, again,  
10 just electrophysiology, and you see his criteria  
11 listed there. And 41 percent had at least one  
12 criteria. So basically, criteria are frequently  
13 abnormal, indicating focal ulnar nerve dysfunction.  
14 Most of the patients have diffuse polyneuropathy  
15 and very few have clinical ulnar neuropathy.  
16 That's distinct.  
17 What about surgery? Their failure of  
18 surgery is related or unrelated to the presence of  
19 diabetes depending on the report you read, but in  
20 1987 and 26, generally, ulnar nerve surgery has  
21 poor outcomes in 30 percent of people with 3  
22 percent needing revision. And this doesn't matter

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1 if they have diabetes or not. When I was studying  
2 in Denmark, the percentage of failures for ulnar  
3 nerve transposition was even higher than this. I  
4 think it depends on the chronicity of the study  
5 you're doing. But again, no prospective good  
6 studies in those with and without diabetes and  
7 ulnar nerve transposition.  
8 So any comments on ulnar nerve?  
9 DR. RUSSELL: So before you go onto that,  
10 how about ultrasound? Because you actually have  
11 quite a lot of experience. What do you think of it  
12 as a diagnostic tool and the sensitivity, et  
13 cetera?  
14 DR. BRIL: We have looked at ultrasound in  
15 patients with diffuse diabetic neuropathy and the  
16 healthy controls. And I haven't done enough  
17 prospective studies in patients looking  
18 specifically at the ulnar nerve. I have done it in  
19 diabetes subjects broadly, but not really paid  
20 attention to neuropathy and the other measures well  
21 enough to answer that.  
22 We think it might be helpful, but I can't

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1 even say that. Again, it needs more study.  
2 DR. TESFAYE: Vera, does chronicity prior to  
3 presentation have an impact on the extent of  
4 recovery?  
5 DR. BRIL: Apparently not from these. I  
6 mean, I think it's severity, but again, we don't  
7 know. We can't say this. There need to be  
8 prospective studies on all of this. A lot of this  
9 is just retrospective, just collecting data from  
10 clinics.  
11 DR. FREEMAN: Again, going back to mission,  
12 core diagnostic criteria, how will they differ from  
13 what's out there in diabetic patients? Are there  
14 diagnostic criteria in diabetic patients? I've not  
15 thought about this, read about this, the problem of  
16 diagnosing a compressive entrapment neuropathy in a  
17 patient who has an underlying polyneuropathy.  
18 DR. BRIL: You saw the problem here was that  
19 they used the common criteria that we would use for  
20 any ulnar neuropathy. Most of them had diffuse  
21 neuropathy, and only a small number had clinical  
22 ulnar neuropathy. So I'm not sure you could do the

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1 comparison. I don't know that it's being done. We  
2 haven't done it. We've done it in carpal tunnel,  
3 and I would think it's not going to be helpful  
4 because of our experience in carpal tunnel.  
5 DR. BRUEHL: Can I ask a stupid question?  
6 So basically, you're saying that this particular  
7 subgroup does not really show clinical signs or  
8 symptoms of ulnar neuropathy. Why would we  
9 diagnose something that the patient is not  
10 complaining of?  
11 DR. BRIL: Because the question really is,  
12 other than nerve conductions, do they have abnormal  
13 function of those nerves at sites of potential  
14 compression? And the answer seems to be yes in a  
15 high percentage. And maybe the neuropathy that  
16 they have underlying it makes them more prone to  
17 that in ulnar nerve. That's what we found in  
18 carpal tunnel.  
19 So these were done as studies, right, to  
20 look at the ulnar nerve to see if there was change  
21 in electrophysiology, then that would tend to limit  
22 its usefulness in clinical diagnosis. But you have

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1 to put the two together and they haven't been done  
2 properly yet.  
3 So we went to carpal tunnel. Anything else  
4 you want to say about ulnar? I hope I'm not going  
5 too quickly.  
6 DR. PELTIER: I would just say that I think  
7 we all see a handful of patients who have symptoms  
8 referable to an ulnar nerve lesion, and it may have  
9 electrodiagnostic findings consistent with that,  
10 but they don't do very well with treatment, with  
11 surgical treatment.  
12 So there's always a question mark of, well,  
13 is it even a bother sending them on to a surgeon to  
14 look at since most of them don't do well.  
15 DR. BRIL: I think that's the ulnar nerve  
16 myself, but I think my best example of someone who  
17 did well was someone who had acute trauma and acute  
18 block, and then he went, and he did well, but that  
19 was very quickly after the injury and the block,  
20 and he did well. But who knows what would have  
21 happened if I just followed him as well?  
22 Carpal tunnel. This is the most common

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1 upper limb mononeuropathy. There's a lifetime risk  
2 of 10 percent, so I don't know how many people in  
3 the room, but 3 of us are at least going to have  
4 carpal tunnel, or 4; I don't know. The risk is the  
5 basic anatomy. You may have a small canal, limited  
6 longitudinal sliding of the nerve, higher BMI is no  
7 good, greater AP diameter of the canal, a small  
8 hand, the presence of a palmaris longus and flexor  
9 digitorum superficialis, an anomalous artery,  
10 ganglion cyst, all anatomical variance in and  
11 around the carpal tunnel, or idiopathic enlarged  
12 nerves are seen very commonly. This is on  
13 ultrasound. Women get it very frequently,  
14 particularly during pregnancy, but also other  
15 times. Age, dominant hand, use of a cane or  
16 crutches, if you put pressure on the hand.  
17 Now, back to this study, because you know he  
18 studied the nerves, so I thought it was fair enough  
19 to be consistent, 642 patients, 40 with carpal  
20 tunnel. There were 522 who had carpal tunnel, so  
21 you can see right away that the predominant  
22 mononeuropathy in that population was carpal

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1 tunnel, as it is at any of our clinics. And 7.7  
2 percent had diabetes.  
3 Then Pourmemari in 2016 did a review, and  
4 this was with case control studies, and the risk of  
5 CTS in diabetes was increased by 1.97 or 1.67 in  
6 case control studies.  
7 DR. SMITH: Is that clinically defined?  
8 DR. BRIL: I'm not sure that it's clinically  
9 defined, and I'd have to go back and check. But  
10 what is the diagnosis? How do we diagnose it? And  
11 this is the same with the ulnar and this. Is it a  
12 clinical diagnosis or is it electrophysiology?  
13 Albers in '96 found that 23 percent  
14 fulfilled in the DCCT cohort criteria, or in that  
15 cohort of diabetes he was studying, for median  
16 mononeuropathy independent of diabetes. But he  
17 excluded subjects with greater  
18 DR. POP-BUSUI: [Inaudible – off mic].  
19 DR. BRIL: Yeah, it's too early, isn't it?  
20 DR. POP-BUSUI: No, because [inaudible – off  
21 mic].  
22 DR. BRIL: Yes. So we had type 2 as well as

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1 the type 1. Yes. He excluded people with greater  
2 than mild symptoms of carpal tunnel or those with  
3 absent lower limb or sural or peroneal responses.  
4 Mild carpal tunnel symptoms are still carpal tunnel  
5 symptoms, so I think that this is a bit of a  
6 crowded population.  
7 So I was going a little crazy because I was  
8 getting patients referred. Do they have diabetic  
9 neuropathy? And you know our standard is upper  
10 limb, motor and sensory, lower limb, motor and  
11 sensory, for polyneuropathy. Right?  
12 So we did the peroneal and sural, and  
13 they're normal or maybe not, and then we'd do the  
14 upper limb, and we'd find what would be classical  
15 carpal tunnel, increased distal motor latency,  
16 slowed sensory conduction velocity, I thought, but  
17 they didn't have any carpal tunnel. They don't  
18 have any carpal tunnel. But this was so frequent.  
19 So our question was, how many of our  
20 patients had clinical carpal tunnel? And the  
21 diagnosis was based on these criteria. And you had  
22 to have 4 of the 6 criteria to establish it:

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1 paresthesia in the hands or marked preponderance of  
2 sensory symptoms in the hands; nocturnal hand  
3 symptoms awakening the patient; symptoms  
4 precipitated by activities such as holding a  
5 newspaper or driving a car and relief by  
6 handshaking; predilection for the radial digits;  
7 weak thenar muscles; or upper limb sensory loss  
8 solely within the distribution of the median nerve.  
9 So 4 of those 6 made a diagnosis, a clinical  
10 diagnosis of carpal tunnel. And we found that, in  
11 our patients, in our referenced healthy population,  
12 one patient had it. Fourteen percent of those  
13 without diabetic neuropathy defined by lower limb  
14 changes and the clinical evaluation had it, and 30  
15 percent of those with established neuropathy had  
16 it.  
17 So then we were thinking, can we tell the  
18 difference between those who have clinical carpal  
19 tunnel and those who don't with nerve conduction?  
20 You're going to like this, Gordon. You're going to  
21 like this so much.  
22 So we did nerve conduction; median, ulnar,

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1 sural. And we did all these parameters, distal  
2 motor, median latency, distal median sensory  
3 latency, distal median motor amplitude, distal  
4 median sensory amplitude, distal median sensory  
5 conduction velocity, proximal median sensory  
6 latency, and so on. And then we also did ulnar, so  
7 beside the absolute values, we did ratios. We did  
8 distal median latency to distal ulnar motor  
9 latency. We did the amplitude, the median to the  
10 ulnar. We did median sensory amplitude to the  
11 ulnar sensory amplitude; the motors and the  
12 sensories for both the motor latency, sensory  
13 latencies; the sensory CV for median to ulnar  
14 sensory CV; the proximal sensory CV to the distal  
15 sensory; and all of this to this, finding focal  
16 slowing here; the distal median sensory latency to  
17 the sural latency; the median sensory amp to sural  
18 amp; et cetera, et cetera, et cetera.  
19 None could distinguish clinical carpal  
20 tunnel from those who didn't have carpal tunnel.  
21 None were different, except in the one healthy  
22 volunteer, they had a --

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1 DR. FREEMAN: How did you look at the  
2 difference or lack thereof? When you say none were  
3 different, were these means? Were these  
4 distributions? What kind of statistics?  
5 DR. BRIL: They were means. They were  
6 pretty much means and standard deviations, I'm  
7 pretty sure.  
8 DR. FREEMAN: Is that the best way to look  
9 at it?  
10 DR. BRIL: Maybe not. I don't know. We  
11 might reanalyze it if you --  
12 DR. FREEMAN: I'm just wondering because I  
13 think this is an -- nobody criticized you for the  
14 number nerve conduction studies.  
15 (Laughter.)  
16 DR. FREEMAN: I'm surprised. Just you've  
17 got 20 there. I would have thought you would have  
18 found one just by coincidence.  
19 DR. BRIL: That was in the healthy  
20 volunteer, where the median sensory amplitude was  
21 half in the ulnar sensory amplitude, but because  
22 only one patient had that. What could I tell from

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1 that?  
2 So basically, we couldn't find something.  
3 And you read a paper and say, do this and it'll be  
4 more sensitive, do that and it'll be more  
5 sensitive. But in this study, nothing was more  
6 sensitive. It was just the clinical criteria. So  
7 it showed us that the median nerve, too, is  
8 sensitive to the state of diabetic neuropathy.  
9 Basically, all of these parameters  
10 absolutely worsened with the degree of diabetic  
11 neuropathy, from no neuropathy, mild, moderate,  
12 severe. All the parameters worsened directly with  
13 how severe the underlying diffuse polyneuropathy  
14 was. So that median nerve is affected early and  
15 worsens in line with the polyneuropathy, but not  
16 with clinical carpal tunnel.  
17 So what is carpal tunnel syndrome? It  
18 should, I think, be defined clinically. The  
19 patients were treated, the ones who had carpal  
20 tunnel, but this was a cross-sectional thing. We  
21 didn't do a prospective thing where we had diabetes  
22 and non-diabetes such as with carpal tunnel, sent

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1 them to surgery, and brought them back, which we  
2 would have to do in order to compare the outcome to  
3 treatments in these two groups.  
4 The other thing we didn't do was get a  
5 larger population of healthy volunteers with carpal  
6 tunnel, non-diabetes patients with carpal tunnel,  
7 and making sure they didn't have metabolic syndrome  
8 or pre-diabetes and the rest of it. But doing  
9 that, I think that was another thing we could have  
10 done to see, in the healthy volunteers, if you have  
11 more discriminatory power from your  
12 electrophysiology, but in the diabetes subjects,  
13 you didn't.  
14 DR. POP-BUSUI: Vera, in fact, we did assess  
15 cheiroarthropathy in the DCCT edict, and we  
16 published this data three years ago. And the way  
17 we did it, we assessed cheiro by looking at other  
18 adhesive capsulitis, and then also clinical  
19 examination for carpal tunnel and ulnar tunnel  
20 syndromes. And what we found was that carpal  
21 tunnel was by far the most prevalent, and it was  
22 prevalent in 30 percent of the cohort with a mean

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1 duration of about 22 years of type 1 diabetes and a  
2 mean age of about 50 to 55 years.  
3 Then the most prevalent complication that  
4 this risk for carpal tunnel was actually confirmed  
5 clinical neuropathy because at the same time, we  
6 also had evaluated the DPN and repeated dose  
7 evaluations.  
8 DR. BRIL: It's the same.  
9 DR. POP-BUSUI: Yes.  
10 DR. BRIL: It's the same, 30 percent in  
11 those with diabetes. And the risk is the severity  
12 of the neuropathy for the electrophysiological  
13 findings.  
14 DR. POP-BUSUI: But I think that's maybe  
15 something I think we should think about because,  
16 clearly, this advanced glycation may be a reason  
17 that causes this entrapment, and in the diagnostic  
18 criteria, having other clinical manifestations of  
19 cheiroarthropathy may be pointing towards a  
20 potential entrapment in addition to just  
21 symmetrical distal.  
22 DR. BRIL: I was very disappointed that we

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1 couldn't have any electrophysiology that would  
2 point out those who had the clinical syndrome  
3 properly in this population.  
4       There you are, Gordon.  
5       DR. SMITH: Yes. We have the same data from  
6 type 2. I can't remember. We presented this at  
7 the PNS about 10 years ago, that about a third of  
8 patients who don't have neuropathy have  
9 electrophysiologic evidence of median slowing.  
10       Have you tried skin biopsy, though? That  
11 might be a -- or CCM as a way of --  
12       (Laughter.)  
13       DR. BRIL: No. This was done before the  
14 days of CCM, Gordon. We've tried ultrasound. And  
15 again, this shows different results in different  
16 studies, in showing carpal tunnel in those who have  
17 diabetes.  
18       DR. TESHAYE: The current approach in my  
19 clinic is when patients have the symptomatic carpal  
20 tunnel syndrome, I always send them to have median  
21 latency done. If it is just mild entrapment, we go  
22 for non-surgical interventions such as injections,

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1 steroids, et cetera. But if there is moderate to  
2 severe, they respond very well to surgical  
3 treatment.  
4       So I think it has a role, the nerve  
5 conduction. Am I right?  
6       DR. BRIL: You see, my study would say that  
7 you would see that slowing in someone without any  
8 carpal tunnel symptoms just the same, at the same  
9 stage of polyneuropathy that your patient is.  
10 That's what we found, that we couldn't use it to  
11 assess the carpal tunnel, because it assessed more  
12 the severity of neuropathy. Now, I know they  
13 respond to surgery and we do it.  
14       I have a little more studies, but Dan, you  
15 had something?  
16       DR. ZIEGLER: Did you compare both sides?  
17 So maybe that could be a clue, to compare the  
18 damage on the side of the CTS versus the other  
19 side.  
20       DR. BRIL: I'm not so sure, but we certainly  
21 compared to other nerves in the region that were  
22 not affected or should not have been. Yes.

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1       DR. ZIEGLER: But you did not do bilateral  
2 measurement?  
3       DR. BRIL: We usually do in carpal tunnel,  
4 so I can't remember the data, but our standard in  
5 the lab is if it's abnormal on one side, we do the  
6 other, so I can't really remember.  
7       DR. ZIEGLER: I could imagine that there  
8 could be a difference.  
9       DR. BRIL: But we wouldn't have done it in  
10 many of these, because we would only do that in a  
11 carpal tunnel, whereas we do the standard  
12 neuropathy work-up in a patient with  
13 polyneuropathy, which is median, motor, and sensory  
14 in the upper limb, and peroneal and sural in the  
15 lower limb. I could go back and look because --  
16       DR. ZIEGLER: It would be interesting.  
17       DR. BRIL: -- we may still have that. And  
18 the other thing, we know the studies are pretty  
19 symmetrical from the other study we represented  
20 years ago. In Portugal, actually, we presented on  
21 symmetry of the nerve conduction studies in  
22 diabetes. That's why, in the symmetrical

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1 neuropathy, we only do the one. But I will go back  
2 and look.  
3       DR. RUSSELL: Vera, how about weakness in  
4 the ABP muscle or denervation in the ABP? Does  
5 that help you at all in your diagnostic criteria?  
6       DR. BRIL: No. I think that would help  
7 in -- I can't really answer that. I know the  
8 amplitudes were no different. It all represented  
9 the severity of the underlying diabetic neuropathy,  
10 not the presence of carpal tunnel. Many of these  
11 patients didn't have any motor weakness.  
12       DR. TESHAYE: Vera, your center is the  
13 Center for Excellence for Neuropathy Research, so a  
14 lot of your patients have come to you. Is there a  
15 selection bias? Your control group will have sort  
16 of a neuropathy element to them, so when you  
17 compare with the other group that has carpal tunnel  
18 syndrome, maybe there isn't a difference, but  
19 actually, if you had a different cohort of diabetic  
20 people --  
21       DR. BRIL: Absolutely  
22       DR. TESHAYE: -- maybe there would be a

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1 clear difference.  
2 DR. BRIL: That's possible. In these  
3 screening studies, we were open to all comers. And  
4 our distribution of patients really surprisingly is  
5 similar to what you find in a community  
6 neurologist's practice. We just saw that recently  
7 when we were looking at underlying etiologies.  
8 DR. TESFAYE: Why would they come to your  
9 clinic if they have no neuropathy?  
10 DR. BRIL: Because at the time, we were  
11 looking for patients with a broad spectrum of  
12 neuropathy and diabetes, from no neuropathy to  
13 neuropathy. So these were part of research trials,  
14 where we were trying to recruit the cohorts.  
15 But I do think the other control group  
16 should be -- well, I don't even know how to do that  
17 properly. Like, you would have to get -- we had  
18 the healthy population, and one out of them had  
19 carpal tunnel. I guess you'd have to get more of  
20 the healthy population, see how much unsuspected  
21 carpal tunnel they had, because if they already had  
22 carpal tunnel, then I don't know how you would read

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1 the electrophysiology.  
2 Let me just talk about the outcome of  
3 treatment. Ozkul in 2002 published 22 subjects  
4 with diabetes and 25 without and followed them for  
5 a year. And everything improved, but the  
6 improvement was less in those with diabetes. And  
7 Gulabi in 2014 did a prospective study, and all  
8 improved immediately. And he followed them for 10  
9 years, and those with diabetes did not do as well.  
10 But they all got better, so I think it's worth the  
11 effort, and some of them get completely better,  
12 their symptoms go. But there are, even in patients  
13 who don't have diabetes, often some persistent  
14 electrophysiological abnormalities.  
15 One of the issues we have is -- this is  
16 where the referral bias come in -- if I get center  
17 field [ph] carpal tunnel, it's often that I haven't  
18 done the preliminary studies. And they can be all  
19 over the place; what's done, how it's done, the lab  
20 it's done in, how it's interpreted. I know this  
21 because I was involved in a WSIB study where we  
22 tried to look at the outcome of carpal tunnel

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1 surgery with a hand surgeon, and there was  
2 electrophysiology from all over the province and it  
3 was just dreadful.  
4 I don't mean the quality of the studies, but  
5 it was such a forest of different methods, and  
6 techniques, and reporting styles, and all of that,  
7 that I couldn't even drag comparable figures from  
8 all the reports. We had to go from normal or  
9 abnormal. It was that difficult. Yes?  
10 DR. ZOCHODNE: I think, even if you  
11 successfully decompress the carpal tunnel, there's  
12 probably at least a 10 percent drop in conduction  
13 velocity that's persistent, and that's because  
14 they're shortened internodes at the demyelinating  
15 segment, so you see that.  
16 DR. BRIL: I actually think also, because of  
17 the diffuse underlying neuropathy that has produced  
18 changes in asymptomatic patients to begin with, so  
19 the nerve there functions less well.  
20 That's it. That's all I have to say, so I  
21 don't know if I rushed through that too quickly.  
22 (Applause.)

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1 DR. FREEMAN: Comments? Questions?  
2 Q & A and Panel Discussion  
3 DR. KOLB: I think, particularly for carpal  
4 tunnel, this is a place where ultrasound may play a  
5 more helpful role in the future. I mean, I don't  
6 think there have been enough prospective studies to  
7 see if you can look at which patients will benefit  
8 from carpal tunnel surgery, but it's certainly  
9 reasonable to think that, as ultrasound evolves,  
10 this may be really helpful, particularly in the  
11 setting of people who have substantial neuropathy.  
12 DR. BRIL: I agree. And let me say that we  
13 did this study with a hundred normal reference  
14 subjects and then a hundred with diabetes. And we  
15 found the nerves were generally a bit bigger in  
16 diabetes wherever we measured them.  
17 So that is different from what other people  
18 have found with ultrasound, but you would expect  
19 larger changes at sites like the carpal tunnel or  
20 ulnar nerve, not always the case. It's quite  
21 surprising, the discrepancy sometimes, but yes, I  
22 agree. There need to be a lot more prospective



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1 studies, prospective studies on surgery, follow-up  
2 studies, consistent studies, standardized testing,  
3 and assessments.  
4 DR. HARATI: How about imaging just to see  
5 the structure abnormalities?  
6 DR. BRIL: Sometimes we have done MR  
7 neurography, particularly on an ulnar nerve that's  
8 not well localized, but not often. It's hard to  
9 get. They wait a long time. And it's expensive in  
10 our system.  
11 DR. HERRMANN: Clearly, the clinical  
12 syndrome should be the driver of the decision  
13 making with neuropathy and carpal tunnel.  
14 DR. BRIL: I would think so.  
15 DR. HERRMANN: Not to dismiss  
16 electrophysiology entirely, if you had more  
17 stringent cutoffs, not the traditional --  
18 DR. BRIL: Had more? Sorry?  
19 DR. HERRMANN: -- stringent cutoffs for  
20 abnormality -- in other words, with just diabetic  
21 neuropathy alone, is there a range of slowing or  
22 latency prolongation if it's with diabetic

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1 neuropathy alone? And then if you have compression  
2 on top of that, so you have a more restrictive  
3 cutoff.  
4 DR. BRIL: So you're talking about the  
5 distribution the way Roy was. I'd have to go back  
6 and look because I don't know. I can't answer that  
7 at the moment. But that would be a good thing to  
8 look into  
9 DR. FREEMAN: I'm just wondering, and I know  
10 you must have looked at that. You went through  
11 your 20 studies quickly. But median on the  
12 comparison studies, radial digit 1 comparison  
13 studies, where you're looking -- so the story of if  
14 this is a generalized polyneuropathy, then you're  
15 going to see symmetry in nerves of non-compression,  
16 whereas if it's compressive neuropathy --  
17 DR. BRIL: But that's the theory --  
18 DR. FREEMAN: It did that.  
19 DR. BRIL: -- and it didn't hold up. We  
20 used the sural, yes, and it didn't hold up. And  
21 that was the biggest disappointment for us because,  
22 okay, the ulnar, we've gone through now and we see

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1 that there's a lot of ulnar nerve dysfunction, so  
2 maybe that could explain that.  
3 DR. FREEMAN: The digit 1 as well?  
4 DR. BRIL: We didn't look at radial, but we  
5 looked at sural, and in the past, sural to radial  
6 amplitudes.  
7 DR. FREEMAN: Again, not asking you to  
8 reinvent your study or repeat it, but radial would  
9 be quite important because the ulnar is another  
10 potential site of entrapment.  
11 DR. BRIL: But the sural isn't, and that  
12 actually reflects the diffuse polyneuropathy more,  
13 so we used the sural. Yes?  
14 DR. MALIK: So Vera, is it possible to do a  
15 Bril correction factor from your data, i.e., take  
16 into account the neuropathy that's already present  
17 and somehow work out an adjustment almost for your  
18 latencies that you see in the median nerve?  
19 DR. BRIL: Don't know  
20 DR. PELTIER: Basically, a higher threshold  
21 to diagnose for --  
22 DR. MALIK: Yes, from the data set.

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1 DR. BRIL: This is the question about the  
2 distributions, the cutoffs, and we have to go back  
3 and look at the data. I don't know that right now  
4 because I can't -- I know we looked at  
5 distributions then, but I don't recall because it  
6 was a while ago. I don't recall any such -- I just  
7 recall a lot of disappointment because we said, all  
8 right, let's compare this, all right, let's compare  
9 that, all right, let's compare this.  
10 We went on and on because we thought some  
11 things should differ. And the only thing -- in  
12 that one healthy person who had carpal tunnel, had  
13 a difference in one parameter. Yes?  
14 DR. RUSSELL: So Vera, there may be two  
15 factors here, so your clinical carpal tunnel is, I  
16 agree with you, clearly you have to go there on  
17 symptoms and signs. But you've also got this issue  
18 of pre-clinical, which is sort of the median  
19 mononeuropathy at the wrist.  
20 So I guess the question is, do you have two  
21 criteria, one clinical carpal tunnel, which will  
22 really be all the clinical measurements you've

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1 mentioned, and the second is this concept of the  
2 median mononeuropathy at the wrist, or do we just  
3 say that's really not important to find that?  
4 DR. BRIL: We were trying to find something  
5 that would identify the median mononeuropathy at  
6 the wrist if you wanted to, the carpal tunnel.  
7 That's the whole purpose of the study, because at  
8 that time, I had come through a lot of diabetic  
9 neuropathy studies, and they said, if you have  
10 carpal tunnel as defined by the distal latency or  
11 whatever, you can't get in the study. And I was  
12 finding a lot of patients with that, so I was  
13 trying to find cutoffs, or parameters, or  
14 comparisons that would allow patients, but I  
15 couldn't find them.  
16 DR. RUSSELL: So I do accept that, but in a  
17 sense, what I'm talking about is sort of pre-  
18 clinical, if you could maybe look at it that way.  
19 So in other words, these are people who would  
20 absolutely have no clinical features, but you would  
21 define what median nerve slowing across the wrist  
22 may be. I'm just saying, do you consider that

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1 important in any way or should we just throw all of  
2 that out?  
3 DR. BRIL: I'd have to look at the  
4 distributions to get cutoffs because we found  
5 abnormal results, but they related to severity of  
6 the diffuse neuropathy, not to the median  
7 mononeuropathy at the wrist. They were part and  
8 parcel. So I'll look at the distributions again  
9 and see if we have cutoffs that we can find, but  
10 not at this point.  
11 Teresa?  
12 DR. JONES: So I'm sorry to go back to the  
13 foot with this. I know that's a problem. I get  
14 these e-mails from an investigator -- I'm sure we  
15 all do -- about how great the surgery is.  
16 Do you think you're going to be able to get  
17 a dichotomous criteria for people who would benefit  
18 from the surgery or not? Let's say somebody is out  
19 there, a person with it, and they can see all the  
20 news. They go to their doctor and they really want  
21 to know whether it's going to help them or not.  
22 DR. FREEMAN: Before you answer that, can I

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1 ask another question which is so closely related to  
2 that? My concern is how -- on the one hand, there  
3 seemed to be a consensus that in the upper  
4 extremity, classical ulnar neuropathy symptoms,  
5 classical carpal tunnel syndromes, it's acceptable  
6 to have surgery in the absence of confirmatory  
7 nerve conduction studies.  
8 DR. BRIL: For the carpal tunnel?  
9 DR. FREEMAN: For the carpal tunnel, not for  
10 the ulnar.  
11 DR. BRIL: All the outcomes are so  
12 different.  
13 DR. FREEMAN: No. And I agree, I agree.  
14 Let's just say for the carpal tunnel. For somebody  
15 who is sitting in this room from Mars, what's the  
16 difference between that and what they're doing in  
17 the lakes?  
18 DR. BRIL: So let me just say a couple of  
19 comparisons. Carpal tunnel is extremely frequent,  
20 10-time lifetime risk. Tarsal tunnel, which we  
21 probably have all seen, is extremely rare, like  
22 hen's teeth. Outcome of surgery for carpal tunnel

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1 is pretty good. I don't know what your outcomes of  
2 surgery for tarsal tunnel release have been, but  
3 mine have been not great.  
4 The other thing is, carpal tunnel is usually  
5 asymmetrical, usually one hand, sometimes both. I  
6 haven't seen too many patients who say it started  
7 in both hands immediately and it's the same,  
8 whereas for diabetic polyneuropathy, it starts in  
9 both feet usually the same.  
10 So you might have the argument for  
11 unilateral involvement of the foot or highly  
12 asymmetrical findings, plus evidence of focal  
13 blocks along those nerves, which when we look for  
14 them we hardly ever find, but maybe that could help  
15 you and direct you. But for a diffuse  
16 polyneuropathy, and especially one that has come  
17 above the ankle, I just don't see the value of  
18 decompression.  
19 DR. JONES: Thanks.  
20 DR. BRIL: I mean, do people here agree with  
21 that?  
22 DR. BENNETT: Yes. I completely agree.

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1 Yes. And I think your rationale is a good one,  
2 that carpal tunnel is a well-defined syndrome,  
3 localized to one nerve. It's completely different  
4 to the idea of a more diffuse neuropathic process  
5 in the legs. So I think they're quite distinct.  
6 DR. FREEMAN: Yes. I mean, I'm a little  
7 more hard-nosed about it, actually; I'd like to  
8 see. But I was not aware of your study, which  
9 maybe makes me a little more flexible.  
10 So again, getting back to business, two  
11 things --  
12 (Dr. Bril gestures to leave podium.)  
13 DR. FREEMAN: No, not yet.  
14 (Laughter.)  
15 DR. FREEMAN: You can lean, though, if you  
16 want to.  
17 DR. BRIL: I'm leaning.  
18 DR. FREEMAN: So two things, one, you make a  
19 fairly convincing point that this is not quite as  
20 relevant in diabetes, these compression entrapment  
21 neuropathies, as one would have thought, and does  
22 this topic have a place in what we are doing. And

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1 I would argue, yes, it does because I think those  
2 questions are so important.  
3 So what I'm thinking about when I think  
4 about manuscripts and how to do this is that what  
5 will be unique about what you spearhead is talking  
6 about the criteria and the assessments. And I  
7 don't think we're looking at treatments.  
8 We're looking at the taxonomy, the criteria,  
9 and the assessments of the diabetic patient, who  
10 has a potential compression entrapment neuropathy.  
11 And a lot of it may be just as you've said, that  
12 despite what we thought, it's actually not so easy  
13 to discriminate an entrapment neuropathy in the  
14 setting of a generalized polyneuropathy. The  
15 principles that I think I at least had in my mind,  
16 without knowing the literature as well as you do,  
17 don't hold up as well in reality.  
18 So that would be my take on it. I wonder  
19 what others think. I would hear maybe the panel,  
20 who did we decide would be on this panel? I know  
21 Doug was there.  
22 DR. BENNETT: So I'm on the panel, and I

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1 agree. I think maybe it should be clinically  
2 defined, that we should target. I do think it's an  
3 important issue to cover. I think one of the  
4 challenges is we may not simply be able to just  
5 transpose the pre-existing criteria for isolated  
6 CTS in ulnar, et cetera, because that's in the  
7 context of someone that doesn't have a generalized  
8 neuropathy. And we might need to think about some  
9 comment on accentuated involvement of a particular  
10 nerve relative to others.  
11 So we might need to go back to those  
12 criteria and just see, because that is difficult to  
13 hear, how we're pulling out more involvement of one  
14 nerve in the context of a generalized  
15 polyneuropathy. That might be a bit of a challenge  
16 when we come down to write the criteria.  
17 DR. BRIL: I think we can alert people to  
18 the fact that you can't rely so much on the studies  
19 and the current criteria and maybe develop a way to  
20 study it further as we go, because I'm convinced  
21 there's a way for electrophysiology always, Gordon.  
22 DR. BENNETT: I agree.

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1 (Laughter.)  
2 DR. BRIL: Rayaz, too.  
3 DR. FREEMAN: Can I ask one other very quick  
4 question before we go back to the panel? I mean,  
5 every now and again, I get sent articles to review  
6 on small fiber type assessments. Now, I know  
7 Gordon was joking -- or at least I hope he  
8 was -- when he said corneal confocal microscopy.  
9 But people have looked at laser Doppler,  
10 pseudomotor function.  
11 Did anything emerge? You obviously didn't  
12 do that, but is it possible that the small nerve  
13 fibers might be affected first and early and could  
14 be a more sensitive way of looking at this?  
15 DR. BRIL: Diabetes patients with and  
16 without CTS, perhaps. I don't know.  
17 DR. FREEMAN: Comparison of the two sides,  
18 the same way one.  
19 DR. BRIL: Yes, maybe. I don't know.  
20 DR. FREEMAN: Maybe, yes.  
21 DR. BRIL: I don't know. Same with ulnar, I  
22 have no idea.

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1 DR. BENNETT: I mean, we did a little bit of  
2 work not in the context of diabetes, but just  
3 carpal tunnel. And there is a small group of  
4 patients where they have typical symptoms of carpal  
5 tunnel and normal nerve conduction studies. And  
6 when you do a skin biopsy and median enervate the  
7 territory, the intraepidermal nerve fiber density  
8 is reduced. But I have to say that is really quite  
9 a rare occurrence. And I don't think it's going to  
10 be replacing a more traditional assessment.  
11 DR. FREEMAN: James?  
12 DR. RUSSELL: I think I've said most of the  
13 things I've said. And I guess at this point,  
14 really, the main thing you need to decide is are  
15 you going to go with pure clinical criteria, and it  
16 sounds like, in fact, you've presented a very good  
17 argument with that.  
18 Do you actually then say, well, perhaps we  
19 can use some confirmatory tests or some  
20 exclusionary tests, perhaps in a subnote to your  
21 clinical criteria? And that's for further  
22 discussion.

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1 DR. FREEMAN: Gordon and then Amanda?  
2 DR. SMITH: I agree. I mean, I think this  
3 is what you said. I think this is really important  
4 because it's a comment on a clinical problem. And  
5 I think the data you've summarized would come as a  
6 surprise to many people in practices. So this is  
7 going to be very valuable to the community.  
8 DR. MALIK: Should we also take the  
9 opportunity in whatever document that comes out to  
10 address the issue with this unnecessary surgery?  
11 Because the last one was 2016, so by the time we  
12 get anything done, there will be more evidence, I  
13 guess, to address it.  
14 DR. BRIL: Well, I'd like to see this paper.  
15 I think so. I think you can't talk about  
16 entrapments without talking about that, to be  
17 honest.  
18 DR. FREEMAN: Obviously, it's not the focus,  
19 but it's a byproduct and I think we can.  
20 DR. BRIL: I did want to leave it out.  
21 DR. FREEMAN: Amanda?  
22 DR. PELTIER: I was just going to comment

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1 that this might be something that could be studied  
2 further. When we did our diabetic labor skin  
3 biopsy study, we actually found that our healthy  
4 control with carpal tunnel increased incidence of  
5 segmental demyelination. So there might be a  
6 signal there that you could look at.  
7 DR. FREEMAN: Noah, any comment?  
8 DR. KOLB: Yes. I think one other thing  
9 that's a little bit different about this type of  
10 neuropathy than some of the others we've talked  
11 about, like for instance Rob's this morning, we  
12 talked about being a little inclusive in terms of  
13 our diagnostic criteria and the taxonomy. And I  
14 think, for these specific focal neuropathies, it's  
15 important that we be fairly tight in our definition  
16 just because it's likely going to come down to  
17 clinical diagnosis, comparing one nerve  
18 distribution of clinical symptoms to another.  
19 So I think we just have to be careful while  
20 being pretty specific in terms of defining the  
21 criteria.  
22 DR. FREEMAN: The other panel member?

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1 DR. HARATI: I have nothing to say. I agree  
2 with what Dr. Bennett mentioned. Another factor  
3 about carpal tunnel is that it is a fairly common  
4 condition. I remember years ago a pathologist at  
5 Duke decided to look at flexor retinaculum that  
6 they will cut during the surgery and blindly did  
7 the Congo red stain in all of them, and 2 of the 70  
8 had amyloidosis.  
9 DR. BRUEHL: Can I ask one question here  
10 before you go?  
11 DR. BRIL: Yes, last question.  
12 DR. BRUEHL: So back to the bigger picture  
13 again with this, so there are pre-existing carpal  
14 tunnel syndrome criteria that are accepted.  
15 DR. BRIL: Yes.  
16 DR. BRUEHL: The clinical challenge here in  
17 this particular diabetic context would seem to be  
18 distinguishing carpal tunnel from more generalized  
19 peripheral neuropathy.  
20 DR. BRIL: Not clinically, but on the  
21 electrophysiology.  
22 DR. BRUEHL: But that's the two clinical

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1 entities you're trying to distinguish.  
2 DR. BENNETT: Even clinical, we might need  
3 to be careful because they're not written in the  
4 context of a more generalized neuropathy. If we  
5 just translate them, it might not work.  
6 DR. BRIL: Yes.  
7 DR. BRUEHL: That's kind of what my point  
8 is. So if the objective testing is not  
9 particularly helpful, is there something  
10 clinically -- based on just your knowing the  
11 literature and clinically seeing patients like  
12 this, is there something about the clinical picture  
13 that is unique in carpal tunnel that would  
14 distinguish it from more generalized? Is it just  
15 that it's unilateral?  
16 DR. BRIL: No.  
17 DR. BRUEHL: Is it adherence to a particular  
18 distribution?  
19 DR. BRIL: It's the distribution, the  
20 activity relationship, the relief by changing hand  
21 postures or shaking? I think those are more.  
22 Waking you up at night can happen with symptoms

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1 anywhere. I don't know. But these are the ways I  
2 would go, so the distribution, the activity  
3 relationship, and the relief by shaking your hand,  
4 I think are -- of course, if you had thenar  
5 weakness and no other weakness in any muscles, that  
6 would go with this.  
7 DR. FREEMAN: So in your study, just to  
8 answer that question, you had a nice list of and  
9 you said 4 of whatever many there were. Are you  
10 happy with that?  
11 DR. BRIL: But some of them are not  
12 specific, so the waking up at night. But you don't  
13 wake up at night with usually not just symptoms in  
14 your hands. It would be symptoms, pain in your  
15 feet that wakes you up rather than the hand  
16 symptoms. So I was pretty happy, but I think this  
17 is for more discussion.  
18 DR. BRUEHL: Those things that are less  
19 specific like that, like the indicators like waking  
20 up at night and that kind of thing, that might be  
21 something that would fit well with saying in one of  
22 the following, and you have a choice of three, and

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1 hopefully, even though any one isn't specific, the  
2 combination of the set of three might be more  
3 specific.  
4 DR. BRIL: I think that would be a really  
5 good discussion point with the people who are going  
6 to be helping do this. Don't all put your hands up  
7 at once.  
8 (Applause.)  
9 DR. FREEMAN: We arranged lunch for 12:00,  
10 so I thought we could spend a few minutes just  
11 talking about work product. And what I think I'll  
12 do is say what I envisioned and what I think are  
13 the possibilities and where I am uncertain to get a  
14 sense of what people think.  
15 So typically, as you saw from these  
16 meetings, there are one or more manuscripts.  
17 Everybody is an author, provided they contribute,  
18 of course. It's usually spearheaded by a group of  
19 people, and they are usually landmark papers that  
20 are widely quoted, widely cited. And I have no  
21 doubt that what comes out of this meeting, the same  
22 will apply.

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1 What I envisioned is that there would be one  
2 paper, which I christened Jennifer will take  
3 responsibility for that will predominantly be on  
4 Dimension 1. That will be the central paper that  
5 summarizes in brief, Dimension 1, and that covers  
6 all of the five conditions that we discussed. And  
7 everybody of course will be an author on it, and  
8 everybody will contribute.  
9 Here is where I'm not certain. I am leaning  
10 towards there being 5 individual papers. The lead  
11 author, if they are in agreement, will be the  
12 individuals who gave the talk. The primary work  
13 group for those papers will be Chris and me, as  
14 well as the people who should have been on the  
15 panel, who are listed on the panel, but I think had  
16 worked very well without the panel.  
17 That's what I think. Another way of doing  
18 this would be to combine what we'll call the  
19 Singleton-Ziegler syndrome together with the  
20 generalized polyneuropathy paper. To me, I think  
21 that's too much and it doesn't really fit, but I  
22 want to hear what people think, combining perhaps

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1 Chris and Jim's talk as this entity that is  
2 subacute and onset, is painful, one motor, one  
3 sensory, some overlap, or perhaps combining Jim and  
4 Vera's together. Both of them are focal segmental  
5 asymmetrical.  
6 But to me, I think it's artificial, but I do  
7 want to hear what people think about that.  
8 DR. TESHAYE: I'm in favor of your first  
9 option. I think you need a summary paper, which we  
10 had with the Toronto.  
11 DR. FREEMAN: I think that very similarly  
12 that's the model.  
13 DR. TESHAYE: We had a summary paper, which  
14 will be the main paper, because people won't read  
15 everything, but then have the groups, as you say,  
16 leading on their specific areas in more detail,  
17 which would be in the public domain as well, which  
18 would be of interest. I think that would be my  
19 preferred option.  
20 DR. BRUEHL: So when we did the APT papers,  
21 what we did for certain conditions was a single  
22 paper devoted to describing all five dimensions for

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1 a given condition. There are some where multiple  
2 conditions were combined.  
3 The challenge in writing papers like that,  
4 where you're combining, is the Dimension 1, like  
5 how we're going to diagnose this clinically, makes  
6 the most sense in context of some background  
7 literature that explains what's already out there,  
8 and what we know and don't know, and here's how we  
9 came up with this.  
10 If you have too many conditions addressed in  
11 one paper, it gets large, unwieldy, and hard to  
12 follow unless it's broken up like, first, it's all  
13 this condition; then it's all this condition, like  
14 that. And I like the idea of a summary paper that  
15 has Dimension 1 for all the conditions covered.  
16 That would be a nice reference for people to use  
17 clinically. I would be concerned about being able  
18 to provide adequate background for all of those in  
19 the same paper unless you already had more detailed  
20 papers to refer the reader to.  
21 DR. FREEMAN: Yes. I do think it's doable.  
22 I think it's possible.

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1 Any other comments? Everybody is in  
2 agreement? Can I just take it that the speakers  
3 have agreed to take the lead, and the panels have  
4 agreed to help? I'll take that as a yes.  
5 Then I suppose we should think a little bit  
6 about journals and also whether we want to seek  
7 endorsement from other societies. Clearly, we have  
8 whatever that group is called from Sitges, and we  
9 will have the CONCEPPT ACTTION endorsement and all  
10 of that which is related.  
11 But do we want to look for support from the  
12 American Academy of Neurology, the American  
13 Diabetes Association, and any others along the  
14 lines that John England, for example, did in his  
15 paper? Is that possible? Is it reasonable? Is it  
16 important?  
17 DR. BENNETT: What if they said to you, Roy,  
18 yes, but we would like to now input some of our  
19 members to contribute? That might be their  
20 response. What would you say? That's fine?  
21 DR. FREEMAN: That's against the rules.  
22 (Laughter.)

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1 DR. BRIL: Roy, John England -- I was on one  
2 of those practice parameters. Those are actually  
3 sponsored by --  
4 DR. FREEMAN: Sponsored by, yes.  
5 DR. BRIL: -- and they're set up by their  
6 quality committees.  
7 DR. FREEMAN: I understand it was set  
8 by -- yes.  
9 DR. BRIL: I mean, they pick the lead  
10 author, and then they have leads, and you do  
11 everything with them.  
12 DR. SMITH: So there is a way of doing it at  
13 the AAN, and the person who can tell you most about  
14 it is Brian because he sits on -- actually the  
15 committee is JEDI, I think, because it's an  
16 affirmation. So there's no way this is going to be  
17 an AAN practice parameter. But we review all the  
18 time other guidelines such as this from other  
19 organizations that is reviewed by the subcommittee  
20 and rolls all the way up to the board.  
21 I don't know whether it would fare well, but  
22 Brian can explain the process and tell you whether

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1 or not it would be appropriate.  
2 DR. FREEMAN: Just as a matter of interest,  
3 the other side of the coin, I was involved in  
4 writing one of these guidances for another society  
5 as just the neurology representative, and they  
6 wanted American Academy of Neurology endorsement.  
7 I actually resigned from the guidance, a long and  
8 interesting story. And the AAN asked me to be the  
9 representative, and then I had to convince the AAN  
10 as to why they actually should not endorse it.  
11 So that happened beforehand. I was the AAN  
12 representative, and they had before -- it was a  
13 very high-level society -- agreed to endorse it  
14 presumably. But I think we should look into that.  
15 DR. BRUEHL: So this is something that would  
16 potentially impact timelines as well as  
17 endorsements and things like that. As it stands  
18 right now, given what's happening here, this is all  
19 based on literature review and expert consensus, I  
20 guess.  
21 I think a potential strength of the general  
22 approach of the effort for chronic pain was some

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1 willingness to make an effort to use data to  
2 support that. Literature review is some data, but  
3 it sounded like at least two or three of the groups  
4 here have pre-existing data sets that could maybe  
5 not provide definitive validation or anything,  
6 would at least be able to provide some information  
7 that says we're not totally way off base here  
8 because here's what our data show.  
9 I think it would be worth the effort to try  
10 to do those analyses and incorporate that in the  
11 publications because I think they'd be more likely  
12 to get accepted by other people if there's some  
13 evidence that it wasn't just pulled out of a hat.  
14 DR. POP-BUSUI: I actually agree with this  
15 comment quite a lot. I think it's going to be  
16 important because you don't want just to reinvent  
17 the wheel and create yet another paper with yet  
18 another taxonomy or classification. There have  
19 been already lots of them. Indeed, there are lots  
20 of trials in which we have important information,  
21 may not be the perfect one, but you will never be  
22 able to do a perfect trial.

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1 Secondly, the American Diabetes Association  
2 has already changed their policies as of this year.  
3 We are going to continuously update the statement  
4 and also the clinical care practice. We are not  
5 going to have annual updates. We update them as  
6 they come and we have now a committee in charge  
7 that could evaluate very critically any new  
8 evidence that it's not, for instance, a diabetic  
9 neuropathy statement. But that's also true for  
10 every other statement-related other complications  
11 or the clinical care. So that's something that we  
12 clearly can have access to.  
13 DR. FREEMAN: So I think that's worth  
14 considering. Any other points? Yes, Solomon?  
15 DR. TESFAYE: I think where you publish this  
16 paper is critically important. If it's in an  
17 obscure pain journal, nobody's going to look at it.  
18 And if it is in something mainstream where doctors  
19 and clinicians, et cetera, have access to that, the  
20 easily visible is important. So some thought needs  
21 to go into that.  
22 DR. FREEMAN: Yes. Any ideas? Do you want

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1 to be more specific as to what's obscure and what's  
2 not?  
3 DR. TESFAYE: Something superb. I mean, we  
4 published our stuff in Diabetes Care. It's  
5 visible. It has a high impact track, something  
6 like 11 points and 11 percent or whatever.  
7 So it is highly cited and a lot of people  
8 have access to it. Or maybe publish it in two  
9 journals. Sometimes you can do it for the diabetes  
10 community and for the neurology community. But you  
11 need to discuss this with the editors, actually,  
12 which is what we did. We negotiated with the  
13 editorial staff.  
14 DR. FREEMAN: That would be ideal, yes.  
15 DR. SINGLETON: I can imagine this might be  
16 most impactful if all or most of these were  
17 published together as a suite of articles that may  
18 be more difficult to arrange, but would be more  
19 impactful if that were to happen.  
20 DR. FREEMAN: Yes. I suspect what will  
21 happen is that not all will be accepted into the  
22 same journal, but that's what we had.

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1 DR. TESFAYE: Exactly to that point. We  
2 wanted to push everything to Diabetes Care, but  
3 what they came back and said to us is, look, we're  
4 interested in the summary paper. So we went to  
5 diabetes metabolism research reviews. We published  
6 these other five papers.  
7 DR. FREEMAN: Yes. But I do think that some  
8 of these papers would be highly impactful in  
9 probably some major journals, one in top tier and  
10 the rest in -- I wouldn't call them obscure, but  
11 lower level journals.  
12 So what do you think, Vera?  
13 DR. BRIL: I was agreeing with Solomon. I  
14 think the summary paper to Diabetes Care would be  
15 great, but I think the sub-papers are a little more  
16 than perhaps they may want to read in Diabetes  
17 Care. And I would agree they should be directed  
18 into neurology literature.  
19 I'm wondering, Gordon, if the AAN did  
20 sponsor it, would they then be more likely to  
21 publish in Neurology? Because I do think that they  
22 should be impactful, but something like Neurology

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1 may be where we want to get.  
2 DR. SMITH: I think that they're not going  
3 to sponsor this. They might affirm it.  
4 DR. BRIL: I mean affirmation.  
5 DR. SMITH: I'm doubtful that would have an  
6 impact, but we could talk to Bob and ask him, I  
7 think. I like the idea of co-publishing the main  
8 paper in the diabetes and neurology literature.  
9 And I suspect there might be enthusiasm on Bob's  
10 part and maybe even for some of the other component  
11 papers, particularly things like the TIND and DLRPN  
12 papers.  
13 DR. FREEMAN: David, then Jen?  
14 DR. HERRMANN: Certainly, for the neurology  
15 practice guidelines and practice parameters, the  
16 level of evidence and the formula for which you  
17 arrive at it is -- because we were involved in the  
18 neuropathy sort of testing one -- is very, very  
19 restrictive. And I think the process will be  
20 vigorous, particularly if you have some validation  
21 in some of the data sets, but it might be hard to  
22 fit the process that you're following here into

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1 that model.  
2 But they may accept it in some sort of a  
3 review as a review of some sort, as outside of the  
4 guideline type format.  
5 DR. SMITH: This would not go in as a  
6 guideline because it's not a guideline. So the  
7 whole affirmation process through the practice  
8 committee and the academy is really separate from  
9 the publication issue and the general neurology.  
10 DR. HERRMANN: So this could be as reviews,  
11 really.  
12 DR. SMITH: I mean, they're just  
13 disconnected. I don't think the affirmation, which  
14 may be difficult because of the reasons you bring  
15 up, would really be connected to the publication.  
16 DR. FREEMAN: Somewhat along the  
17 lines -- and Jen, you're going to speak now -- of  
18 the manuscript that was published on the  
19 chemotherapy peripheral neuropathy.  
20 DR. GEWANDTER: Yes. I was just going to  
21 say, last time for that manuscript, Dr. Roche just  
22 asked me to send it to him. And obviously, he has

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1 to recuse himself because I'm on the paper. But he  
2 just told me yes or no, so once it's drafted, we  
3 could do the same.  
4 But also, I will say that paper was  
5 definitely a systematic review based on data, so  
6 I'm not sure it's the same. But then I was going  
7 to say also that the way we did APT was as a  
8 supplement that everything was together. So even  
9 if the main paper was published in Neurology, I  
10 think it would be a good idea to try to put the  
11 rest together and find a journal that was  
12 interested in doing that.  
13 DR. FREEMAN: Teresa?  
14 DR. JONES: I think Amanda's actually been  
15 really -- you go first.  
16 DR. PELTIER: No. I was just going to make  
17 two points. One is, I do think, taking Steven's  
18 point, that the more that we can validate these by  
19 running them through our databases, I think better  
20 because, otherwise, I think you just suffer from  
21 being the 17th set of diabetic neuropathy criteria,  
22 number one.



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1 Then number two, also, the better you do  
2 this, the more you can open up to other things.  
3 Like, for example, we completely left out diabetic  
4 autonomic neuropathy, even though we circled around  
5 it. And that would to me be the next item on the  
6 agenda list as far as the next ones to address.  
7 DR. FREEMAN: No, agree. I just thought it  
8 was too challenging to do and do a session, but I  
9 agree.  
10 DR. PELTIER: I agree. You have to limit it  
11 somewhere.  
12 DR. FREEMAN: So Teresa, are you ready?  
13 DR. JONES: Yes, so two things. One, we  
14 have an R21 program for secondary data analysis.  
15 R21s are hard to get, but if it came in as a group,  
16 it might be better well received and you could pay  
17 for a biostatistician and all of that.  
18 The other thing when you're writing these  
19 papers, it's really helpful for me with initiatives  
20 if you have some specific high-priority research  
21 needs or opportunities, because then we can refer  
22 to it. But again, high priority and specific would

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1 be good. Thank you.  
2 DR. FREEMAN: Great. That's really very  
3 helpful, and we should definitely consider that.  
4 Rayaz?  
5 DR. MALIK: So I guess is it going to be a  
6 narrative review a systematic review, or a meta-  
7 analysis?  
8 DR. FREEMAN: I think it's going to be a  
9 narrative review, expert consensus. I think it's  
10 of that ilk. It's not meta-analysis, although  
11 there should be some meta-analyses that go into the  
12 decision such as it is.  
13 DR. MALIK: I think if you put it in as a  
14 systematic review, there is a process, and the  
15 journals are more receptive to that because they  
16 then see that it might be treatment-induced  
17 neuropathy, but you've got 4 papers or 10 papers,  
18 and this is what it shows.  
19 DR. FREEMAN: Yes. I think, where possible,  
20 search strategies should be published, and I think  
21 we can do our best to make this a systematic  
22 review. I'm not sure it's going to be that easy.

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1 Vera, do you think your topic, which I think  
2 probably, is best suited to a systematic review?  
3 DR. BRIL: No, not systematic so much, but  
4 I'm wondering, Rodica's group, our group, some of  
5 the others, whether we can put those together. I'm  
6 not sure that this is where that is. But doing the  
7 extra data analysis, I think, is important, looking  
8 at the data set, trying to find cutoffs. To get  
9 fresh data to put in might be interesting, so  
10 that's what I was thinking.  
11 Rodica, what do you think?  
12 DR. FREEMAN: We can talk about research  
13 agenda. My concern is the balance between having a  
14 work product and getting it out and not losing.  
15 Individual enthusiasm is easy to maintain. Group  
16 enthusiasm is substantially harder, and my concern  
17 is that this will get put on everybody's back  
18 burner. So I'm leaning towards --  
19 DR. BRIL: Descriptive.  
20 DR. FREEMAN: -- making do with what we  
21 have, with as much data analysis we can do quickly,  
22 and then research agenda.

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1 DR. POP-BUSUI: I also think that we should  
2 strive for getting something which is unique and we  
3 have chance to do so. So why not do it in the  
4 right way?  
5 DR. BRIL: Rodica, I agree, but as I'm  
6 sitting here, what I've been thinking about is,  
7 where are those data files, what computer are they  
8 sitting on, what shape are they in, where are they  
9 stored? I'm thinking practical, retrieving it,  
10 retrieving all that, which maybe it should have it  
11 all classified and beautifully laid out, but  
12 getting exactly that data may be feasible.  
13 DR. FREEMAN: I do think that what we're  
14 doing is unique. I think that we can argue as to  
15 how different it is, but I think it's different.  
16 And I think the more original data we can put into  
17 it, the better, but we'll talk after lunch about a  
18 research agenda. And I think that's when all of  
19 these can emerge. Doug?  
20 DR. ZOCHODNE: Sorry. I may have missed it  
21 at the beginning of your talk. Did we cover  
22 intercostal neuropathies, meralgia paresthetica, or

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1 ocular motor paralysis?  
2 DR. FREEMAN: No. I didn't think you missed  
3 it.  
4 (Crosstalk.)  
5 MALE VOICE: We probably need to, right?  
6 FEMALE VOICE: I have that on the list for  
7 round 2.  
8 (Crosstalk.)  
9 DR. BRIL: Is intercostal one of Jim Dyck's?  
10 DR. FREEMAN: Stephen?  
11 DR. BRUEHL: Just I realize that if we were  
12 to try to find databases, find the right  
13 statisticians to do it, I mean, do all that  
14 process, that would slow things down. I think it  
15 would be good to do it, but if we opted not to  
16 include that in the first round, you or somebody  
17 here mentioned earlier a Delphi process. And I'm  
18 wondering if, once we have a draft of things set  
19 up, there's a way to format it as a formal Delphi  
20 process, because I think that at least would show  
21 that there was a systematic means of trying to come  
22 up with this, make it easier itself.

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1 DR. FREEMAN: I think that's a great idea.  
2 I spoke to the group in the small room about the  
3 possibility. Dave Bennett and I were involved in a  
4 Delphi process assessment, interestingly enough, of  
5 the symptoms of small fiber neuropathy, which was  
6 actually fascinating. I don't know if you enjoyed  
7 it as much as I did. It was really interesting,  
8 and it's very relevant to what we will be talking  
9 about after lunch. And hat does add a data-driven  
10 element to everything that we have discussed.  
11 I'm not an expert in doing this, but it  
12 certainly was relatively easy to do. There were  
13 rounds of voting, and then the voting was then  
14 distilled, and then there were second rounds of  
15 voting. It was actually fascinating, and maybe  
16 that's something to explore.  
17 Does anybody know more about Delphi  
18 processes than I do, which is not saying -- you  
19 don't have to know much to know more than -- no,  
20 no. David?  
21 DR. ZIEGLER: Yes. I participated in  
22 several ones. You have your catalog of questions

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1 and you just say yes or no. It's pretty  
2 straightforward.  
3 DR. FREEMAN: And you just vote 1, 2, 3?  
4 DR. ZIEGLER: Yes, yes.  
5 DR. FREEMAN: We voted 1, 2, 3, 4, and then  
6 that new vote then created a new set, and then we  
7 voted. So I think that's something worth  
8 considering with an aspect of it. And we can talk  
9 about that, I think, after lunch, when we talk  
10 because that's going to be quite critical. That's  
11 where that really becomes relevant. I think, with  
12 some talks, it's not as relevant as others.  
13 Anything else? Yes?  
14 DR. ZIEGLER: The question is what is your  
15 plan regarding the first paper and the second ones,  
16 whether you want to publish those sequentially or  
17 altogether because that's also a question for the  
18 journal selection. Maybe the first one will be  
19 going faster.  
20 DR. FREEMAN: How did you do that, Solomon?  
21 DR. ZIEGLER: I mean, in Corona, it was the  
22 case. So the individual papers came out in 2011

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1 and the first was in 2010.  
2 DR. TESFAYE: The summary paper came first.  
3 DR. ZIEGLER: Yes.  
4 DR. TESFAYE: And as I mentioned, try and  
5 see if we can get it in a good popular journal,  
6 maybe in a neurology journal.  
7 DR. ZIEGLER: Especially if you want to go  
8 into depth, and new databases, and so on, that will  
9 take time. So that would slow down the first one.  
10 I was wondering if Diabetes Care would not be  
11 interested, whether Annals of Neurology is a place  
12 for the first one.  
13 DR. TESFAYE: I think it's important to note  
14 that it will undergo peer review again, so it's  
15 going to go through a rigorous peer review. And so  
16 all the stuff that we put in, we put in this test.  
17 You have to back it up. Is there a level A  
18 evidence for these, et cetera? But that, we can  
19 do.  
20 DR. ZIEGLER: But it's conceivable that they  
21 say we just have the consensus and not that much  
22 interest in it, so we should take that into

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1 account, although I think there are ways.  
2 DR. FREEMAN: Yes, no. I think the argument  
3 that this is totally different, this is for  
4 research, the consensus was clinical. But  
5 hopefully, they will accept that.  
6 DR. RUSSELL: Who will be left in the  
7 diabetic neuropathy field to peer review this since  
8 we've actually got virtually everyone here?  
9 (Laughter.)  
10 DR. RUSSELL: There are thousands of others.  
11 (Crosstalk.)  
12 DR. FREEMAN: On that note, let us eat. So  
13 it's now 12:00, lunch 12:00 to 1:00, and then if we  
14 can come back and flesh out a few things.  
15 (Whereupon, at 12:00 p.m., a lunch recess  
16 was taken.)  
17  
18  
19  
20  
21  
22

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1 AFTERNOON SESSION  
2 (1:04 p.m.)  
3 Final Discussion  
4 DR. FREEMAN: Two items on the agenda this  
5 afternoon or maybe three.  
6 Do you have any diabetic neuropathy  
7 consortium business?  
8 DR. GIBBONS: No. I'll be sending around a  
9 summary of all the things we talked about, and I'll  
10 be roping everybody into work. Thank you.  
11 DR. PELTIER: We come up with a name yet?  
12 DR. GIBBONS: No. We're waiting [inaudible  
13 – off mic].  
14 DR. FREEMAN: Two pieces of the agenda, one  
15 is research agenda, and that's a big picture and  
16 small picture. Based on this meeting, I wrote down  
17 a couple of things that we thought would be good,  
18 and I just want people to throw out whatever else.  
19 One idea was empiric validation, and that  
20 was using perhaps EDIC, DCCT, other databases, and  
21 I would hope that Rodica would help us with that.  
22 Is there anybody else who has any other

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1 database that we could use for empiric validation  
2 of signs and symptoms, perhaps using cluster  
3 analysis or some of the other CART type analysis  
4 that Steven mentioned?  
5 DR. TESFAYE: Yes. Somebody quoted it  
6 yesterday.  
7 DR. FREEMAN: Yes, exactly, yours, yes. Rob  
8 quoted this morning, I think, yes.  
9 DR. TESFAYE: [Inaudible – off mic] --  
10 depression, anxiety, painful neuropathy.  
11 DR. FREEMAN: But what about the database  
12 that Rob quoted this morning, that you used, that  
13 big European database?  
14 So any thoughts as to how to actually  
15 implement that? Rodica's not here, but you are.  
16 Any?  
17 (Laughter.)  
18 DR. BRIL: Sounds like a punishment now.  
19 DR. GIBBONS: So Rodica did ask me to say  
20 make sure that we do this. And she is willing to  
21 cooperate on the data side from that data.  
22 DR. SMITH: I wonder if the International

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1 Diabetic Neuropathy Consortium have these type  
2 [inaudible – off mic].  
3 DR. FREEMAN: Talking about Troel's?  
4 DR. SMITH: They're doing something in  
5 Michigan and I don't know what kind of data they're  
6 collecting.  
7 DR. BENNETT: Troels will have some of that  
8 data, yes, because, as part of the DD2 study in  
9 Denmark, they've sent out a screening  
10 questionnaire. Then they're bringing patients  
11 back, and that will be a mixture of neuropathy and  
12 no neuropathy. And there will be, quite highly,  
13 phenotypes. So yes.  
14 DR. FREEMAN: So is it something that you'd  
15 be interested in helping with?  
16 DR. BENNETT: I can certainly speak to him  
17 about it, yes.  
18 DR. FREEMAN: Yes.  
19 DR. TESFAYE: The other database is the  
20 German -- it's going to be anonymized. It's going  
21 to just have the demographic data, et cetera. So  
22 what's the politics of sharing this sort of stuff?

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1 DR. ZIEGLER: The GDS will be difficult, I  
2 think, several hurdles. I don't know. I cannot  
3 promise whether that works, but I could have a  
4 look, whatever. If there is a need, I could do my  
5 own analyses, so with the CORA data regarding the  
6 metabolic syndrome.  
7 DR. FREEMAN: Yes, exactly. And that's also  
8 on the list, but that would be different.  
9 DR. BRIL: So Roy, I would have to get  
10 ethics approval before I could share data with  
11 anybody. I mean, it would be a global ethics  
12 approval for a database, but I couldn't just share  
13 it or pool it without going through my ethics  
14 committee.  
15 DR. FREEMAN: Right, no. Of course, I  
16 understand. So I think there are two  
17 possibilities. The one possibility is that this be  
18 done at an individual level, as I guess Dan is  
19 suggesting, that he could look at his database and  
20 give us data to support whatever assertions we will  
21 make. And the other is that this be done as a  
22 group effort with people volunteering and helping.

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1 I'm sure we have enough work to do. Either one is  
2 fine.  
3 Yes?  
4 DR. MALIK: So there is NIH-funded DP3  
5 multiple consortia data. It's about five centers  
6 where we have got very detailed phenotyping in  
7 diabetic patients, probably a cohort of around a  
8 thousand-plus patients and then follow-up data as  
9 well up to 7 to 8 years with detailed phenotyping.  
10 Bruce Perkins, myself, and Nathan Efrom were  
11 part of the consortium, and Vera, so obviously I  
12 don't know if there are aspects that you want to  
13 interrogate, that you think are important, and then  
14 I'm sure we can consider that.  
15 DR. BRIL: But it's the same thing. Even if  
16 I look at my own database to share outside, and if  
17 I'm doing stuff that I didn't originally have  
18 ethics approval for, I have to go get it; and I'm  
19 sure for the consortium as well.  
20 DR. MALIK: But it's fine. You can put it  
21 in ethics --  
22 DR. BRIL: But that's not an issue. You can

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1 do it, but it'll take time.  
2 DR. FREEMAN: It's a hurdle. So the  
3 question is next steps. Okay? So we've got a  
4 couple of databases. We've got a couple of people  
5 who have either direct or partial ownership of the  
6 databases. Give me a message as to what direction  
7 or a road map as to how we can take the next step.  
8 I think it's kind of important.  
9 It seems to me that probably we're going to  
10 be doing this based on -- and I like the idea of  
11 the Delphi method, but it would be, I think,  
12 important for us to actually have some empiric  
13 data.  
14 DR. BRIL: If it's reanalysis of what  
15 already exists and what we did, we could just go  
16 ahead and do it. If we're going to add to our  
17 database from outside, it wouldn't matter to us.  
18 It wouldn't matter to whoever's giving it to us.  
19 But if we're just taking the existing database and  
20 looking at the distributions --  
21 DR. FREEMAN: So that's, I think, what we're  
22 suggesting.

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1 DR. BRIL: -- then that's fine. We could do  
2 that.  
3 DR. BRUEHL: That's what I was thinking,  
4 instead of trying to go out of your way to get more  
5 data at this point, is just take whatever happens  
6 to be archived, the best data sets we've got.  
7 What I might think is, it looks like we've  
8 already got at least draft versions of most of the  
9 sets of criteria and have everybody think about, if  
10 we had a giant database, like Rayaz was just saying  
11 about diabetics with all kinds of phenotyping data,  
12 if we were to do a cluster analysis, for example,  
13 and have that divvy up the patients based on X, Y,  
14 and Z characteristics, which you have to specify,  
15 what would you expect to see if you think that the  
16 criteria are valid?  
17 How would you expect it to break out?  
18 Because I think the strongest thing we can address  
19 with existing data is do real patients break out  
20 into categorizations that look more or less like  
21 the categories we've created.  
22 But it's garbage in, garbage out. So we

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1 have to think about what do you want to go into the  
2 analysis. And looking at the list of features that  
3 we had yesterday in our group, we had a list of, I  
4 don't know, maybe eight or so features for the  
5 sensory changes, pain-related characteristics.  
6 With a large data set, you could include 15 or more  
7 variables and have it classified based on that.  
8 DR. FREEMAN: So are you suggesting a  
9 hypothesis-driven analysis or an agnostic,  
10 hierarchical kind of analysis?  
11 DR. BRUEHL: You could do both. I mean, the  
12 first thing I would say is, it doesn't take any  
13 more time to do it. You just include a massive set  
14 of variables you're interested in, and with enough  
15 patients, you can just do a cluster analysis on the  
16 whole thing, see how many categorizations there  
17 are, look at the patterns of signs, and symptoms,  
18 and test results within each of those, and just  
19 have everybody look at that and say, what would you  
20 call this; does this remind you of anything, some  
21 diagnostic entity.  
22 Then the flip side is, take our individual

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1 criteria, include only those features we've  
2 included in our criteria, and see, if we  
3 look -- ideally it would be a group that you think  
4 would meet the criteria and another group that  
5 clearly doesn't, cluster based on the features and  
6 diagnosis you're interested in and see if it pops  
7 out as two different categories. That's more  
8 hypothesis driven.  
9 DR. BENNETT: Anything I would say about the  
10 completely non-hypothesis driven is, all the  
11 databases all have different measures, different  
12 levels of granularity. So it might be easier  
13 actually to get the criteria first and then see how  
14 those map on because, actually, when we have that,  
15 we'll at least know what databases have the right  
16 information in them.  
17 DR. BRUEHL: Correct, yes.  
18 DR. BENNETT: Otherwise, we could all spend  
19 a lot of work on different databases, then find  
20 they don't map to each other all the criteria in an  
21 easy way at all.  
22 DR. SMITH: Yes. I was going to make that

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1 same point, but I wonder if [inaudible – off mic].  
2 Sorry.  
3 So let's say that Vera's database has the  
4 right categories of symptom and sign descriptors to  
5 allow this sort of agnostic approach. One could do  
6 the agnostic approach with one database, look at  
7 the data, then do a Delphi sort of model based on  
8 that information, derive the criteria, and then  
9 validate them in a different database that also has  
10 similar granularity. And if that's plausible or  
11 attractive, then the first step would be just to  
12 know what databases are available, what the look  
13 like, and which might be useful for this.  
14 DR. BRUEHL: I think it would be important,  
15 just based on what we've done so far, that  
16 whichever database we pick has the data elements  
17 that are in what we're considering. If there's one  
18 that's missing key features, that makes it  
19 difficult to do that validation.  
20 DR. FREEMAN: That's not going to be key  
21 features, but I think the degree of granularity may  
22 differ among the databases.

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1 What I think I'd like to ask is, is there  
2 anybody who would like to spearhead that initiative  
3 by communicating with everybody? To me, it seems a  
4 great project for somebody.  
5 DR. TESFAYE: Rodica maybe.  
6 (Laughter.)  
7 DR. BRUEHL: I can tell you from  
8 conversations outside the meeting she's already  
9 volunteered to do this.  
10 DR. FREEMAN: We're talking about not only  
11 her database, but speaking to David, speaking to  
12 Vera. It's funny. I was going to have the exact  
13 same approach. I said, it seems a good approach  
14 for somebody young. And I was going to volunteer  
15 Noah to do it, but Rodica, if she's enthusiastic,  
16 that's great. Good. And who shall I say nominated  
17 her?  
18 (Laughter.)  
19 DR. BRUEHL: All of us. I will, and I will  
20 offer to help guide her on this.  
21 DR. FREEMAN: Look, I think this is really,  
22 really important.

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1 DR. BENNETT: I do think it's much easier  
2 once we've got some idea of what the core features  
3 might be.  
4 DR. FREEMAN: That's to come, so let me keep  
5 moving. While we're on this, then, because this  
6 seemed rather critical, Dan's database, it looked  
7 like there's the possibility of you actually  
8 enthusiastically looking at the features of the  
9 metabolic syndrome in the same fashion that you  
10 looked at impaired glucose tolerance.  
11 I think that would really put this entity on  
12 the map or take it off the map. Do you trust Dan  
13 to do this by the way?  
14 DR. SINGLETON: I think I'd like to talk to  
15 Dan about the phenotyping of neuropathy that you  
16 have, because as I said before, I think that's  
17 where other databases are weak.  
18 DR. FREEMAN: Are there other databases  
19 other than --  
20 DR. SINGLETON: Neurologists have  
21 collections of patients with impaired glucose  
22 tolerance and neuropathy, and I think that there is

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1 some value in aggregating those patients. Teresa  
2 Jones was suggesting to me that she would be very  
3 interested in more outcome data about those people.  
4 What happens to them? What's their fate over time?  
5 Do they go on to develop diabetes? If they don't,  
6 does their neuropathy get worse despite not going  
7 on to getting diabetes?  
8 I think that we in this room have large  
9 collections of well-phenotyped pre-diabetic  
10 neuropathy patients, and seeing how their natural  
11 history evolves would help to answer this question  
12 as well.  
13 DR. ZIEGLER: Actually, what we have now is  
14 7-year prospective data, so the stuff you  
15 presented, we published. We now have the follow-  
16 ups. But of course, the neuropathy assessment is  
17 screwed [indiscernible] using the MNSI, although in  
18 the follow-up, we also have nerve conduction, but  
19 point of care with a DPN check, but there's nerve  
20 conduction data there.  
21 Of course, we could model the role of the  
22 metabolic syndrome in the incidence progression of

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1 neuropathy during that 7-year prospective follow-  
2 up, which is, I think, unique. And that's  
3 population based. The only thing is, it's an  
4 elderly population, so there will be a number of  
5 deaths, of course. But that gives you also some  
6 room for mortality analyses.  
7 DR. SINGLETON: Is Dan's database unique?  
8 Do we have other ones that we can roll together  
9 with?  
10 DR. FREEMAN: Any other community-based  
11 anything, EURODIAB, NEURODIAB?  
12 DR. TESFAYE: We've got access to EURODIAB  
13 data, but it depends, as David mentioned. We need  
14 to have a hypothesis as well. There's two ways of  
15 looking at these. One is to have a hypothesis-  
16 driven mining of data and being careful to make  
17 sure that there aren't major confounders, selection  
18 bias. All these needs to be done very carefully.  
19 For instance, if you wanted to look at the  
20 severity of pain and the severity of neuropathy,  
21 you can mine any data. You're looking at two  
22 associations. Even if there is selection bias, it

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1 doesn't matter. You're looking at pain severity.  
2 So you can do that, so as long as there is a  
3 good hypothesis, the data is there in London.  
4 DR. FREEMAN: I think we're talking about  
5 the pre-diabetic, metabolic syndrome features.  
6 DR. TESFAYE: The type 1 patients.  
7 DR. FREEMAN: Yes.  
8 DR. GIBBONS: Just one thing as well -- I  
9 mean, obviously we've had changing guidelines and  
10 requirements in terms of treatment care. So one of  
11 the things we'd seen in our own database was that  
12 the introduction of things like ACE inhibitors,  
13 angiotensin receptor blockers, have all of that  
14 modification of the other risk factors, does in  
15 fact modify the risk factors. So particularly  
16 statin use and everything else, when those are  
17 introduced, that does add variables that we have to  
18 think about.  
19 DR. ZIEGLER: So we can adjust for whatever  
20 you want. So this information of course we have in  
21 CORA.  
22 DR. SINGLETON: Maybe, Dan, you and I could

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1 just think about the questions we want to ask about  
2 this.  
3 DR. ZIEGLER: We can also model the early  
4 course of neuropathy. Of course, then, if it's a  
5 GDS study, based on whatever you want, nerve  
6 conduction, thermal thresholds, vibration, QSD,  
7 it's all there. Some patients also have skin  
8 biopsy and CCM. And for those, we now have some  
9 200 to 300 people from within the first year from  
10 diagnosis over 5 years, prospectively.  
11 That's for type 1, type 2, so we had two  
12 groups and, for the type 2, you can model the  
13 metabolic syndrome and the questions of interest.  
14 DR. SINGLETON: Just to be clear, are they  
15 patients with diabetes and metabolic syndrome?  
16 DR. ZIEGLER: They're all diabetic, so those  
17 GDS-driven diabetes studies are all diabetics. So  
18 the starting point is within the first year after  
19 diagnosis, and then the first five years. So  
20 that's early neuropathy, extremely well phenotyped.  
21 By the way, they all have the glucose claims, so we  
22 have insulin sensitivity, which by the way does not

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1 correlate with the neuropathy. I would have  
2 published that, but it correlates with autonomic  
3 neuropathy.  
4 So that's one part. On the other part, the  
5 CORA is -- this is not population based. So there  
6 is some kind of selection there. And CORA is  
7 population based, and most of these people actually  
8 have normal glucose tolerance as it is distributed  
9 in the population. It is population based. All  
10 have the OGGT done at baseline and after seven  
11 years.  
12 DR. SINGLETON: It seems like the most  
13 useful would be to focus on study participants  
14 before their diagnosis of diabetes. Look for those  
15 who do or do not have other features of metabolic  
16 syndrome by ATPIII criteria.  
17 DR. ZIEGLER: Yes. Actually, what we have  
18 of course is incident diabetes there, so the  
19 translation from pre-diabetes to diabetes. And you  
20 can see why the metabolic syndrome was a predictor  
21 of that. I'm not sure whether the groups are large  
22 enough. That needs to be seen by the statistician.

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1 So the group is something like 700 in total,  
2 and I guess at least one-third has died of course  
3 within seven years.  
4 DR. FREEMAN: That's interesting. I'd be  
5 particularly interested in looking at the incidence  
6 of retinopathy and microalbuminuria. And often,  
7 when as a neurologist I talk about this entity,  
8 whatever it is, I say, what about nephropathy, what  
9 about retinopathy, why neuropathy? And I'm sure  
10 you guys may have had to answer that question as  
11 well. And I've heard Eva say, oh, it does occur,  
12 but I'm not so sure the diabetologists buy that.  
13 DR. ZIEGLER: You mean pre-diabetes and  
14 microvascular? There's controversy there. It's  
15 not generally accepted that this really exists.  
16 DR. FREEMAN: Yes, no, I understand. And  
17 that's an argument that is often given to counter  
18 the neuropathy story.  
19 So the next point was, somebody raised the  
20 possibly of a vignette approach to Chris and Jim's  
21 data. I think it was Gordon who thought it was a  
22 good idea.

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1 Do you want to elaborate? What should Chris  
2 do? What should Jim do?  
3 DR. SMITH: I think I was more interested in  
4 the idea of using this agnostic approach with  
5 Chris's data because you have these categories  
6 fairly well worked out and in four different  
7 groups. I'm trying to remember my comment about  
8 the vignette, and I think that was for Jim's data.  
9 DR. FREEMAN: It was.  
10 DR. SMITH: Yes, because I think we all  
11 think we know what it looks like.  
12 DR. FREEMAN: Yes, no. And I think it was  
13 prompted by, I don't know, isolated peroneal  
14 neuropathies and things that we might think were  
15 something else and whether there's a gray zone on  
16 the edge in what people thought of that.  
17 I think it would be interesting. I don't  
18 know if it's that critical. I think the database  
19 mining and the cluster analysis would be rather  
20 interesting with Chris's database as well, which it  
21 seems like there is a lot of data there, and that's  
22 something that perhaps Chris needn't put on

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1 Rodica's plate.  
2 DR. SMITH: I think that would make perfect  
3 sense to really refine those questions.  
4 DR. SINGLETON: Right. Well, as we talked  
5 about, a data mining exercise to try and better  
6 establish a true incidence or prevalence of this  
7 condition would be valuable, because right now, you  
8 obviously have a remarkably skewed population.  
9 That would in itself be a great goal.  
10 DR. FREEMAN: But as David Bennett said, I  
11 don't know how biased your examinations are on  
12 those patients who you think have the entity versus  
13 those patients you think don't have the entity. So  
14 I think it would be a great idea.  
15 DR. GIBBONS: The good news is they all had  
16 the same exam.  
17 DR. FREEMAN: So that's really good. Steve?  
18 DR. SMITH: I think Rob has a really  
19 interesting point, though, because the mild  
20 phenotype of TIND looks very much like in DPN. So  
21 it might be that this is actually very common and  
22 we just don't know.

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1 I mean, clearly, the classic phenotype, as  
2 to my experience, is quite uncommon. But if it's  
3 possible using a larger jaws on database to go back  
4 and look in an unbiased way at the prevalence of  
5 neuropathy or incident neuropathy in relation to  
6 change in glycemic control, that could really be  
7 informative to the criteria for this, if it's clear  
8 that there's a large milder phenotype that we want  
9 to catch.  
10 DR. FREEMAN: Steve?  
11 DR. BUEHLER: Yes. And a couple of points  
12 here just to keep in the back of your mind as  
13 you're thinking of ideas in this regard, one is,  
14 for example, if you've got validated instruments  
15 that you use to assess sensory symptoms, rather  
16 than just the total score, if you've got the  
17 individual items in the database, it's nice because  
18 then you can start to ignore where it came from,  
19 and we can mix and match -- in a cluster analysis,  
20 you can mix and match from different measures by  
21 standardizing the scaling of all of them.  
22 That would be preferable, I think, just not

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1 be stuck with a total score from some existing  
2 measure, but be able to look individual items.  
3 That's one point.  
4 Another point is, if you're looking at,  
5 like, how big a data set do I need to be able to do  
6 something like this, just as a rough estimate,  
7 think about having as a bare minimum about 10  
8 patients for every variable that you want to look  
9 at.  
10 So if you're interested in 10 clinical  
11 features, you'd need at minimum 100, preferably  
12 more than that, but you'd probably be able to  
13 publish it with that few. And some of these data  
14 sets that have been talked about, if they're really  
15 large, like a thousand people, it would be really  
16 nice because the best approach would probably be to  
17 do random subsamples from that, split it into two,  
18 do one database that's discovery and then try to  
19 replicate the finding in the second database. And  
20 that would be really compelling if we were trying  
21 to publish it.  
22 DR. FREEMAN: That's great. I think the

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1 next point was, that at least I wrote down, the  
2 Delphi analysis or Delphi approach to what we'll  
3 talk about next, and I want you to look at what we  
4 present with that in mind.  
5 Everybody's familiar with the Delphi  
6 process? I sort of view it as the wisdom of  
7 crowds, which some might say is the stupidity of  
8 crowds, though Alabama gives perhaps a little bit  
9 of hope.  
10 (Laughter.)  
11 DR. FREEMAN: But essentially, experts then  
12 vote on what they think is appropriate and, in a  
13 series of iterations, the view is that wisdom  
14 ultimately prevails. I think it did in the one  
15 that we did, didn't it?  
16 DR. BENNETT: Yes, it did, yes.  
17 DR. FREEMAN: I don't know. Has anybody  
18 else been involved in a Delphi process here?  
19 DR. BRUEHL: I did one for CRPS, that one.  
20 DR. FREEMAN: Did wisdom prevail?  
21 DR. BRUEHL: Yes. It pretty much fit what I  
22 would have expected, yes.



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1 DR. FREEMAN: Yes. So I think it does  
2 provide at least some sense that this was done in  
3 a, if not evidence base that was a reasonable  
4 distillation of what experts feel --  
5 DR. BENNETT: The only thing I would say,  
6 Roy, is that the general thing would be to do the  
7 survey before the meeting, put everyone in a room,  
8 discuss, and then repeat. I don't know; it would  
9 be a very big telecom. But you'd need some kind of  
10 discussion after the initial survey; otherwise,  
11 wisdom doesn't have a chance.  
12 DR. BRUEHL: Can I suggest an alternative  
13 here? we've biased ourselves for doing a Delphi  
14 method within the group here, but we now know what  
15 the lay of the land is, all the things that we'd be  
16 interested in looking at. Is it possible to set  
17 this up and distribute to some mailing list of  
18 diabetic researchers that weren't involved in this  
19 or neurologists that weren't involved in this a  
20 little more broadly?  
21 DR. FREEMAN: That's an interesting idea.  
22 What do people think? Is it possible to do? Or we

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1 could just call it a modified Delphi approach.  
2 We're allowed to do that. But you're right. Do  
3 you think we could find 20 neurologists,  
4 diabetologists with an interest? It might be  
5 interesting to do that as well.  
6 Anything else that emerged that others think  
7 would be worthwhile doing? I've got one or two  
8 things on my agenda, but they more relate to future  
9 activities. Any other research projects that came  
10 to mind as a consequence of this?  
11 (No response.)  
12 DR. FREEMAN: So I think what I'd like to do  
13 is just quickly say my view, as I said earlier, is  
14 that we do need to deconstruct everything that  
15 we've done so far, and begin again, and to think  
16 about standardization and things.  
17 As I was discussing with James, I mentioned  
18 about my first ever assay sensitivity. We really  
19 don't know how sensitive our measures are to change  
20 to talk about placebo response, to talk about the  
21 various instruments and outcomes. All of those  
22 things, I think we need to take a long hard look at

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1 what we have. I know that some have done this more  
2 than others, but I think, to me, that's part of the  
3 research agenda. And I think that's something to  
4 think about. I don't know.  
5 James, I know that you've thought about this  
6 a lot. Vera, you've thought about this a lot. Do  
7 you want to maybe just give a little discussion on  
8 that and maybe provide a framework as to where we  
9 could go next?  
10 DR. RUSSELL: We had a careful discussion  
11 about this, and I said that I think we really need  
12 to separate what we're doing here at this meeting,  
13 which is coming up with predominantly clinical  
14 criteria, from how we're going to look at  
15 endpoints. One of the problems -- and I've looked  
16 at the various clinical scales that are being used  
17 and other measures that are being used or developed  
18 by many people, some by ourselves.  
19 The one problem with the clinical measures  
20 is that there's a large degree of variance, and  
21 that really affects your prior analysis. So when  
22 you're looking to do a diabetic neuropathy study,

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1 the problem is you're always looking at the amount  
2 of funding, and therefore the amount of available  
3 patients you'll have. And unfortunately, that  
4 amount of variance that you have in many of these  
5 clinical scales -- and this is true also for  
6 outcome measures -- really is your enemy.  
7 So we have to approach this. So you can  
8 either say we need something which has a lower  
9 variance, and therefore we would have to require  
10 much fewer patients as an outcome measure, or we  
11 can say perhaps we should go back and we should try  
12 to refine the clinical scales and come up with  
13 clinical scales that have lower variance and  
14 therefore would require a much smaller number of  
15 subjects in the ultimate study.  
16 Now, the other thing is that many of us,  
17 when we do this, we use our own data sets, and many  
18 of those data sets have been very carefully  
19 collected. So in other words, you have someone who  
20 really is trying to be as careful as they can and  
21 reproducible as they can. If you were to use those  
22 clinical scales with centers where people are

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1 perhaps going to be less rigorous about applying  
2 them, you have an even bigger problem.  
3 So all of these things have to be taken into  
4 account and I believe you really have to separate  
5 out the clinical measures as definitions of  
6 neuropathy versus using them in clinical trials.  
7 And I think, at this point, we have a real problem  
8 with that, and perhaps we should think how can we  
9 make those clinical measures a lot more refined, a  
10 lot more reproducible, and therefore have a much  
11 lower variance.  
12 DR. FREEMAN: Vera?  
13 DR. BRIL: I really agree with what James  
14 just said and with what you've been outlining in  
15 the meeting. I'm not sure I have much to add.  
16 You've covered an awful lot.  
17 I would say we are defining. I mean, it's  
18 taxonomy for the definitions of these different  
19 entities. Some of the definitions include more  
20 than clinical items. I mean, we have the clinical  
21 definitions, the confirmations, so I think it's a  
22 bit more than that. But as a first step, I think

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1 we've made a lot of progress to a lot of these.  
2 DR. FREEMAN: I want to view this  
3 sequentially, that if we look at the clinical  
4 trial, what we've attempted to do in these past two  
5 days is to look at inclusion and exclusion  
6 criteria. I think what we didn't do and didn't do  
7 well enough -- and this may be, to me, one of the  
8 next items on the agenda, and I have a  
9 suggestion -- is standardization, because I think  
10 standardization comes through the next step, the  
11 clinical trial itself and the outcomes, the  
12 instruments. And I think standardization is really  
13 important as well as reducing variability, which I  
14 think may be part of the same process.  
15 But I think we need to discuss a little how  
16 to deal with standardization when we talk in just a  
17 moment. But I think let's think about that, and  
18 that would be hopefully the next meeting or the  
19 next item on the agenda.  
20 So I want to now begin to, in the time  
21 that's remaining -- does anybody have a hard stop  
22 at 2:00?

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1 (No response.)  
2 DR. FREEMAN: Yes, okay, so enough. So this  
3 is our aim. This is what we want. And when I  
4 speak about inclusion criteria/exclusion criteria,  
5 this was the aim of the meeting, I think  
6 beautifully quoted.  
7 Next slide. This is the kind of thing we  
8 want to come up with. We haven't quite done it.  
9 The formatting looks very similar to our  
10 formatting, but this is where we want to go.  
11 Can we see the next set of slides? And  
12 that'll be the PowerPoint one. So I don't know if  
13 you remember from yesterday.  
14 DR. BRIL: Could you go back to that?  
15 DR. FREEMAN: Which one?  
16 DR. BRIL: The one you just had up.  
17 DR. FREEMAN: The migraine one, yes.  
18 DR. BRIL: How was TIA excluded? I'm  
19 curious.  
20 DR. BRUEHL: [Inaudible – off mic] -- it's  
21 like, whatever you would use clinically to diagnose  
22 TIA, if they need that [inaudible – off mic].

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1 DR. BRIL: So clinically, but it didn't  
2 include imaging or vascular studies?  
3 DR. BRUEHL: No. That's actually preferable  
4 for rule-outs like that since in many cases, it can  
5 be really broad; so leave it just kind of generic  
6 and say if they have this condition or other  
7 conditions, you don't get the diagnosis, and not  
8 really go into how you determine that.  
9 DR. BRIL: So in other words, you're very  
10 specific about the elements of migraine, but how  
11 you exclude other things is very generic.  
12 DR. BRUEHL: Very generic.  
13 DR. FREEMAN: It's an interesting point with  
14 regard to the question that David raised this  
15 morning about the neuropathy of the Ziegler-  
16 Singleton syndrome.  
17 (Laughter.)  
18 DR. FREEMAN: What do you need to exclude?  
19 Do you specify as they didn't do over here or do  
20 you say B12, SBP, IP?  
21 DR. BRIL: So when we talk confirmatory  
22 tests, do you have to list them then? Because I'm

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1 just curious. This is all about the clinical  
2 definition and that, and you're not being very  
3 specific. So the question is -- and this is to  
4 what we're doing here now. How specific do we have  
5 to be about confirmatory tests?  
6 DR. BRUEHL: This is just my opinion. If  
7 having looked at all this literature, you're  
8 convinced that one test is the gold standard and  
9 the others aren't as good, it might be worth saying  
10 that to use that test. Otherwise, you could just  
11 certainly say confirmed by testing and you could  
12 just say EG in parentheses and list a couple  
13 without saying what exactly a person could do,  
14 which makes the job much easier in creating the  
15 criteria, because then you don't have to assess so  
16 much exactly about what readings on this test would  
17 mean this.  
18 DR. FREEMAN: Let's go to the next  
19 PowerPoint. So this was the group and the small  
20 group, which was Eva and Gordon. And I just wanted  
21 to go through this and I have a couple of  
22 questions. So my red, a possible neuropathy

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1 symptoms or signs, one or more symptoms or signs,  
2 and the first discussion is, for possible, one set  
3 of symptoms okay and one sign okay for possible  
4 neuropathy?  
5 I'm assuming that for possible sensitivities  
6 is what will be our goal, so it might be  
7 reasonable, but I want to hear people's thoughts.  
8 Pain, I thought we could actually go back to the  
9 Delphi manuscript that Dave and I were involved in  
10 because it actually addresses that question  
11 directly. And we could then make some kind of  
12 approach to that. And I think we came up with a  
13 menu even of that.  
14 DR. BRUEHL: I'm sorry. Can you clarify  
15 what you're saying? Because I sat in the group  
16 that did this, and literally, if we were to use  
17 something like this, it would mean that anybody  
18 reporting pain would be considered possible  
19 neuropathy. Now, that's true in the strictest  
20 sense. It's also ridiculously broad.  
21 Would you narrow the pain to a particular  
22 type of pain?

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1 DR. BRIL: Symptoms in a bilateral,  
2 symmetrical link-dependent fashion in the lower  
3 limbs. That is the first sentence. So it's not  
4 pain --  
5 DR. BRUEHL: So it's in the context of this  
6 having pain. Gotcha.  
7 DR. FREEMAN: I'm assuming that we're all on  
8 the same page, which we somewhat are, and we're  
9 saying neuropathic pain and these are the features  
10 of neuropathic pain.  
11 Any comments on that? I had some questions  
12 about negative symptoms, numbness, dead, how to  
13 quite do that, how to refine that. I thought some  
14 clarification was necessary; could do it, but I  
15 wanted to -- yes?  
16 DR. HERRMANN: I have a little topic from  
17 your questions. It says one or more symptoms or  
18 signs. Under that signs being multiple, you could  
19 have three signs. You could have loss of pinprick,  
20 vibration and that might take you out of the  
21 possibles.  
22 DR. SMITH: It should be one symptom or

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1 sign.  
2 DR. BRUEHL: Should be one symptom.  
3 DR. HERRMANN: One symptom or one sign.  
4 DR. SMITH: Actually one plus.  
5 DR. BRUEHL: No. It is absolutely one plus.  
6 DR. BRIL: Originally, we had done one  
7 symptom or one sign.  
8 DR. FREEMAN: One sign, that's what I  
9 thought.  
10 DR. BRIL: But then yesterday, after the  
11 discussion in the group, it came to this because  
12 everybody was talking about plantar fasciitis.  
13 There's nothing at all specific about this. This  
14 is sensitive.  
15 DR. SMITH: Yes, no. I think this was a  
16 typographical error on the slide.  
17 (Crosstalk.)  
18 DR. SMITH: Yes. So it's supposed to be one  
19 symptom or sign.  
20 DR. FREEMAN: Yes. So who's writing notes?  
21 Somebody, one of your group, please write notes as  
22 to how to change this. And we'll send it round to

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1 you again.  
2 Does anybody have good wording for negative  
3 symptoms?  
4 MALE VOICE: It's numbness or dead feeling.  
5 And I mean, we have nothing.  
6 DR. GIBBONS: Absence of detectible  
7 sensation.  
8 DR. FREEMAN: That's a sign.  
9 (Crosstalk.)  
10 DR. GIBBONS: They report that they can't  
11 feel their feet on the floor.  
12 DR. ZIEGLER: Why don't you simply replace  
13 the wording positive neuropathic symptoms and don't  
14 do that differentiation? I mean, what is it good  
15 for?  
16 DR. BRIL: I agree. I always thought we  
17 should take out the positive and negative.  
18 MALE VOICE: I think it's confusing.  
19 DR. FREEMAN: Okay, but let's have the  
20 negative. How would you put the negative in?  
21 What's that?  
22 MALE VOICE: Make another symptom that you

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1 notice --  
2 DR. ZIEGLER: No, just neuropathic symptoms  
3 and you have three symptoms there. That's it.  
4 DR. FREEMAN: So you're saying pain,  
5 numbness.  
6 DR. ZIEGLER: It's all symptoms. Whether  
7 it's positive or negative, who cares?  
8 DR. FREEMAN: So we're not categorizing  
9 them, but we do have to have the absent symptoms.  
10 You've got pain.  
11 DR. ZIEGLER: That's the signs. That's the  
12 signs.  
13 DR. FREEMAN: No, no, no. Patients will  
14 complain of something.  
15 (Crosstalk.)  
16 MALE VOICE: In terms of numbness and dead  
17 feeling.  
18 DR. SMITH: So I thought we said that there  
19 were going to be non-painful paresthesias, which  
20 could encapsulate these painful paresthesias or  
21 symptoms of sensory loss was the other, as opposed  
22 to that.

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1 MALE VOICE: Yes. I would prefer that, so  
2 you can say painful and non-painful.  
3 (Crosstalk.)  
4 DR. FREEMAN: Symptoms of sensory loss. Can  
5 you write that down? Will you keep track of that?  
6 MALE VOICE: You can put parenthesis  
7 examples, too.  
8 DR. FREEMAN: Yes. And then give your  
9 examples, numbness, deadness, whatever. I think  
10 that's fine.  
11 DR. BENNETT: I think essentially there are  
12 three categories, pain, tingling, numbness.  
13 DR. FREEMAN: Exactly.  
14 DR. BENNETT: We can elucidate those a bit  
15 more, but I think those three categories are used.  
16 DR. FREEMAN: Very happy with that, yes.  
17 Good.  
18 Signs are pretty straightforward. I want to  
19 talk a little bit about signs since we have them  
20 here. I spoke about standardization. We haven't  
21 done that. We do need to do that. One possible  
22 solution to that is Jen and Chris are doing this

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1 assessment of all of the clinical scales, some of  
2 which in the scale mention how to and some of them  
3 don't.  
4 If we take what we think are the better or  
5 best of the how-tos of those 17 instruments -- how  
6 many were there, 16, 17, 18 -- 18, and deal with  
7 these from there and with appropriate citations, is  
8 that good enough for the moment?  
9 DR. BRIL: Yes, to start.  
10 DR. FREEMAN: Good.  
11 DR. RUSSELL: The one thing which may not be  
12 on there is actually the temperature, the cooling.  
13 DR. FREEMAN: It is right there in red.  
14 DR. RUSSELL: So I kind of like it, but you  
15 have to have the right equipment to do it  
16 correctly, and it may not be that everyone has  
17 that. So I personally like it, but I'm not sure  
18 that it's going to be feasible for everyone to do  
19 it accurately.  
20 DR. FREEMAN: I find Boston in winter, it  
21 doesn't work.  
22 DR. BRIL: You can acclimatize people. You

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1 can make sure their feet are warm and use a cool  
2 tuning fork. We've done this forever. I don't  
3 think we should eliminate it.  
4 DR. FREEMAN: You don't want to eliminate  
5 it.  
6 DR. BRIL: No.  
7 DR. GIBBONS: I think the EMG labs are very  
8 good at the warming. I think the clinical  
9 situations are not, and I think there is a  
10 difference.  
11 (Crosstalk.)  
12 DR. BRIL: These are going to be for  
13 research. Right?  
14 DR. FREEMAN: Exactly, with rigorous  
15 attention to ambient temperature.  
16 DR. BRIL: Yes.  
17 DR. FREEMAN: We'll take a look and see  
18 what's out there.  
19 DR. PELTIER: Are we going to be putting a  
20 caveat in for age?  
21 DR. FREEMAN: We certainly can.  
22 DR. PELTIER: I mean, if patients are over

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1 the age of 75, maybe require two signs just because  
2 if you have absent ankle jerks, then you're done.  
3 Then you're just saying everybody has ankle jerks  
4 over 75.  
5 DR. FREEMAN: The ankle jerk applicability  
6 with age. You okay with that, Gordon?  
7 DR. SMITH: With two signs, maybe. I think  
8 all of these change with age to some extent, so I  
9 guess the question is whether you want to be  
10 definitive about what those cutoffs are or just  
11 include a qualifier.  
12 DR. FREEMAN: Yes. I mean, in the NIS-LL  
13 plus X, they were quite clear. Over 75, ankle  
14 reflexes don't count or something like that, that  
15 kind of thing. So think we're moving along.  
16 Here, one symptom and one sign or more than  
17 one symptom or more than one sign. I think we  
18 resolved that with the first question, are we happy  
19 with this over here?  
20 So that is the probable, and here we are  
21 edging to greater specificity and less sensitivity,  
22 one symptom and one sign, or more than one symptom,

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1 or more than one sign.  
2 DR. SMITH: So I think my recollection was  
3 that we agreed that there had to be more than one  
4 sign. If that's the case, it's really symptomatic  
5 or asymptomatic for probable neuropathy based on  
6 two signs.  
7 DR. BRUEHL: So I'm sorry. So are you  
8 saying one symptom and one sign or multiple signs?  
9 DR. SMITH: No. I thought two or more signs  
10 was the definition of probable and that we would  
11 sub-categorize this as symptomatic or symptomatic  
12 based on the presence of a single, one or more  
13 neuropathy signs or symptoms rather.  
14 DR. FREEMAN: So we've gone here from a  
15 symptom-weighted assessment to moving away from  
16 symptoms to signs. And it can be asymptomatic or  
17 symptomatic. It fits quite nicely with James's  
18 approach.  
19 DR. BENNETT: I'm really worried about small  
20 fiber neuropathy with that, if we go for that.  
21 DR. BRIL: I was going to say you could  
22 easily envision somebody with pain and loss of pin,

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1 that most people would say have a probable chance  
2 of having a small fiber neuropathy.  
3 DR. SMITH: Right. So keep in mind that we  
4 have the small fiber neuropathy criteria that the  
5 other group derived, and that was going to be an  
6 exception to this.  
7 DR. FREEMAN: But that's a problem because  
8 you do want these to stand alone. Just say Dave is  
9 doing a trial and he doesn't care about small fiber  
10 neuropathy specifically, but he wants to include  
11 patients who have a high likelihood of having  
12 neuropathy. He would say, quite reasonably,  
13 burning pain plus one sign, pin prick -- and Chris  
14 and you guys weigh in on this -- he would say  
15 that's highly probable; in fact, that's definitive  
16 clinical diagnosis of small fiber neuropathy.  
17 I mean, the point is reasonable. What would  
18 you say, Gordon?  
19 DR. SMITH: I'm saying the same thing, that  
20 those would be part of the definition of probable  
21 neuropathy. So it would be A or B. A is this; B  
22 is that.

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1 DR. FREEMAN: Can you come up with a way to  
2 make Dave Bennett happy?  
3 (Laughter.)  
4 DR. PELTIER: We have to go back to one  
5 sign, because I don't know that you can be slacker  
6 with small fiber than you can be with large fiber  
7 neuropathy. You've got two small fiber  
8 examinations there; and light touches, both,  
9 actually, small and large. So you've got three  
10 small fiber exams.  
11 DR. SINGLETON: I thought we talked about  
12 including allodynia or tactile hyperalgesia as an  
13 additional sign here.  
14 DR. BRIL: Yes.  
15 DR. SINGLETON: I think we should because I  
16 think it's relevant.  
17 DR. FREEMAN: They didn't, Chris, and your  
18 group did. Yes?  
19 DR. TESFAYE: I think to be a bit careful  
20 here. This is probable neuropathy. These are not  
21 patients who are going to be selected for a  
22 clinical trial.

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1 DR. FREEMAN: No, I think they are.  
2 DR. TESFAYE: Well, not with probable.  
3 (Crosstalk.)  
4 DR. TESFAYE: You need to have a confirmed  
5 diagnosis. If we're going to do a proper clinical  
6 trial, there's got to be more rigorous confirmation  
7 of neuropathy. This is just to guide clinicians to  
8 be aware. In fact, it's better to err on the side  
9 of caution and include patients with potential  
10 neuropathy with this. If we tried to be too  
11 prescriptive with these, I don't think that's the  
12 right course.  
13 DR. FREEMAN: Perhaps the name "probable" is  
14 not perfect, and these possible/probable definite  
15 names are not, because definite is not definite.  
16 But this is the kind of patient that, definitely,  
17 this classification would be included in a pain  
18 trial. It may not be included in a disease-  
19 modifying trial, but certainly would be included in  
20 a pain trial. It's not unusual for a diabetic  
21 neuropathy pain trial to say that we include  
22 patients who have -- they often say just

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1 neuropathic pain.  
2 DR. TESFAYE: That's been surpassed. I  
3 mean, if you look at the impact of recommendations  
4 in 2012, it's a lot more rigorous. Now, we are  
5 talking about patient factors here, which is the  
6 first bit. Actually, there is study design  
7 factors. I mean, future things that we're going to  
8 look at will be site factors, how many sites you  
9 have, the frequency of measurement.  
10 This is just the beginning of actually just  
11 identifying potential subjects, and I don't think  
12 this would be adequate in my opinion to do a  
13 rigorous clinical trial. This will be adequate to  
14 identify potential subjects, but these patients  
15 then will have to be screened for the right kind of  
16 patients.  
17 DR. FREEMAN: So for example, pregabalin  
18 trials, duloxetine trials that you're involved in,  
19 diabetic peripheral neuropathy was not diagnosed  
20 with nerve conduction studies. I mean, those were  
21 all based on clinical criteria.  
22 DR. ZIEGLER: MNSI greater or equal than 3.

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1 That's duloxetine.  
2 DR. FREEMAN: Many of the pregabalin trials  
3 did not do that.  
4 DR. ZIEGLER: Glycosamide didn't, and that's  
5 why they support the trial.  
6 DR. FREEMAN: Some of the originals did not  
7 do that at all.  
8 DR. ZIEGLER: I just wanted to say that this  
9 is diabetic neuropathy, and I'm wondering why there  
10 is light touch instead of touching pressure using  
11 the monofilament. Each and every diabetologist, if  
12 anything, is using the monofilament. So why isn't  
13 that included? And it's a predictor of foot  
14 ulcers, so it would be a mistake.  
15 (Crosstalk.)  
16 DR. FREEMAN: I think we agreed yesterday to  
17 add it. We agreed to add it.  
18 (Crosstalk.)  
19 DR. BENNETT: Although I still feel like  
20 that's late, I mean, that's really late.  
21 DR. FREEMAN: That's the point. That's the  
22 critique. I mean, here, you'll have this as a

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1 neurologist. Let's deal with the small fiber  
2 quickly, and then we'll come back to this.  
3 DR. BENNETT: Can we square the circle by  
4 saying probable is one symptom and one sign or two  
5 signs?  
6 DR. FREEMAN: Yes.  
7 DR. BENNETT: So there's an "or" there.  
8 DR. ZIEGLER: Especially if you add  
9 allodynia/hyperalgesia, the more items you add, the  
10 more rigorous your criteria must be. So if you add  
11 two criteria, you certainly need two, because  
12 otherwise you are not --  
13 DR. FREEMAN: I think that solves that  
14 problem. We can debate what to do with it.  
15 DR. HERRMANN: If you start with the more  
16 inclusive one symptom and one sign or two signs, I  
17 think it's important then to test that against some  
18 standard as part of research going forth, because  
19 as I said, I would encourage you to look at the HIV  
20 literature because they did look at this as they  
21 were looking for different screening tools. And  
22 when they just used one sign, they found that the

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1 specificity went down substantially. So I think it  
2 does require a little bit of validation in that  
3 case.  
4 DR. SMITH: So the situation, my synthesis  
5 from yesterday, was that in a patient who did not  
6 have neuropathic pain, there was a need for  
7 multiple signs, but in patients who had neuropathic  
8 pain, there was not. So why don't we just say, if  
9 you don't have pain, you need two signs. If you  
10 have neuropathic pain that conforms to this  
11 description, you need one sign. I thought that's  
12 where we ended yesterday.  
13 DR. ZIEGLER: One small fiber sign.  
14 DR. PELTIER: You don't have to qualify it.  
15 You could just say one symptom, one sign.  
16 DR. SMITH: So someone has neuropathic pain  
17 that's distal, symmetric in the feet, who has  
18 absent reflexes. I think we would agree that's  
19 probably --  
20 DR. ZIEGLER: It's not too old.  
21 DR. SMITH: -- not too old and not too  
22 young, just right.

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1 DR. SINGLETON: Back to your point, I do  
2 think that people will want to use this for  
3 clinical trials without confirming neuropathy, so I  
4 would suggest the possibility of using clinically  
5 defined neuropathy as a description here rather  
6 than probable because that's what we have, a  
7 clinically defined neuropathy.  
8 We think this is sufficient to define the  
9 disease clinically, but we haven't confirmed it  
10 with a confirmatory test. So we should look.  
11 (Crosstalk.)  
12 DR. BRUEHL: That's where our talk went at  
13 one point.  
14 DR. FREEMAN: We should look at the James'  
15 group criteria next, which we will do.  
16 DR. BRUEHL: I'm sorry. So I still am  
17 confused about what we're doing. Why do we even  
18 have symptoms listed if you don't think it has any  
19 relevance to diagnosis?  
20 DR. FREEMAN: We just decided that.  
21 DR. BRUEHL: So it is one symptom and one  
22 sign or two or more?

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1 DR. FREEMAN: Yes, one symptom and one sign  
2 if that symptom is pain. Gordon?  
3 DR. SMITH: We have two different competing  
4 ideas. One is one or more symptoms with one sign,  
5 or two signs, or the idea of defining neuropathic  
6 pain plus one sign as a separate way of fulfilling  
7 the criteria.  
8 DR. BRIL: We have one symptom and one sign  
9 already, so whether it's pain plus a sign or more  
10 than one sign, for those who are asymptomatic, that  
11 covers both of those, large and small fiber.  
12 DR. SMITH: Right. I guess we changed our  
13 mind. That's fine, but yesterday, there was outcry  
14 over one symptom, one sign because of the lack of  
15 specificity with one sign.  
16 DR. BRIL: It's going to not be specific.  
17 None of this can be specific.  
18 DR. BRUEHL: Yes. I think if we have a data  
19 set that has this, we can compile exactly how many  
20 patients would meet criteria with different levels  
21 and see. And if it turns out that 100 percent meet  
22 it with one symptom and one sign, and then you

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1 increase it to two signs and it's 95 percent, then  
2 it's not making much difference, but it's  
3 empirical.  
4 DR. FREEMAN: Yes. It would be nice to  
5 know.  
6 DR. BRUEHL: I think the thing is we don't  
7 have to be perfect on the numbers we pick here.  
8 The idea is to at least get a starting point and  
9 then use that as a basis to start evaluating these  
10 questions to fine-tune it.  
11 DR. FREEMAN: I think that should be the  
12 approach. Gordon, are you okay? You've got enough  
13 to work with yet or do you have questions?  
14 DR. SMITH: I think we're good, yes.  
15 DR. FREEMAN: Next slide?  
16 DR. BRUEHL: That was it.  
17 DR. FREEMAN: No, no, no. So this is  
18 definite, all of the above, that we discussed, plus  
19 these neurophysiologies. And this is a good time  
20 to talk about it. James's group had quantitative  
21 sensory testing and corneal confocal microscopy as  
22 their confirmatory tests.

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1 When I called for questions, somebody said  
2 that QST, presumably somebody from this group, and  
3 corneal confocal, the weight of evidence wasn't  
4 there for those to be called confirmatory tests.  
5 And I think we need to, on some level, initiate  
6 that discussion. This is what Gordon's group said.  
7 DR. BRIL: This was my question. Do we have  
8 to be specific about the confirmatory tests? That  
9 was it, because the definition is clinical. We've  
10 gone through the definition. Now, how specific do  
11 we have to be about the confirmatory tests? That  
12 was the whole point.  
13 DR. PELTIER: I would argue one confirmatory  
14 test, which should be sufficient, because the  
15 problem is that you're going to have a lot of  
16 studies that are not necessarily going to do  
17 multiple tests. Then two, I would add CCMs since  
18 there's a huge body of evidence and there's norms,  
19 but I would leave out QST because of the issues of  
20 QST is not necessarily diagnostic since we know  
21 it's more of a subjective test as opposed to all  
22 the other ones.

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1 DR. FREEMAN: What are the others? Any  
2 other views on this?  
3 DR. RUSSELL: Yes. So I think this whole  
4 area is incredibly controversial. I mean, even if  
5 you look at these confirmatory tests, we've already  
6 looked at all the problems with nerve conduction  
7 studies and which ones you actually choose.  
8 There were the skin biopsies, which I think  
9 is a great test. Again, you have to apply the  
10 criteria developed by Laura and colleagues  
11 published in PNS or the European Federation, and  
12 you've got to follow those exact criteria if you're  
13 going to get reproducibility and if you're going to  
14 use the normative data that's been published. So I  
15 mean, even with that, which is a very good test,  
16 you have to be very specific about what you're  
17 going to do.  
18 So I think all of these tests have their  
19 caveats. And I would maybe go with Vera or whoever  
20 said it and maybe say you would use a confirmatory  
21 test.  
22 DR. FREEMAN: I think we can't just say --

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1 DR. TESFAYE: Class A evidence.  
2 DR. FREEMAN: Which are those that have  
3 class A evidence?  
4 DR. TESFAYE: Class A evidence in my view is  
5 does a test that you do have predictive validity  
6 for the future development of peripheral  
7 neuropathy? And I think that -- we don't have  
8 prospective stuff. I think we need to be as robust  
9 as we can.  
10 DR. ZIEGLER: So there is evidence for nerve  
11 conduction, number one, number two the  
12 monofilament, number three VPT. Those are the  
13 predictors of foot ulcers. There are studies  
14 showing evidence for that.  
15 (Crosstalk.)  
16 DR. ZIEGLER: We are going back. We are now  
17 going back to the monofilament bedside test. And  
18 you can also argue that QST and nothing else is  
19 more pre-sized bedside testing. That is my take.  
20 So why not use it as confirmatory if it's more pre-  
21 sized than the bedside on which we base our  
22 clinical judgment?



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1 DR. SINGLETON: I think the problem with QST  
2 has been that it doesn't test peripheral nerves.  
3 It's a neurophysiologic assessment, not a nerve  
4 test.  
5 DR. BENNETT: Don't you think that's kind of  
6 theoretical rather than evidence based?  
7 DR. SINGLETON: No. It's not. It's pretty  
8 hard. I mean, you can have a central nervous  
9 system problem that makes your vibration sense  
10 reduced.  
11 DR. BENNETT: Yes. So you add a caveat  
12 which is -- I mean, we're pragmatic clinicians, so  
13 this is for pragmatic clinicians. So you add a  
14 caveat, which we've seen all the time in diagnostic  
15 criteria. To be honest, most of the time, when  
16 I've seen that situation, it's been pretty obvious  
17 there's a CNS problem when you put it in the  
18 context of examination of other findings on the  
19 patient. The fact that there is evidence from  
20 [indiscernible] Larrier [ph], actually, when he  
21 compared clinical examination, QST, and skin  
22 biopsy, there was a role for QST.

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1 So I think it's difficult just on that  
2 pragmatic level to say we're going to push this out  
3 because of the theoretical -- I agree it's a real  
4 issue, but I'm just saying that if we go on  
5 evidence, then actually there is evidence that QST  
6 is informative.  
7 DR. BRIL: So I would just use confirmatory  
8 tests, in brackets, e.g., nerve conduction,  
9 electrophysiology, skin biopsy, QST, because you  
10 can do thermal as well, and CCM, for example, in  
11 the brackets because, I can't see doing skin  
12 biopsies on everybody. That costs a lot. It's  
13 invasive.  
14 So maybe we'll do them in a study if the  
15 sponsor's going to pay, maybe not. They don't  
16 often want to pay in studies of pain. I mean,  
17 sometimes they will.  
18 DR. FREEMAN: There are two or three small  
19 fiber neuropathy studies ongoing, where skin biopsy  
20 is the gold standard.  
21 DR. BRIL: Now, but you can't say that's  
22 going to go on indefinitely, so I think you should

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1 have a choice of what you do.  
2 DR. FREEMAN: No, no, no. I understand.  
3 But as long as it's on the list, that's acceptable.  
4 Gordon?  
5 DR. SMITH: My concern isn't the repertoire  
6 of tests that we've been talking about. And you  
7 know my feelings about this. I'm not very  
8 enthusiastic about either one of these, so I think  
9 adding QST whatever, I'm fine with. It's the other  
10 kind of crazy tests that are out there.  
11 We can't just say confirm. We could say,  
12 "confirmed with," and you couldn't really say level  
13 A evidence, but some sort of caveat about strength  
14 of evidence, and then, for example, nerve  
15 conduction studies, INFD, QST, CCM, whatever.  
16 But I'm not worried about that. I'm worried  
17 about the people that are doing the nerve  
18 decompression surgery. Dellon's created this sort  
19 of quasi-TNL QST thing. And so if we just say  
20 confirmatory test, then who knows? They may use  
21 that.  
22 DR. FREEMAN: How about we actually specify

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1 the big 4, and we actually add the caveats for all  
2 four of them.  
3 DR. BRUEHL: But are you saying confirmed by  
4 one of the following?  
5 DR. FREEMAN: One of the following. I think  
6 that's the consensus, but we satisfy everybody by  
7 saying whatever longitudinal data do not exist,  
8 that QST measures the entire nervous system as does  
9 the rest of the sensory exam, of course, by the  
10 way, and nerve conduction studies. So we do all of  
11 that and we had a series of provisos.  
12 I think that takes care of this one. Let's  
13 move on to the first Word document, which is called  
14 "severity." This is James. This is the QST nerve  
15 conduction study. I think we covered that, earlier  
16 comment on class A, reduce sensory signs.  
17 These were the questions. This is pre-  
18 clinical. And then he moves on to clinically mild.  
19 And mild has reduced sensory signs, and the  
20 question is how are we going to define reduced but  
21 not lost? And then the question was what signs and  
22 standardization? And I discussed standardization

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1 earlier, so the question is what signs?  
2 James, are you happy with the same signs?  
3 DR. RUSSELL: Yes. So the signs are  
4 actually at the bottom. They're in the notes. You  
5 read off the notes. The signs we allowed, touch  
6 vibrational --  
7 DR. FREEMAN: Let's keep going --  
8 DR. RUSSELL: -- [inaudible - crosstalk].  
9 DR. FREEMAN: Let's keep going. So at least  
10 to abnormalities, on confirmatory tests, James says  
11 two for moderate. How does this fit in with  
12 definite?  
13 DR. GIBBONS: I just want to back up a  
14 little bit, went a little too far. I think it gets  
15 to some of the questions we had yesterday about how  
16 many tests do we need and do we need two for  
17 confirmatory.  
18 DR. RUSSELL: So I think, for the  
19 confirmatory test, can we just go with what we  
20 decided previously? So there's just going to be a  
21 little note down there saying you're going to get  
22 one or more of the following, which will be

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1 confirmatory. And then that's out of it, and  
2 everyone agrees. So let's just focus on the  
3 clinical part.  
4 Is that okay, Roy?  
5 DR. FREEMAN: In a way yes and in a way no,  
6 because I think we need to actually get some kind  
7 of concordance between Gordon's assessment, where  
8 it was one of the following, when he's gone, or  
9 definite, and you're saying two with  
10 moderate -- well, specific. So I think there needs  
11 to be some degree of concordance, which to me it  
12 seems definite and moderate -- do we think that  
13 specificity of classification of moderate is  
14 greater?  
15 DR. RUSSELL: So when I put in the  
16 confirmatory test, what I was saying is that there  
17 should be a large and a small fiber. So the idea  
18 would be that by the time you get to moderate, it's  
19 going to be either mixed, which is what I think it  
20 would be, rather than small fiber. So at that  
21 point, if you really are going to use a  
22 confirmatory test, you would want a large and a

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1 small fiber measure, at least one.  
2 DR. HOKE: But I mean, in clinical practice,  
3 if the nerve conductions are abnormal, you really  
4 don't do any of the small fiber confirmatory  
5 modalities. And it's really going to change how we  
6 practice or even do research.  
7 DR. FREEMAN: Remember, this is not  
8 practice. This is research.  
9 DR. HOKE: But even for research, I mean,  
10 you're going to have trouble adding another layer  
11 of testing when you know, if somebody has absent  
12 sensory motor responses and nerve conductions in  
13 the legs, that's going to be a moderate neuropathy.  
14 I mean, it's not going to be mild or you can argue  
15 maybe it's severe. But adding small fiber modality  
16 confirmatory tests, I don't know what --  
17 DR. RUSSELL: I mean, Ahmet, I agree with  
18 you. Part of the problem here is I didn't want  
19 someone to go along and just use the vibration  
20 perception threshold, and not do the nerve  
21 conduction studies because that is a problem.  
22 DR. HOKE: I agree it could be nerve

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1 conductions alone.  
2 DR. RUSSELL: I mean, we could, yes. The  
3 trouble is, if people are not going to do nerve  
4 conduction studies in a lot of these large  
5 epidemiological studies, they're just using  
6 vibration or perception thresholds, and we have to  
7 find something for that.  
8 DR. FREEMAN: Can you do a proviso and do  
9 the Central Africa proviso, the epidemiological  
10 study proviso and say if nerve conduction studies  
11 are not available, an alternative would be to --  
12 DR. GIBBONS: But they're all listed  
13 already, as you've already got them ranked. So  
14 these are just, again, as you mentioned yesterday,  
15 confirmatory tests only.  
16 DR. RUSSELL: Yes, that's right, right.  
17 DR. GIBBONS: So none of these have to be  
18 confirmed.  
19 DR. RUSSELL: So none of this has to be  
20 done. If you decide you're going to do it  
21 clinically, then you're finished. So we could  
22 adjust this and say maybe you'd have to have at

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1 least one abnormal test at the 97.5th percentile.  
2 Okay? We could do that, I suppose. Again, I just  
3 don't want people to do this just on vibration  
4 perception threshold or cold because I don't think  
5 that's moderate.  
6 DR. GIBBONS: So just say that, specify  
7 that.  
8 DR. HOKE: Yes, but why not use two measures  
9 of nerve conductions? I mean, moderate could be  
10 somebody who has both abnormal sensory or motor  
11 evoke responses.  
12 DR. RUSSELL: Ahmet, I agree with you.  
13 Okay? We would do that. But if we're doing an  
14 epidemiological study, and let's say all you've got  
15 there is you've got your little vibrometer  
16 methodology, or you've got some sort of machine  
17 that measures cold perception thresholds, so you're  
18 not doing the nerve conduction studies, what could  
19 you use as a confirmatory test? So that's the  
20 problem.  
21 DR. BENNETT: This is severity. [Inaudible  
22 - off mic].

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1 DR. RUSSELL: Yes. So the clinical is  
2 there. I mean, in Africa, you'd use the clinical  
3 scales. So I mean, my personal preference would be  
4 to move all these confirmatory tests and say you  
5 can just do a confirmatory test if you want.  
6 DR. BENNETT: I agree. I think the  
7 confirmatory tests are a bit of a red herring. I  
8 think they should be using --  
9 DR. FREEMAN: You want to then, as you've  
10 done -- if we move those -- is that a general  
11 consensus? It's easier to get consensus now.  
12 (Laughter.)  
13 DR. BRIL: I think you have to have  
14 electrophysiology for severity myself or some test  
15 showing where it is, because then how are you going  
16 to do confirmatory tests for diagnosis?  
17 DR. FREEMAN: Yes, no. Look, I'm  
18 sympathetic to that view.  
19 DR. BRIL: You know what I'm saying? If  
20 these all have to align, you're going to put these  
21 as completely optional, how do they become  
22 necessary? I mean, or do they? Can you do that?

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1 DR. BENNETT: I mean, I'm going to do two  
2 things here, which is [inaudible - off mic]. This  
3 should just be severity.  
4 DR. MALIK: I think that was exactly the  
5 rationale. We thought that there has to be an  
6 objective measure, small, large, or both, but there  
7 has to be a subjective way, the way you've got, a  
8 way to define severity.  
9 DR. ZIEGLER: To delete QST again. Yes, you  
10 could argue that the other three are objective,  
11 either morphology or function and CV, therefore,  
12 there is no place for QST because this is  
13 psychophysical. Variability is higher.  
14 DR. MALIK: Yes. That's fine.  
15 DR. ZIEGLER: So there's a rationale for  
16 that.  
17 DR. FREEMAN: You're okay with that?  
18 DR. RUSSELL: Yes.  
19 DR. ZIEGLER: It fits with your VPT problem.  
20 DR. RUSSELL: How about we say, for  
21 moderate, then, you would have to have either an  
22 abnormal nerve conduction study value greater than

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1 the 97.5th percentile or two other abnormal  
2 measures that are greater than that percentile?  
3 DR. ZIEGLER: For confirmation, you would  
4 require only one in each case of severity. You can  
5 define it by percentile. So as it stands, you can  
6 go 79.5 for the moderate and 99 for the severe.  
7 DR. RUSSELL: Right. Yes. The only thing  
8 was, what do we do about the vibration, the cold  
9 perception?  
10 DR. ZIEGLER: It's out now.  
11 DR. RUSSELL: So we're taking it out  
12 completely? Okay.  
13 DR. FREEMAN: I think you're taking it out  
14 and you put your --  
15 (Crosstalk.)  
16 DR. BRIL: I think there's a lot of work  
17 Andrew did about vibration with a biophysiometer.  
18 And it may not be so reproducible, but that's not  
19 what you're trying to do here. But if you have  
20 someone who's off scale on those instruments,  
21 they're at risk of foot ulceration, and you have  
22 people who are less.

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1 DR. FREEMAN: Andrew would feel very  
2 strongly about that.  
3 DR. BRIL: I think you can use either.  
4 DR. FREEMAN: Yes. So the one possibility  
5 is to take the Dan approach and put it as a  
6 proviso, that if nerve conduction studies are not  
7 available, as they obviously are not in Manchester,  
8 do the vibrometer.  
9 DR. BRIL: Yes. I really think you could.  
10 I mean, they're not the most reliable and I  
11 understand.  
12 (Crosstalk.)  
13 DR. GIBBONS: I still wonder if we're  
14 arguing about potentially different issues --  
15 DR. BRIL: Yes.  
16 DR. GIBBONS: -- where I still think, as  
17 Stephen had mentioned for our overall schema, we  
18 may have different foci for the trial. This may be  
19 a clinically severe small fiber, large fiber, et  
20 cetera. Maybe we just need to, again, put the  
21 examples in parenthesis and leave it there.  
22 DR. BRIL: I totally think that's a good

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1 thing to do.  
2 (Crosstalk.)  
3 DR. FREEMAN: Yes. So what about your small  
4 fiber question over here? Just say a patient has a  
5 small fiber neuropathy and we're dumping the "and,"  
6 but could we say "or" with the possibility that  
7 that then is a small fiber neuropathy? I think  
8 that might be a way to deal with that. I think  
9 that would work.  
10 James, are you with us on that?  
11 DR. RUSSELL: So I'm going to say all for  
12 the confirmatory. Okay?  
13 DR. ZIEGLER: Could you maybe go back to the  
14 definition of moderate? Because I'm not happy with  
15 that loss of two sensory signs. That's far too  
16 aggressive for moderate. Loss is not measurable.  
17 DR. RUSSELL: As opposed to reduction, yes.  
18 DR. FREEMAN: Go up to mild.  
19 DR. ZIEGLER: But for example, that would be  
20 on a tuning fork [inaudible – off mic].  
21 DR. RUSSELL: Absent vibration.  
22 DR. FREEMAN: Could you scroll up a little

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1 bit?  
2 (Crosstalk.)  
3 DR. RUSSELL: So mild, we said at least two  
4 reduced sensory signs. Okay? So the problem with  
5 this is that we need to talk about severe. So with  
6 severe, the thing was, everyone agreed that we were  
7 not specific and it wasn't -- the abnormality of  
8 signs was not severe enough to really determine  
9 severe.  
10 DR. ZIEGLER: Here, we could say moderate,  
11 just one, one absent, not more.  
12 DR. RUSSELL: So loss of one sensory sign --  
13 DR. BRIL: Reduction into others? Because I  
14 don't know where I've lost vibration and lost  
15 pinprick and not had an abnormality of thermal  
16 sensation and starting vibration. So you could say  
17 loss of one. That means complete loss. And then  
18 reduction and two others could be clinically  
19 moderate.  
20 DR. RUSSELL: So Vera, I would agree with  
21 you, that you're not going to get one where you're  
22 going to lose one, but not have the others reduced.

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1 The one thing -- so when thinking about this, I  
2 said, if you see a patient and call perception is  
3 completely gone, but everything else is just  
4 reduced, would you call that patient moderate?  
5 Because I would have a problem with that.  
6 DR. GIBBONS: Do you want to just use that  
7 proviso, the following things?  
8 DR. RUSSELL: I would call it more towards  
9 mild than moderate.  
10 DR. ZIEGLER: For me, it's fine. For me, it  
11 would be moderate.  
12 DR. BRIL: It would be moderate. Yes.  
13 DR. RUSSELL: So just call perception lost.  
14 DR. BENNETT: So I hate to add another  
15 issue, but this is all at the [inaudible – off  
16 mic].  
17 DR. FREEMAN: Yes. I was thinking the same  
18 thing. We're not thinking typographically as well.  
19 DR. BENNETT: Actually, it's very helpful  
20 when I mentally grade it if I see signs up to the  
21 knees.  
22 DR. FREEMAN: I was thinking that.

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1 DR. RUSSELL: Why don't we take a vote on  
2 that? So if we say just loss of one, okay,  
3 including the fact that I have no problem with the  
4 loss of one as vibration or the loss of one as  
5 pinprick, but cold, I would have a bit of an issue  
6 of that with a loss.  
7 DR. FREEMAN: I think we all agree. Are you  
8 okay with that, Dan, or not yet?  
9 DR. ZIEGLER: I would have a different  
10 approach. I would classify this along the number  
11 of abnormalities, so you could say three  
12 abnormalities without loss, for example, for  
13 moderate.  
14 DR. RUSSELL: So reduction of at least  
15 three?  
16 (Crosstalk.)  
17 DR. FREEMAN: Last does not include cold.  
18 DR. ZIEGLER: Then with severe, you would be  
19 also more than three, but at least one or two  
20 loses.  
21 DR. GIBBONS: Also, while we're trying to  
22 figure that out, can we also say reduced to the

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1 ankle might be moving us to reduced --  
2 DR. FREEMAN: This is going to be very easy  
3 as soon as Ahmet leaves because there's just two of  
4 us there.  
5 (Laughter.)  
6 DR. GIBBONS: Exactly. Then get it done.  
7 DR. GIBBONS: But I wonder. I mean, I  
8 think, for most of us, once we see something at the  
9 level of the ankle, we assume it's now moderate.  
10 DR. BRIL: Yes, distally is mild.  
11 DR. GIBBONS: Yes, and ankle is moderate.  
12 Once you're mid-shin, you're severe or above.  
13 DR. FREEMAN: I think we've got to add the  
14 topography.  
15 (Crosstalk.)  
16 DR. BENNETT: I mean, I would really suggest  
17 that we come up with a schema.  
18 DR. FREEMAN: So in contrast to the other  
19 guys -- by the way, I don't think we should do the  
20 phenotype. We'll stop after this. Proprioception  
21 was not included, James felt. The other guys  
22 didn't mind proprioception. What do you think?

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1 DR. ZIEGLER: I think it should be included.  
2 MALE VOICE: I think it's important.  
3 MALE VOICE: Yes. I use it. I think it's  
4 helpful.  
5 DR. RUSSELL: So the problem with this is, I  
6 have nothing against proprioception, but if you  
7 actually include proprioception, then when you say  
8 you're going to lose, you're going to have reduced,  
9 you actually come up with a problem because  
10 proprioception only is actually lost once you get  
11 to severe. So you can't really grade it for mild  
12 and moderate very well. All the rest, you can more  
13 or less grade across the spectrum.  
14 So you have to come up with caveats. You're  
15 allowed to lose three, but you can't necessarily  
16 say it's loss of proprioception, et cetera. So see  
17 what I'm saying? The problem is trying to separate  
18 out mild, moderate, and severe.  
19 DR. GIBBONS: I think you're overthinking it  
20 because I think you're absolutely right, but I  
21 wonder if what we're saying is -- if that's the  
22 case, then those others should be absent, too, and

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1 they'll automatically go to severe anyway.  
2 DR. RUSSELL: Yeah. But I guess the problem  
3 then becomes you can say if proprioception were  
4 completely lost, but the other ones were not lost,  
5 they were reduced, then where would you put that  
6 patient?  
7 DR. GIBBONS: I would put that patient in  
8 the send-it-to-somebody-else-for-an-exam category.  
9 (Laughter.)  
10 DR. BRIL: I would put it in the myelopathy-  
11 not-diabetic-neuropathy category.  
12 DR. RUSSELL: So this is the problem with  
13 proprioception. This is why I left it out.  
14 DR. FREEMAN: So give us some guidance on  
15 what to do with proprioception, and then I think we  
16 can probably call it a day.  
17 Dave, proprioception? David, Vera,  
18 proprioception? Dan, proprioception? What are we  
19 going to do? Help.  
20 DR. BRIL: Proprioception for me is sever if  
21 it's impaired, sometimes moderate if you're very  
22 careful?

1 DR. GIBBONS: Maybe just move it to the  
2 severe category and not list it in the mild and  
3 moderate.  
4 DR. ZIEGLER: The question is, do we rely  
5 upon it? That's the question.  
6 DR. BRIL: As much as any of this stuff is  
7 reliable.  
8 DR. ZIEGLER: It may be less.  
9 DR. BRIL: Yes.  
10 DR. ZIEGLER: You rarely see it in normal.  
11 MALE VOICE: I can check that because we  
12 have some data on that.  
13 (Crosstalk.)  
14 DR. BRIL: Yes. It's less frequently  
15 abnormal than the rest.  
16 (Crosstalk.)  
17 DR. BENNETT: But maybe that's helpful.  
18 DR. FREEMAN: Anything else that you'd like  
19 to discuss?  
20 DR. RUSSELL: The severe group, are we still  
21 saying you're going to have loss of all the sensory  
22 signs or are we going to --

1 MALE VOICE: No, no, at least, I don't know,  
2 two or so, three.  
3 DR. RUSSELL: So severe would now be loss of  
4 at least two.  
5 Adjournment  
6 DR. FREEMAN: Yes, loss of at least two.  
7 Great to see you.  
8 (Whereupon, at 2:25 p.m., the meeting was  
9 adjourned.)  
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**ACTTION - CONCEPPT/IDNC MEETING ON  
DIABETIC PERIPHERAL NEUROPATHIES**

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