ACTTION - CONCEPPT/IDNC MEETING ON DIABETIC PERIPHERAL NEUROPATHIES

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ACTTION

CONCEPPT/IDNC MEETING ON

DIABETIC PERIPHERAL NEUROPATHIES

EVIDENCE BASED TAXONOMY FOR

DIABETIC PERIPHERAL NEUROPATHIES CONCEPPT/IDNC

Wednesday, December 13, 2017

8:01 a.m. to 2:25 p.m.

W Hotel

Washington, DC

C O N T E N T S

P R O C E E D I N G S

DR. FREEMAN: So I believe, as you may have noticed, we are one talk behind, which is Chris's talk, which will be the first talk today. Can I get some sense of who is leaving before lunch?

Nobody? Okay. So just to the afternoon session, which will begin shortly after lunch, it's really to tie up the loose ends. And it's, I think, quite a critical session.

I think Jim's talk was pretty much packaged at the end, and I think we did very well. And I think we'll do the same with the talks today. But the challenge is going to be the generalized and I think there are lots of comments. I have attempted to collate those, and try and clean that up, and we'll follow that up with e-mail.

But let's get this show on the road. So first, Chris. And what I think we'll do is Chris's talk, followed by Rob's talk, followed by the panel.

Presentation – Christopher Gibbons

DR. GIBBONS: Good morning again, everybody.

Welcome back. So I'm hoping mine will be relatively concise, I think probably far less debate about things. Part of that is because the publications on this particular topic, treatment-induced neuropathy, aren't going to be nearly as voluminous as maybe other topics we talked about.

For better or for worse, I have an immense amount of bias on the topic mostly because my name is on a lot of the publications, as is Roy's, so we have kind of a particular perspective on this. So with that, unfortunately, comes a single-center experience, but we're we'll just talk through some of the challenges.

This is basically summary slide for the problem, and I think it highlights relatively clearly the challenges we face. Essentially, what this slide is showing is basically the severity of neuropathic pain getting worse, as is the distribution of neuropathic pain by a relative change in glycemic control over a period of time, arbitrarily selected as 3 months, again single-center experience, but at Joslin get hemoglobin A1c

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scores every 3 months, so it just happened to be a very convenient way to measure a change in glucose control.

As you magnify or increase your change in glucose control, your risk of neuropathy development goes up, so this is the absolute risk of developing neuropathy. And you can see, by the time you exceed a 6-piont change in hemoglobin A1c over 3 months, you have a nearly 100 percent chance of developing the neuropathy. And the distribution, again, increases over time.

Red is really burning pain. The gray are people who have variable amounts of pain. And it's really a selective small fiber presentations. This is the classic distribution that I'm seeing in my own clinical patients.

In terms of the data we had to generate this, looking at a group of individuals referred in for diabetic neuropathy, looking at change in glycemic control and the relationship to the development of this neuropathy.

Basically, those who had a hemoglobin A1c

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change or 2 points or more in the last 3 months, we looked at those selectively and found that 104 of those actually met criteria for treatment-induced neuropathy; so in other words, they had a sudden change in glucose control, resulting in a dramatic increase in neuropathic pain in a link-dependent fashion with some associated autonomic features.

This again took us to the distribution of the pain and the severity, and this is really what it looked like. So if your hemoglobin A1c drops a modest amount, these are pain scores. These are hemoglobin A1c scores. So if you're dropping on the 2 to 4 range, basically, your pain score would go up to about 6. This is on the Likert scale, a 0 to 10 scale.

There's no pain prior to this. There's a time lock development of pain, and it's typically presented with burning pain in the feet, the classic neuropathic pain that we think about. But if you had a larger change in hemoglobin A1c, the distribution was larger and the pain score was actually greater.

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Then finally, if you had a very significant change, these are people who had essentially hemoglobin A1c changes of about 6 points or more in 3 months, a very large distribution of pain, very high pain scores. So this is for the distribution and the representation.

DR. ZOCHODNE: Chris, those diagrams, that's not sensory loss, right?

DR. GIBBONS: So this is distribution of pain. And sensory loss actually would be associated with this in small fiber, so pain and temperature. Thermal sensitivity would typically be lost in most cases in the red situation. It does depend on the timing of your assessment. So if you have a very rapid change and you catch it early, you may still have hyperalgesia, some hypersensitivity. If you wait a series of months, they actually are pretty profoundly denervated. So if you're doing biopsies of the sites that are red, essentially there are no nerve fibers.

DR. ZOCHODNE: The pain, though, the intensity of the pain is related to its

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geographical distribution like you've shown or is it more intense in the afflicted areas?

DR. GIBBONS: Yes. And it's a little tough to tease that out because the pain is extremely intense. It seems to be intense. The intensity is worse and the distribution is worse. So it does seem that this is painful, but it hurts, it's really uncomfortable, but it's mostly at night.

That's the typical neuropathic pain distribution and presentation. It is a little bit more than one might expect, but by the time you get to here, these are people who essentially are almost walking around in clothing like this because anything touching them is extraordinarily uncomfortable. They're restless. They can't touch anything.

So it's a pretty severe kind of descriptor, and most of these people on multi-modal pain therapy are still uncomfortable.

DR. WRIGHT: I'm sorry. Did you say they had a decrease in their INF?

DR. GIBBONS: Yes. So it depends on the

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timing. We did a serial on some of these patients, and there's a fairly rapid decline in neurofiber density for about 2 months. And then if you wait out -- and I'll talk about this a little bit more later in terms of the natural history -- then there's an improvement in some patients over time later, but it does seem to tie in.

DR. WRIGHT: Did you see that widespread picture you've seen with the higher decrease also in those with lower or is it always like we described here?

DR. GIBBONS: So it seems to be link dependent, but the magnitude goes, as your larger change here, you tend to be moving up in terms of the distribution.

DR. WRIGHT: But my question is, have you seen patients who had that widespread pattern with the lower decrease in A1c? Do you see that?

DR. GIBBONS: So you do get variability in terms of who presents with what.

DR. WRIGHT: So that's possible, that's possible.

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DR. GIBBONS: It is possible. I'm suspicious about whether it's simply a measurement issue. In other words, maybe they dropped before we measured the A1c and then they dropped again, and we didn't. So I think there are many potential errors in measurement here, but that distribution.

Rayaz and then --

DR. MALIK: Is this a prospective study?

DR. GIBBONS: No. This was prospectively following people who were referred in from my clinic, but it was basically also a retrospective review of what had happened prior.

DR. TESFAY: Did some of these patients develop proliferative retinopathy or changes in their --

DR. GIBBONS: They all did. They all did. Yes, yes.

DR. POP-BUSUI: Did you say that this is in 3 months, this decrease in A1c?

DR. GIBBONS: So this is within 3 months, yes.

DR. POP-BUSUI: How many patients did you

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see with that decrease of 7 points?

DR. GIBBONS: So this was about 35.

DR. POP-BUSUI: Is it depending on treatment or regardless of what type of agents have been used to decrease the A1c at such magnitude?

DR. GIBBONS: So I actually have a slide on that, so we'll talk through that as well.

DR. ZOCHODNE: Did you biopsy the arm?

DR. GIBBONS: So I did in some patients. So this is the distribution. The pain in this case was fairly clearly tied to where the small fiber damage was occurring, so I did biopsies at different sites to try and understand if this was in fact tied to the problem, and it did seem to be fairly clearly tied.

DR. HARATI: I just wanted to be clear what number you used. You said 168 patients and 104 of them developed this. That's a very large number.

MALE VOICE: That's biased.

DR. POP-BUSUI: That is referral bias because you get to see them.

DR. GIBBONS: It is absolutely referral

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bias. It's absolutely referral bias. And that was why I started that with my bias slide.

DR. HARATI: These patients, 104, had no indication of any pain or neuropathy before that? In other words, the term that they used as treatment induced, I want to be sure that is the correct term and is not treatment aggravated.

DR. GIBBONS: Correct. So there are two aspects to that question that I think you have to think about. So these were people who didn't have any neuropathic pain to speak of beforehand with a few exceptions. There were some people who had some general distal burning pain that was very mild. It was not of a degree that they had cared to bother seeing a neurologist or even their endocrinologist to any degree. They did say, in hindsight, yeah, my feet had burned a little bit in the past, never really bothered me.

But the presentation was essentially very rapid onset of this picture, so something changed dramatically, and I'll get to the specifics of what that meant in this population.

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

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

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

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

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had a patient, a woman who had a very rapid correction in her hemoglobin A1c that a colleague of mine saw. And all she really had was to come in with acute burning pain in one lower extremity that was clearly not a monoradiculopathy or mononeuropathy.

There was no weakness associated with it, so we wondered is this a form first of what Jim spoke to yesterday, but of course, weakness is the hallmark there; had a little bit of weight loss, but not a lot. And so that put her somewhere between this and what Jim spoke to. And we do see those patients once in a while.

DR. GIBBONS: So there's probably a bigger picture out here that we don't yet have a handle on.

DR. ZIEGLER: So the cases we've seen were all symmetric, actually, so I think this is typical. And we also observed those cases, which therefore those patients that get stigmatized because they report widespread pain. And of course, a diabetologist wouldn't be expecting a

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distal symmetric polyneuropathy and would not trust him. And therefore, they refer to psychiatrists and so on.

DR. GIBBONS: This distribution is interesting. I actually thought these were ganglionopathy patients when I first started seeing them because many of them were talking about pain in the scalp as well; I mean, it was really diffused. And it was really only when I mapped out the variance in this that I recognized that some were clearly link dependent, and it was in this case much more widespread. So it did seem to be a link-dependent process, but just quite profound.

DR. SMITH: Chris, is there nerve biopsy data?

DR. GIBBONS: I do not have nerve biopsy. I only have skin biopsy data.

DR. TESFAYE: Actually, many years ago, we did serial nerve photography in these patients, and we found that they developed new vessels on the surface of the nerve, on exposure of the nerve, and also they had lots of RCVN shunts [ph], which is

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really a completely disordered picture on the surface of the nerve.

So I think the main hemodynamic factors may have a role either as a consequence of the pain or maybe causing the pain. So it's very interesting.

DR. GIBBONS: Yes. And the paper that you had on that describes well what I think is going on retinally as well, diffuse proliferation of vasculature. And it's widespread, so it seems to be both vaso vasorum as well as looking through retinal/renal as well. So it's an interesting diffuse microvascular process.

So this comes to some of what I'm trying to suggest as core diagnostic criteria and what we're thinking about describing this at least. The diagnostic criteria -- and we'll talk about some more specific details, but it's really a small fiber sensory or autonomic neuropathy. Some potential controversy of this is there are some motor cases that have been reported, but it's interesting. I've only seen motor involvement in recurrent cases of this particular problem, so

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people who have actually had a substantial change in hemoglobin A1c developed a classic picture.

At some point in the future, often several years later, they have returned to severe hyperglycemia and then have another episode where they bring it down rapidly, and then they develop motor involvement. So it's sort of a caveat, but I don't think it changes necessarily the diagnostic criteria.

I had looked at this. I had used this, again, hemoglobin A1c change of 2 points in 3 months, again, with my endocrinology colleagues. They are much better at looking at glycemic control dynamically, and I think that is an option to consider. I don't have good data on what that means. In other words, if I use a glucose monitor on a daily basis, what would I expect as the change?

Also, simultaneously, what is the magnitude and does that matter? If I start at 15 and go to 12, is that the same as 11 to 8? I don't know. The data again suggests that there probably is a

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difference, but I don't have enough numbers across that distribution to answer that, so that's still a controversy.

I looked at pain on a Likert scale of more than 3 points change within that same time frame, in this case developing over 2 weeks of physician severity to seek medical attention. So this was a significant change within 2 weeks of a period of glycemic control change.

This question here is, does this need to be expanded, contracted, that's an unclear question in that this pain and/or autonomic dysfunction actually occurs within 8 weeks, so this classic picture of distribution is within 8 weeks, and similarly, do we need to expand or contract the time frame?

DR. BREUHL: What are you thinking of when you say, like in the third point here, autonomic dysfunction? What would you expect to see reported or what would you observe?

DR. GIBBONS: In terms of autonomic dysfunction, this is where it's a challenge because

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most patients won't necessarily have had autonomic function first. So they won't necessarily have testing that we can see a change to, so it might not be relevant there. However, what they might have is, on orthostatic vital signs at bedside, they might have orthostatic hypotension, and that's something that could be measured and documented that wouldn't have been previously expected.

DR. POP-BUSUI: Chris, I have a couple of questions. Is there any gender difference in the risk of developing this treatment induced?

DR. GIBBONS: There is.

DR. POP-BUSUI: I was wondering, for clinical practice, it would be extremely relevant if, with your data, we could design or actually define the phenotype of people who are at risk of developing these type of complications because it can guide treatment regarding glucose control.

DR. GIBBONS: Yes. So as we go through the diagnostic criteria, I get into demographic distribution issues as well as other medical comorbidities, so I think we'll work into some of

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those questions.

DR. ZIEGLER: Do you have an approximate percentage how many develop autonomic dysfunction?

DR. GIBBONS: So in terms of the magnitude, nearly, I would say, 85 percent developed autonomic dysfunction, but it was often mild. We did do autonomic testing on them, so we could detect that, but again, most of these were in fact subclinical. Things like erectile dysfunction were prominent in men, but again, it's one of those where it's a little challenge. They're in significant pain. They're often now getting pain medications. It gets a little bit complicated.

DR. ZIEGLER: But you even described gastroparesis, correct?

DR. GIBBONS: But again, not with gastric emptying, symptoms of or suggestive of. So yes, there were many subtle things that were leading us in that direction. The hard findings on that side are harder to pick up except for the orthostatic hypotension.

DR. FREEMAN: Just to focus it a

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little -- and we can just flesh this out in detail later, probably when I think of the menu, when I think of same migraine with aura kind of picture, you're going to need to say autonomic dysfunction, 2 of 5, 3 of 5 of the following symptoms.

DR. GIBBONS: Yes, and I'm adding some additional on that. David?

DR. HERRMANN: So clearly, the precursor is a drop in the change of glycemic control, but in the setting of bariatric surgery, can you have a hybrid situation where hemoglobin A1c goes down, but not to the extent that you're talking about, but then you've got all the acute weight loss and the vomiting?

DR. GIBBONS: So it's now been reported. Actually, an Australian group published -- they didn't realize they published the same thing, but they published the same thing after bariatric surgery. I reached out to them, and the timing was the same in terms of the glycemic control, and they were much more in the subtle presentation.

So it does occur in that situation, and

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there are other factors that you worry about, nutritionally, et cetera, so that makes a little bit more of a challenge. I've also seen it in a couple of variances, both bariatric surgery. Pregnancy clinic is another concern. Women with diabetes who are suddenly pregnant want to take better control of the baby's health and suddenly make a change. And we'll get into some of the demographic and psychosocial issues with that.

DR. HERRMANN: You want an asterisk or something in your criteria about some of these typical scenarios. I just throw that in there.

DR. GIBBONS: Yes. And I think that comes in, in core 2 as the variables in that.

DR. TESFAYE: Is core 2 coming?

DR. GIBBONS: Yes. So I'm going to hopefully get all those. James?

DR. RUSSELL: So are you going to specifically state which autonomic signs you will be able to demonstrate by the bedside? Because there are people that aren't going to be able to do autonomic testing.

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DR. GIBBONS: So I'll try and be specific.

DR. RUSSELL: So probably one or two, you can say are really specific.

DR. GIBBONS: Yes. I'll try and be very specific on that as we go through.

DR. SMITH: So the way this is worded now, if I understand, your category or autonomic dysfunction, which implies that there's slated autonomic presentation. Is that true?

DR. GIBBONS: No. I think that's true, and I do want to talk about that a little bit. Some of the patients present with a much more autonomic flavor to it. They have a little bit of pain, but they're actually profound orthostatic hypotensions. There is some variance in terms of how severe it can be. Those are much less common, maybe 5 to 10 percent of the group as a total, but they're also the hardest, I think, to pick up. But there is a spectrum of this, so you have pure pain and then you have almost pure autonomic with a spectrum in between.

DR. TESFAYE: I would agree with that.

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DR. SMITH: If you were doing a trial, would you include both in the trial or does there need to be separate categories?

MALE VOICE: Microphone.

DR. SMITH: I'm sorry. My question is asking whether or not those that are autonomic predominant need to be viewed as a different class and the reason being would you want both in a clinical trial?

DR. GIBBONS: Right. So I think the concept is, we have some insult, which we think there may be some microvascular process going on diffusely as to why it's selecting one territory more so than another. It's not clear that there's a reason. We can maybe have an AB in there, autonomic or sensory predominant. I don't know mechanically from a trial at this point whether it would make any difference. That's very limited data.

DR. TESFAYE: I would agree with that because the patients that we described, a series, we found autonomic dysfunction, which can be actually extremely severe. One patient, we had to

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nurse for 6 weeks flat because as soon as she just lifted her head, her blood pressure just went into her boots. So there's a big spectrum, but it is part of the syndrome.

DR. BRUEHL: I think overall, this looks really good with some additional specifics to operationalize some of those terms. I do think subtype is an option, which would be kind of optional. People can classify if they want to, but it wouldn't be required for the diagnosis.

The other thing -- this is very minor -- is I would avoid the use of the word Likert scale because technically that has negative and positive valence, so I would just call it a pain rating scale.

DR. GIBBONS: Excellent point

DR. BENNETT: I think you really need to set thresholds. I mean, I think, in some ways, what's probably more relevant is type of pain, where the pain is, quality.

DR. GIBBONS: Yes. It's an interesting question.

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

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

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

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

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develop this. It could use that as a comparator. Yes. So that's actually a quick way to look back and check.

DR. SMITH: You could even use your retrospective data set as sort of a developmental data set and then validate it prospectively, so refine it.

DR. SINGLETON: It isn't acute, though, is it?

DR. GIBBONS: I'm sorry?

DR. SINGLETON: It's not acute. It's not within a week or two.

DR. PELTIER: It's pretty acute.

DR. GIBBONS: So it's within 2 weeks, but it maximally general hits within 8 weeks.

DR. SINGLETON: Yeah. I think acute's a bit --

DR. GIBBONS: Subacute? But we'll use numbers, 2 to 8 weeks.

DR. TESFAYE: Chris, I think on the gastric side of things, over the years, I've never come across any patient who says he knows of post-

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prandial fullness or any gastric symptoms. And I think unless you have robust data again, you need to mine it and look that this is a clear indicator of gastroparesis. I would be uncomfortable to put it. That's number one.

Number two, it's at least 6 months of sustained hypoglycemia, and again, there are patients who, even with type 1 diabetes diagnosed, glycemic control improved rapidly. And again, I'm not sure whether putting 6 months is necessary.

DR. GIBBONS: I did put the asterisk there because I knew this was a tricky one, particularly -- and we'll get to the demographics. But those with type 2 that are undiagnosed, we just have no --

DR. TESFAYE: We have no indication of what happens.

DR. GIBBONS: Yes.

DR. POP-BUSUI: Why don't we look at the demographics a little bit before we make a final decision? Because I think that's important.

DR. GIBBONS: So maybe I'll jump forward so

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everybody has a --

DR. MALIK: Chris, there is a very rare entity, hypoglycemic neuropathy. So is there a subtype within this group that you've got that have a history of severe hypoglycemia for example?

DR. GIBBONS: It's an interesting question. So this group has by and large all been severe hyperglycemia for a long period of time, until this episode occurs. They don't have true hypoglycemia during these -- I do have good records on this -- although the concept of relative hypoglycemia compared to where they were before I think is absolutely an important concept to debate. And that I think is where there is a big issue.

DR. TESFAYE: But hypoglycemic neuropathy doesn't present in this manner. Hypoglycemic neuropathy is usually focal, and I think this entity is completely different.

DR. GIBBONS: It's a little different, yes.

DR. ZIEGLER: But the question is whether you have records of documented hypoglycemia, symptomatic, because those may experience

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hypoglycemia at 100 glucose and try to find a relationship between the pain development and the other manifestations. Whether there is a relationship to the frequency or hypoglycemia, for example, would be interesting.

So all of symptomatic hypoglycemia in that context would be very interesting because the DCCT has shown the transient deterioration of retinopathy, which was related to hypoglycemia in the initial lowering of glucose.

So it would be interesting to learn the role of hypoglycemia in that context as well.

DR. POP-BUSUI: But it was not so severe. I mean, we didn't see proliferative in such a short term, but I agree completely it was after the first year that deterioration was clearly there.

DR. GIBBONS: But again, the numbers were really only a change of about 2 points, so they were on the lower side.

So Amanda's been waiting patiently.

DR. POP-BUSUI: Your patients have not only type 1, right? Or they are all type 1?

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

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

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

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

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just rehashed this. I wanted to talk about the differential diagnosis a little bit. Again, I put this up just because of this question of an overlap and phenotype clinically. These are totally different, so this isn't a diagnostic, but from pathophysiology, you have to wonder about these relations.

Again, this is the link-dependent small fiber neuropathy that occurs or predominantly small fiber neuropathy is just time that these are people developing it anyway. That's always a question that comes up, some sort of acute process, whether it's drug or toxin related, and then the possibility of an inflammatory or infectious acute neuropathy. Again, they seem fairly remote, but they're definitely on the differential.

So I moved this to tabular form to try to get at some of these details. And I think we've talked about this and already reviewed some of the details as to why this might or might not work out.

One question, though, is how would we quantify this exam, and I think it fits best to the

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UENS in terms of distribution of small fiber neuropathy. However, I wonder if that actually doesn't grab enough territory to magnify that, but maybe that's something we can think through later. But that was just a question because this component doesn't fit as highlighted yesterday on the NIS-LL scale. It just doesn't fit with a particular problem.

I highlighted these points here. Pain is, again, link dependent but may appear as a whole body in the more severe cases. This part clearly needs to discuss or remove, and then no other diagnosis that better explains the neuropathy.

Common features in demographics.

DR. FREEMAN: I think we are working through this. Can we go back to this a little? If we think of the flow-through criteria, first it's going to be pain score, so starting at the symptoms, the first would be the appearance. What are we going to call it? Subacute or give you a time frame of pain. Then symptoms, you're going to give your menu of autonomic features, the Gordon

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approach or from your clinical experience.

Then I suppose you're going to quantify the pain. I'm seeing 4. That probably is going to go back. You're going to describe the pain.

DR. GIBBONS: This probably will then move into -- yes.

DR. FREEMAN: Yes, so 3 and 4 will be combined.

DR. GIBBONS: Have a menu both for pain in terms of severity distribution and then an autonomic severity distribution.

DR. FREEMAN: I mean timing to severity.

DR. GIBBONS: Yes.

DR. FREEMAN: You led that small fiber group. You probably could on your exam combine conclusions you came to, we will come to later in the day with respect to the examination, and then the background. I think that would probably work.

What do others think about that?

DR. GIBBONS: Dan?

DR. ZIEGLER: I agree with Solomon. I would skip the 6 months.

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DR. GIBBONS: No, I agree, so this will be revised based on that because that's the consensus here, I think.

DR. FREEMAN: We'll go through all of the comments that were made.

DR. GIBBONS: Yes. So thankfully we have a stenographer in the back who's saving us.

DR. BRUEHL: You don't want to include anything in the criteria also that might limit your ability to make the diagnosis just because of absence of information.

DR. GIBBONS: Great point.

DR. TESFAYE: Presumably, the patients in large fiber tests, most of them were normal, but in some, there was some --

DR. GIBBONS: Yes. And I'll address that as we move into this. Gordon?

DR. SMITH: So my predictable question, I suppose, do you need or will you require a confirmatory test? So if you go back on the slide, you talked about neurophysiologic, neuropathologic, do you think you need something like that?

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

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

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

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

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80 percent women. And I'll talk a little bit more about this because I think it's a major pathophysiologic psychosocial issue that we'll get into.

DR. PELTIER: Social, yes.

DR. POP-BUSUI: Yes. And then I had seen that there were a lot of eating disorders in these people.

DR. GIBBONS: A huge amount of eating disorders, so that I think comes in core 3 because of other comorbid illness, so that will be something I talk about. But in terms of this distribution of type 2s, it's far less common as a proportion of the population.

The common features, we've gone through this I think fairly quickly. Hot burning, stabbing, lancinating pain, the classic descriptions. Other complications, autonomic, we talked about this, the retinal and renal.

Epidemiology, again, this is a question where it's pretty limited against single center, and this makes it a little bit more complicated.

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But it was 11 percent of the population referred in just for general diabetic neuropathy. Again, it's hard to extrapolate that to the rest of the population. Certainly, Joslin's is a unique group of patients there, so uniquely dynamic changing glucose is possible. I think they're more than other places.

DR. PELTIER: We see it, too.

DR. GIBBONS: So it is out there, and clearly people see it, but I think the numbers are a little bit more unknown.

DR. PELTIER: In Tennessee, we call it the "Come to Jesus" talk.

(Laughter.)

DR. FREEMAN: Can you comment on any sense of prevalence?

DR. TESFAYE: I don't know. I think I reviewed your paper, Annals of Neurology and all the papers. Eleven percent I think is because of referral biases.

DR. GIBBONS: I agree.

DR. TESFAYE: It's quite exceptionally rare,

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but I think people need to have their brain tuned not to dismiss these patients, because I've had a few patients who have been referred because they did nerve conduction studies, which are normal, and these patients have severe small fiber neuropathic pain, which was not appreciated, and I think probably not as much as 11 percent.

DR. GIBBONS: One of the things that I conducted in terms of this patient population is I actually did a study of how frequently the physicians who referred the patients in recognized the problem, and there was a clear relationship because the prominent the symptoms, the classic picture, the more likely they were to recognize this.

However, as soon as it was more of a distal symmetric kind of really feet only, nobody recognized it. And if it was autonomic predominant, they did not recognize it. They didn't think of that in this disorder. So the relationship to the referrals were definitely inversely reported to the classic presentation.

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DR. ZIEGLER: If it's widespread, the physician would say that it's not due to diabetes. This is what I have frequently heard from the patients coming from psychiatrists and so on.

DR. GIBBONS: It's definitely missed if too secure.

DR. ZIEGLER: I think it's pretty rare. It's very rare, I would say, because if you ask 20 diabetologists about it, maybe one would know it. So it cannot be very frequent in that sense.

DR. GIBBONS: Yes, although I have asked that same question of the diabetologists who referred these patients, and they've said they've never seen it even though they refer these patients. So we get into that same thing.

Ahmet?

DR. HOKE: What's the time lag between these patients who actually have that drop in their hemoglobin A1c and when they were referred to you? I mean, did you see these patients early on in their course?

DR. GIBBONS: I saw them early, yes. So

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

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

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

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

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

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

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

DR. GIBBONS: Yes. So I do as natural history. That's a couple slides ahead here.

So other lifespan considerations, we talk about a question of whether this could occur in pediatric populations, certainly in type 1 diabetes, absolutely, this is I think a big issue. Possibly in type 2. We're seeing unfortunately a lot of type 2 diabetes in the pediatric population as well. I've never seen a case, but I think unfortunately it's inevitable.

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

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

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

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type 1 population in particular.

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

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

DR. TESFAYE: Microvascular dysfunction

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possibly.
DR. GIBBONS: Yes, precipitating, all these things ultimately leading to microvascular dysfunction, and then inflammatory mediators where hypoglycemia causes massive cytokine and hyperalgesia, potentially microvascular change, these are theories and there's some degree of evidence, but again, nothing, I think, has clearly drawn the line across.
DR. ZOCHODNE: That's a tough one, Solomon. I mean, how would you explain loss of terminals and selectively in small fibers in a nerve trunk from a microvascular cause? I mean, it just doesn't fly.
DR. TESFAYE: Recently, in fact, when we go back in the paper, what we found recently is we did a skin biopsy in patients with chronic painful diabetic neuropathy, and we found old stuff, which Rayaz and I published 30 years ago. Actually, there is an abundance of proliferation of microvessels in the dermis of these patients on skin biopsy, stained using von Willebrand factor.
There's also several papers that we

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published many years ago in those with painful neuropathy. There seems to be increased shunting on the surface of the nerve. Is it a consequence? I don't know. What is the metabolism that's driving this? I don't know. But these patients develop proliferative changes in their eyes, and there is association with microalbuminuria. And a similar process could be taking place on the surface of the nerve, rendering the nerve maybe ischemic or hypoxic, leading to pain.
I don't know what the mechanism is, but clear observation, there are vascular changes in these patients. In all the patients that we did, we exposed the nerve, and there was proliferation of blood vessels on the surface.
What's driving this? What are the mechanisms behind this? We don't know.
DR. HOKE: I guess even just a relative reduction in glucose levels in the nerve could lead to the degeneration. In vitro, when you culture neurons, you're culturing them at relatively high glucose levels, 25 millimolar. And if you drop

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that to quote/unquote, "normal" glucose levels, 7 millimolars, a lot of times the axons will degenerate, without doing anything else.
So probably that rapid, I mean, sarcomas, the neurons kind of got used to living at those high glucose levels --
DR. GIBBONS: Relative hypoglycemic state.
DR. HOKE: -- then when you take it away, they undergo --
DR. GIBBONS: That's relative hypoglycemia.
DR. HOKE: Exactly.
DR. ZIEGLER: I thin in these early studies, Gary Whelan actually described some kind of sprouting of those nerves as well.
DR. GIBBONS: Yes, exactly. Gordon?
DR. SMITH: Has anybody attempted to model this in an animal system?
DR. GIBBONS: Nigel has.
DR. WRIGHT: In processing right now, I think this would be really amenable to anti-NGF antibodies. I would suspect that there's probably proliferation of NGF. You're getting an increased

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response. The nerve degeneration is interesting, but it may be secondary because it's a change.
You've got this incredible increase in pain sensitivity. I think C fibers are very modifiable in terms of changing and trying to adapt with the central nervous system, but I think this would be really interesting to model that, and I bet it would be sensitive to anti-NGF antibodies.
DR. GIBBONS: Yes. So I know Nigel Calcutt had been working on that. And he's been working on it for a while, and I haven't seen much out of it. So I think one of the big issues modeling this is that the animals all die, so it's a challenge. And maybe the model he was using --
DR. WRIGHT: Is it because of hypoglycemia?
DR. GIBBONS: Yes. So the issue for the question of having a sustained period of hyperglycemia long enough, then you control, I don't know. I think there's an issue in terms of lifespan in terms of the effects.
DR. WRIGHT: You just have to monitor their glucose better.

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

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

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

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

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inflammatory, cytokine release modifiers, this would be really interesting. Then salvage therapies. Once people develop this, is there anything we can do acutely to prevent it? Again, the approach they've taken in the lumbosacral radiculoplexus neuropathies; can we pulse, hit something hard quickly to prevent or more rapidly recover?

So I'll stop at that point because I want to make sure we stay on time.

(Applause.)

Q & A and Panel Discussion

DR. FREEMAN: So we'll move on to Rob's talk. At this point, [inaudible – off mic] – the switch were meant to be on the Chris, Jim talk, and don't have anything to say.

Eva, not here. Ahmet, anything that you want to [inaudible – off mic].

So where are we? So the rest was Jim, Chris, Ahmet.

Rayaz, any additional comments?

DR. MALIK: I guess is there any way of

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interrogating the big clinical trial data, sets like ACCORD, PADT, DCCT perhaps? Is there something in there that you can potentially get access to, to try and find out how common this problem really is?

DR. GIBBONS: There is signal data that's available in there. In DCCT, they talk about the early and worsening retinopathy. But again, those are the people -- there were still relatively small changes in A1c, so it wasn't the magnitude of the problem that I'm talking about.

I think there is signal data available. And particularly for bariatric surgeries as well, that is, I think, a great and ripe opportunity.

DR. MALIK: If you look at VADT, I think it reported, actually, they did -- an ACCORD as well. They had a list of autonomic symptoms, for example. So they're obviously recording them at time points, and I'm sure all of the trials were doing it in some way, perhaps not pain scores, but certainly autonomic symptoms were recorded.

DR. POP-BUSUI: Autonomic symptoms were not

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recorded in ACCORD.

DR. MALIK: VADT was. I think it was one of them that had --

DR. POP-BUSUI: VADT had some, but I don't know whether the magnitude of A1c reduction was so big -- even in VADT, it was from 8.9 to 7.

DR. MALIK: Yes, but that's the mean. That's the average.

DR. POP-BUSUI: Right.

DR. MALIK: Within that population, if you've got a trial of 10,000 people, you're going to have individuals.

DR. POP-BUSUI: There is a question also whether the two entities may be separate. Is this the same type of painful induced neuropathy in type 1 versus type 2? Because I think that a phenotype of patients is actually very, very different just looking at some of these demographics.

DR. GIBBONS: The clinical phenotype and comorbidities are definitely different. The clinical picture in terms of pain actually is the same, and that's where it's very interesting.

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DR. FREEMAN: Amanda, the other panelists, anything else to say?

DR. PELTIER: The other thing I was going to comment on is whether or not we should look more into the nutritional component more carefully, because if you have a group that's in type 2 that are going from obese to significant weight loss and then the reverse happens in type 1, where you have someone who is essentially underweight or not eating well, and then presumably is going to gain weight significantly or have this rapid shift, that might be something you might want to take into account as a pre-disposing factor.

DR. POP-BUSUI: No. I don't think that you can expect so much weight gain in 3 months just with this improvement of glucose control.

DR. PELTIER: No. They won't.

DR. POP-BUSUI: But the point with the bariatric is actually quite --

DR. PELTIER: Right. Is there some other nutritional component with that shift?

DR. POP-BUSUI: It's very possible that

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these people who had an eating disorder had a baseline nutritional dysfunction that could have just been just triggered by this acute change in glucose levels.

DR. FREEMAN: Last quick word from Dan?

DR. ZIEGLER: We're still missing the aspect of reversibility, because this is the first -- I tell the patient, I reassure them that this will go away. And I think this should be one criterion and clearly differentiation to the chronic DSPN.

DR. GIBBONS: So we did have a recent publication on the reversibility of this. And so you're absolutely right. The classic group that we saw, the majority of those with type 1 got better in 18 to 24 months, but not completely. They didn't go back to baseline, but they definitely got better in all aspects.

However, that was pre-disposed to a stable glycemic control for the entire duration. Those who had significant fluctuations again up or didn't quite have better control to this degree actually got substantially worse. And those with type 2

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diabetes had no improvement. That was unfortunate. So it was only type 1s that showed recovery.

DR. FREEMAN: So I think we've done a really good job with these tight package disorders, germs, diabetic radiculoplexopathy, and this one. Let's move on with similar success to Rob.

Presentation – Robinson Singleton

DR. SINGLETON: Thank you, Roy and Chris. That was the point I was going to make, that we're moving from incredibly well definable disease to a giant baggy sort of vague entity that defies easy definition, so I think that is really the challenge for us.

I just want to tell you about the overall concepts that I want to engage you with here. First, that metabolic syndrome is a complex spectrum disorder with a continuum of injury to nerve and risk for that injury. Metabolic syndrome features, especially obesity and dyslipidemia, contribute to the pathogenesis of neuropathy. And as I've said, the different features of metabolic syndrome contribute probably different degrees of

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risk.

I'm taking an extremely reductionist position with regard to the taxonomy of this disorder because I think that, basically, the neuropathy of pre-diabetes, of metabolic syndrome, is the neuropathy of diabetes, and the diagnostic criteria from a phenotypic evaluation for the most part are the same.

So the discussion that we had yesterday about what defines neuropathy in these patients, really, we've had that discussion. I think we did a good job of that yesterday. It's really not so much about what defines the neuropathy as what are the attributes, what are the contributors to that neuropathy.

I think there's good data basically that features a metabolic syndrome, that contributes something to the pathogenesis of peripheral neuropathy.

So why should we have this be its own entity if it's going to be so vague? I think the most important argument from me is that the risk pool

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for patients who may have a contribution of this type to their neuropathy is huge. Thirty-five percent of the U.S. population has metabolic syndrome and some even larger percentage are obese. Recognizing this disease early means that we have a chance to offer effective treatment, and if we point out that neuropathy can be something that happens in this setting, that brings more patients to effective metabolic control.

But more specifically to the entity, I think recognizing that per-diabetic neuropathy as a disease entity allows practitioners in general practice to consider this diagnosis. It's foundational for examining the consequences of the disorder in terms of progression, and it encourages study of the pathogenic mechanisms. If we don't define this disorder, we don't have a chance to study it effectively.

I think it's important to set this in the context of this spectrum of metabolic disorder, and I think I'm going to come around to talking about, again, how almost certainly genetics, the complex

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multivocal genetics, to some degree will be shown to define the risk for this. Why is it that some patients develop neuropathy in the pre-diabetic period and others do not? I'd say that at least some of that is determined by your genetic make-up.

For a long time, I've thought Homer Simpson is the perfect example of this. He's got a donut in one hand and probably a beer in the other. And these overweight patients develop a neuropathy that is sensory predominant, symmetrical, distal, often painful, sometimes has autonomic involvement, and essentially, it is undifferentiated from the disease of patients with early diabetic neuropathy. And I would argue that nearly any feature of diabetic neuropathy can be seen in the pre-diabetic setting, with perhaps the exception of Chris's disorder. If you haven't been treated, you are not going to have treatment-induced polyneuropathy.

There's a problem with nomenclature. Just getting off the ground, what are we going to call this disorder? And we've used a number of terms. Pre-diabetic neuropathy ties this to diabetes, but

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I think it doesn't recognize the contribution of other features of metabolic syndrome.

We've talked about impaired glucose tolerance neuropathy, which is really the same pre-diabetic neuropathy. Gordon has used and others have used cryptogenic sensory polyneuropathy as really almost a winking choice. We mean metabolic syndrome neuropathy, but we don't want to say so because we worry that our critics will complain about the idea that somehow it's tied to this vague metabolic syndrome.

I think we should consider calling this what it is. It's polyneuropathy in the setting of metabolic syndrome, and I am going to use that term at least for this lecture here, but we could debate whether we want to stick our neck out by making that point.

DR. FREEMAN: Before you move on, [inaudible – off mic].

DR. SINGLETON: I think we're going to get there. I think some of them are in the audience. I just want to say that I'm going to talk about the

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data, about the evidence for polyneuropathy and metabolic syndrome. And this data, the better it's done, in some ways the shakier it gets. But what I want to say is that neuropathy is a multi-contribution disease for many patients, and we see this across the spectrum of metabolic syndrome. So it's not only true in patients with metabolic syndrome, but in patients with diabetes, that we go out looking for their B12 deficiency and their gammopathy in addition, and those things contribute together.

So I want to come away from that idea of saying not that we can necessarily say that metabolic syndrome features provide only cause for neuropathy. I think that's probably not true in most patients, but that instead metabolic syndrome contributes something, something important to the development of injury to these peripheral nerves.

I was going to say that as I go through this, I apologize if I either haven't talked about the important work that you've contributed or if I've mangled important work that you have

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contributed to this disorder.

Basically, this is the main thrust of this. Epidemiology suggests this association, as we'll talk about. Animal models recapitulate the features of pre-diabetic or metabolic syndrome neuropathy. There have been studies looking at the biology of nerve injury in the pre-diabetic setting. And there's been a lot of research that looks at the biology and has developed a plausible pathogenic mechanism, especially for fat and obesity to cause injury to peripheral nerve.

So this is maybe a whole bunch of studies that look at patients with otherwise idiopathic neuropathy and find an excess of features of metabolic syndrome or pre-diabetes in those patients compared to controls.

Dr. Visser at University of Utrecht has done this, but so have lots of other people, including us. There is, in addition to that data, data -- and this is the only time I'm going to try -- I'm going to try and stay away from diabetes, but just to talk a little bit about the

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situation in which you have diabetes, but metabolic syndrome features within diabetes contributes something to the development of neuropathy.

I think Solomon's study, the EURODIAB study, which took patients with type 1 diabetes who did not have neuropathy at baseline and then followed them for a surprisingly long time, for 7 years on average, found that these features of metabolic syndrome were risk factors for the development of incident neuropathy, even in type 1 patients. We had a discussion yesterday from Gordon about how type 1 and type 2 diabetes are different diseases, yet even in type 1 diabetes, these metabolic syndrome features play an important role in the development of neuropathy.

We've done a less good in many ways study where we've taken patients with type 2 diabetes and followed them for a long time to see what happens to them, and to see if they have neuropathy at baseline, and what are the features that are associated with it. I think if there's a strength of our study, it's that if we're focused on

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neuropathy, we're focused on the features of neuropathy in a much more intensive fashion than the Tesfaye study. But here, we found a very strikingly similar result, which is that this is prevalence, not risk factors -- not incident neuropathy. But we can see that metabolic syndrome is associated with an increased prevalence of neuropathy in patients with diabetes compared to those who don't have other features of metabolic syndrome.

Then treatment studies in which there's been multimodal attempts to try and control all the features of metabolic syndrome and not just hyperglycemia have shown that there can be a reduction in the overall risk profile for those patients. This is not so much about neuropathy as it is about showing that you get better control of all the features, the consequences of diabetes, if you treat not just hyperglycemia, but other features of metabolic syndrome.

So turning to the obverse of this, which Dan pointed out yesterday, we want to look not at

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patients who have neuropathy with the inherent referral bias, but instead look at patients who have the underlying condition and then see how many of those patients have neuropathy.

Here, the data is certainly weaker. This study Dr. Ziegler did shows an increasing prevalence in his case control population, both of neuropathy as defined by the MNSI and also of neuropathic pain. And then a study by Vera Bril and Dr. Perkins' group is a larger study looking at patients at great risk for progression to type 2 diabetes, and they found, again using the MNSI as a questionnaire and using a neuroesthesiometer to measure vibration, an excess of injury and reports of neuropathic features in patients who are in the pre-diabetic state.

The biggest, least biased study that I think is out there is Brian Callaghan's study, which he has searched the records of the Health ABC study participants and basically looked at this in a really pure epidemiologic exercise.

What you can see is that there is clearly an

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excess of prevalence in the diabetic group, but not really in the pre-diabetic group. In fact, if you look here, if you don't have other metabolic syndromes somehow in this group, it's protective. If you just have hyperglycemia, you are better than average in terms of your risk for neuropathy. And what he found, though, overall in looking at all this data is that each feature of metabolic syndrome adds about 1.1 percent to your overall prevalence, your risk for the development of peripheral neuropathy and that, amongst the different metabolic syndrome features, waist circumference and dyslipidemia in the form of low HDL had the greatest association with the secondary measures that they did of diabetic sensory polyneuropathy.

We know a lot -- and this is where the mangling comes in. I'm not going to really go very much into this, but we know about dyslipidemia and fat as pro-inflammatory, biologically, hormonally active tissue that has a real influence on the pathogenesis in terms of injury to peripheral

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

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

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

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

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

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

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

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

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

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

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

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

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patients.
We've also used this capsaicin axotomy. So just to describe briefly, we place capsaicin on the skin for 48 hours. That causes the nerve fibers on the skin to die back from the epidermal into the dermal layer. And then by doing serial skin biopsies, we can count the number of their fibers that were there before the patch was placed, or there after to show that we denervated, and then to watch over time as those nerve fibers grow back in. And with that, we can calculate a regeneration rate for the skin.
So this lets us treat humans a lot like rodents, really an experimental model for looking at regenerative capacity. And in this, we've taken patients who have pre-diabetes, but who don't have neuropathy, subjected them to a baseline renervation bout, then giving them 6 months of intensive diet and exercise, and repeated that renervation bout in this last 3 months of that period.
What we've seen is that doing this, we can

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have an impact on the regeneration rate, the number of fibers that regenerate, the fraction of fibers that regenerate at 30 days, and also in the rate of that regeneration.
So here, in patients who don't yet have diabetes, we can nonetheless demonstrate a defect in the biology of these nerve fibers that's reparable by improving their metabolism or sometimes just by exercising.
Yes?
DR. ZOCHODNE: So Rob, just out of interest, I'm wondering if you ever looked at the actual trajectories of the original fibers, the ones that disappeared with capsaicin and the ones that came back. We just had this observation coming out that when they die from capsaicin, it's interesting that they really project back again in their original trajectories, same cells.
DR. SINGLETON: It's really hard to see the same fibers. Michael Polydefkis did nested biopsies, so first 3 millimeter punch biopsy, and then, like, a 5- or a 6-millimeter punch biopsy,

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where they try and look at the surround around the place where the punch happened in order to try and even look at the same fiber so much as to just see the surrounding local environment.
I don't know how I would look at the exact same fibers twice in this setting. Maybe that's not even what you're asking.
DR. ZOCHODNE: That's true. You're right.
DR. SMITH: Have to do a blister presumably, right, because if you do a punch, you're going to be regenerating into a scar. Do a blister and image it.
DR. SINGLETON: So with all of that, as I sat here yesterday, I tried to produce some sort of model for this. And this is super simplistic and limited by my primitive Illustrator skills, but I think it gets at some of the things that I think are operative.
So if we imagine this progressive thing in which severity gets worse as time goes by and metabolic progressive injury occurs, we can define points on this that are normal, and pre-diabetic,

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and diabetic using impaired glucose tolerance or A1c.
Over that period, different aspects of this are operant and contributing to the neuropathy that we might discover. Like, if you're way out over here, if we look at all comers with idiopathic neuropathy, we're going to find probably that a fair number of them have some genetic influence on their disease. And that genetic influence continues throughout this period. We don't know exactly how that risk contributes, but it's still there.
We just got finished saying, and other people have said, that the influence of hyperglycemia on risk and on the manifestations of neuropathy grows over time as you move from the pre-diabetic to the diabetic state. I could just as easily labeled this -- I said time to progression on the X-axis, but really this could be, we'd say, from small to large fiber. Dan's not listening to me. It's like skipping by from mild to moderate, from reversible to irreversible, from

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metabolic to axonal. So as we move up this, we replace small fiber metabolic tip of the axon mitochondrial injury with microvascular injury that is less reversible.

So whether it's caused by hyperglycemia or whether it just is corresponding with the increase in hyperglycemia, nonetheless, we move from a reversible to an irreversible process in this.

The contribution of metabolic syndrome of other features like obesity and dyslipidemia continues through this period, but as we move from the pre-diabetic to diabetic state, as hyperglycemia becomes more operant, the contribution of this from these different aspects of metabolic syndrome grows to be more hyperglycemic and less the other features, perhaps. But at the same time, a chance that when we look at a patient with early diabetes who has neuropathy, diabetes as the primary contributor grows larger; whereas if we're further down the scale, the chance that the cause of your neuropathy is just these items of metabolic syndrome and not something else

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is less.

We're always going to have this other potential risk contributors for neuropathy, either things that we know about like a B12 deficiency or things that we don't yet know about, that we haven't defined. And that stays maybe more or less the same. It's just that as we move further up where diabetes becomes a bigger contributor, other becomes a less important contributor by comparison.

So I say that as we move up the scale or down the scale from diabetes to pre-diabetes, it's not that these things don't play an important role; it's just that it's harder to be sure that they are the primary contributor, and that has obvious implications for our taxonomy exercise.

So that's a ton of talk, and we didn't even talk about taxonomy at all, which is kind of my whole goal here, because when we talk about the diagnostic criteria, first of all, there really are not authority of current diagnostic criteria, so we're free to choose what we like.

My recommendation is that it is exactly the

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symptoms and exam findings of neuropathy and confirmatory testing as we promulgated yesterday, as we talked about for diabetic neuropathy. This is the same entity in a less severe form. We can talk about which metabolic syndrome criteria we should use to define by this. And we would say that this is in a disease that's not better described to another neuropathic disorder, but with the recognition that, in this disorder, the etiology is almost certainly multifactorial.

These seem like the two most likely ATPIII criteria that we would consider. The metabolic syndrome criteria, ATPIII, is agnostic with regard to the metabolic syndrome. So any three of these makes the diagnosis, whereas the World Health Organization pre-supposes that diabetes is the most important. And probably even though ATPIII is more, I'd say, commonly used, in some ways the World Health Organization, because they recognize the primacy of hyperglycemia, might be a more apt choice for the definitional choice in our taxonomy.

Then I just want to finish with these

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controversies.

DR. BRUEHL: Excuse me. Before going into the controversies, can you go back to the actual criteria?

DR. SINGLETON: Here?

DR. BRUEHL: Yes.

DR. SINGLETON: So my quarter slide?

DR. BRUEHL: Yes. I just wanted to mention something just because it got me thinking about this. So what seems to be different about this condition compared to the other ones we're talking about is this is potentially preventative. The analogy to me seems to be like this expansion of recommendation to use statins to try to reduce cardiac risk in people who maybe have a less likelihood of developing it, but they want to capture as many people as possible and prevent as much as possible.

So I think the criteria you come up with here, unlike some of the other conditions, might want to overweight sensitivity to make sure you catch these people because of the possibility of

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prevention. And I guess I would wonder, when you say symptoms and exam findings of neuropathy plus confirmatory testing, that sounds like a pretty high bar, and I wonder if maybe referencing back to what we came up with yesterday for the possible diabetic neuropathy might make more sense before they have to meet the full criteria.

Does that make sense?

DR. SINGLETON: Yes, no. I think what gets worse is not the neuropathy necessarily, but the risk factors for your neuropathy get worse over this spectrum of disease. Some patients are more susceptible to those risk factors than others.

This comes back to Gordon's point that, really, what is it that we're adding by adding a confirmatory test? We're adding some surety to this, but is that really a benefit, especially as you've said, in the setting where the goal is to help practitioners to recognize this entity, and patients to recognize this entity, and to take action for it.

DR. HERRMANN: On the diagnostic criteria,

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just two thoughts. The first is, not to get too specific about the systems, and the exam, and the confirmatory test, but do you think the range of neuropathy phenotype of metabolic syndrome equals the range of neuropathy phenotype of distal symmetric polyneuropathy? So in other words, are there exclusionary caveats?

In some of the early literature, from you, Gordon, and others, pain was a big feature, painless less so, and large fiber dysfunction was much less common. But of course, how much large fiber dysfunction would be exclusionary. Does this have to be a small fiber or pre-dominantly small fiber phenotype? I'd ask that one question. And then the other point gets to terminology.

I think what you've shown here, and what the literature seems to show, but I may be incorrect, is as a neurologist, when I hear the term pre-diabetes -- I understand the pre-diabetic milieu with metabolic syndrome and all that, but when I hear the term "pre-diabetes," I still think in terms of impaired fasting glucose or IGT. And the

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evidence you show is that if you just have that impaired fasting glucose and IGT, that alone absent some other features of the metabolic syndrome, is not clear that that is enough glucose dysmetabolism to be etiologically linked to the syndrome.

So maybe not using the word "pre-diabetic neuropathy," saying that it's rather using metabolic syndrome. And if you want to use pre-diabetes, just say the pre-diabetic milieu, because if you just use pre-diabetic neuropathy, then I think it could lead to a lot of overdiagnosis and not thinking about other possibilities; I don't know; I just throw those two elements.

DR. SINGLETON: Yes. I think just to touch on a lot of the things you just said, some of them are on this slide. We've said for a long time that pre-diabetes, hyperglycemia in that pre-diabetic state is just a marker for metabolic syndrome. So it's really the metabolic syndrome and not the hyperglycemia itself that may be the driver, especially for small fiber nerve injury.

I think one of the controversies -- not

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controversies, but one of the things we should discuss is should we either give more weight to some metabolic syndrome criteria than others in our diagnostic criteria. Should we call out specific metabolic syndrome features like obesity? Can obesity itself be cause for neuropathy? I think there's not enough data yet to suggest that, but you see where I'm going with this.

Then back to your point, is there a severity of neuropathy that's too severe to be this disorder? I think there is. When we had this discussion yesterday about what constitutes severe neuropathy from a standpoint of our taxonomy, I say anyone who falls into that category in the pre-diabetic metabolic syndrome period is either super unlucky with their genetics or has an identifiable other disease that we should be looking hard for.

So down here at the bottom, because the diagnostic assurance of this is less than for diabetic neuropathy, is it incumbent on practitioners and us to look harder for alternate causes of neuropathy in the pre-diabetic period

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than we do in the diabetic period? And if so, what more should we do?

I think one thing I can imagine is that in the coming world of $50 whole genome genetic testing, we do a genetic panel for every one of these patients. We look for known monogenetic causes of neuropathy to look for pharm [indiscernible] that put people at greater risk. And that's not what I mean at the very bottom here, which we should, I think, as part of our consortium, mount some sort of phenotype/genotype, sort of registry, in order to look for multi-genetic influences in a more systematic way.

Yes, Gordon?

DR. SMITH: Yes. The challenge here is attribution of pathophysiology. In Alabama, which is, I'd like to say, my new favorite state --

(Laughter.)

DR. GORDON: -- half of people there are obese and have metabolic syndrome. So we expect that 50 percent of anyone we pull off the street, whether or not they have neuropathy, are going to

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have metabolic syndrome.

So the attribution of cause in C-SPAN, which is Rick Barron's term -- and actually, the reason I've used it is because we could create a fancy name for a trial called TOPSPIN that had nothing to do with hiding from metabolic syndrome. And in fact, the DSMB-IV forced us to add metabolic syndrome to the trial's name. It's really an amalgam of different risks, so there's the whole voltage-gated sodium channel narrative where there are conflicting data from different groups about the roles of these and if not causing small fiber-predominant C-SPAN, at least driving risk of C-SPAN.

I think the likelihood that we're going to find monogenetic causes in idiopathic neuropathy is relatively low. I mean, there's good data using next-generation panels or whole exome for a neuropathy phenotype and the yield, and in a setting where you expect a high yield is still something like 17 or 18 percent.

But I think it's really the boundary of risk

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versus causality, and I think the relevance of this axis of chaos, which I think is more chaotic than the others, is one that we're living through right now, trying to organize or organizing a trial for this in some sort of coherent way because it's inevitable that there are going to be messy boundaries around this.

Then I question the primacy of pre-diabetes and think either the syndrome or obesity is the way to go if one had to pick.

DR. FREEMAN: To me, I think there may be three issues that I'd like us to flesh out, and Dan's going to do this once I finish. The first is, what are we going to call this? And the second is are we going to -- and whatever we call it is going to depend on the second point -- are we going to say that this is neuropathy associated with, or due to, or in the setting of, or are we going to say that, at this point, we don't know, but these are the criteria were we to do a study where you two submit an NIH grant; this is what I'm going to study; these potential factors of obesity,

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hyperlipidemia, and you break them down.

Then I think it would be good, the point David Herrmann made, to be somewhat restricted, because I think there's no doubt that the extremes, the severe neuropathy, is not part of this picture such as it exists.

Somehow or other -- and I was thinking somewhat similarly to Gordon -- there are 35 million Homer -- Homer Simpson, is he?

DR. SINGLETON: Homer Simpsons, yes.

DR. FREEMAN: -- yes, in the country, yes. And there's a lot of peripheral neuropathy as well.

DR. ZIEGLER: I think it would be very, very premature to call this a metabolic syndrome neuropathy as long as we don't know which components contribute to that kind of neuropathy. So all I can say is that, from the epidemiological standpoint, factors like obesity and dyslipidemia, these are the two factors you're talking about, has there ever been any epidemiological studies showing that, really, in that population base, in those patients who are obese compared to lean patients,

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the prevalence of polyneuropathies is increased? The same for high triglycerides and low HDL, I'm not aware of any appropriate studies.

What I'm aware of is -- and we contributed to this -- that there's an increased prevalence in pre-diabetes of polyneuropathy, except from Peter Dyck's data, which you didn't show, but we have to acknowledge that that group did not find a higher prevalence.

What we see is clearly that especially if you have the combined abnormality, IGT and IFG, the prevalence is as high as in newly detected diabetes or even diabetes, meaning that it looks like the hyperglycemia or even these great swings of hyperglycemia would contribute to the development of neuropathy in people who are prone to this, maybe genetic factors also contributing or whatever.

Has this ever been convincingly shown for dyslipidemia, for hypertension, or for obesity? I think before we call this metabolic syndrome neuropathy, this needs to be done. Which component

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is contributing?

For example, we could say there is an age-induced neuropathy because age is a clear risk factor of polyneuropathy. Why don't we do that? Is there an age neuropathy? Has this been mentioned in our discussions? I'm not aware of that. So as long as I don't know this, these are risk factors associated with polyneuropathy, and that's basically it, unless we have any other convincing data.

But this is interesting, and I will go back to our current database and we will have a look at that, I think, and maybe we will find something. So far, we were mostly interested in the glucose, and it looks like the glucose is important in causing -- of course, this fits to the continuum from pre-diabetes to diabetes, so there is a sound pathophysiological basis for that. I'm not sure whether the pathophysiological basis is really there for the other components. And if you speak about hypertension as an important component of the metabolic syndrome, and now given the lower cutoffs

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now, which have been proposed, many people have, so is there a hypertensive neuropathy? I'm not sure about it. So I think we need some more clear-cut view on the individual components of the metabolic syndrome.

DR. SINGLETON: I kind of liked Roy's statement of neuropathy associated with metabolic syndrome, which is kind of agnostic. It doesn't say we think it's caused by, we think it's associated with. I think that's a fairer statement. And I think it's agnostic with regard to which components are the most powerful.

I totally agree with you, Dan, that we need a good study. Well, we have studies that have had excellent epidemiology on the metabolic syndrome side, but not good phenotyping on the neuropathy side, so someone needs to combine those two pieces.

I think, if we did that, we would find what you've said and what Peter Dyck has said, that if we look carefully, we would discover large fiber neuropathy, asymptomatic large fiber neuropathy in a greater proportion of patients than we expect.

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DR. PELTIER: I think that you do have some epidemiologic data if you look to the DCCT studies. So if you look at factors other than glucose, what pulls out of the DCCT study as far as risk factors for neuropathy? Hypertension, high targeted cholesterol, obesity, smoking obviously, so all those factors --

DR. TESFAYE: Insulin administration.

DR. PELTIER: -- of metabolic syndrome are present in the DCCT study as additional risk factors for neuropathy. So I don't think it's that far to jump to say that those factors are associated in these patients with less hyperglycemia.

DR. SINGLETON: I'm sorry. Vera is next.

DR. BRIL: Thank you. I was just going to say that, even in people without impaired glucose tolerance, even within the normal range of A1c, you can see increasing burden abnormalities on nerve activity and neuropathy within the normal range, which leads me to think that we set the bar for diabetes too high and that the A1c should be even

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

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

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

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

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

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

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

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

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was appropriate to use these criteria for the metabolic syndrome, but we also suggest, if that's what we do suggest, that these features can be alone or in combination and cutoffs for hypolipidemia, for hypotension, for obesity.

So that's the one we're looking at, the setting, and then secondarily, this is the neuropathy. And I think we need to come up with something prescriptive taken from yesterday's talk and what we will discuss this afternoon, what we think is the neuropathy that is typically associated with this, but the variants that exist.

So I wonder if we can just discuss this very briefly -- and I'm going to call, as I did last time; we won't have the panel, but I'll call on panelists at the end -- what disagreement is there with this thesis.

DR. SINGLETON: Rayaz, do you have something?

DR. MALIK: So Roy, I think it is important that we don't try to invent new criteria for cutoffs because I think the message that we want to

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send out to people is that some components of metabolic syndrome, as is recognized by the medical fraternity, is linked. Because if we start creating new, I think that will muddy the waters.

DR. SINGLETON: I agree with that. Yes. Would you go with ATPIII? Would you go with World Health Organization? Do you have a preference?

DR. MALIK: Probably ATPIII, I think, is better because it's more weighted away from the glucose, because I think WHO is very much weighted to the glucose. And I think one of the issues with that is that the original cutoffs were based on retinopathy as opposed to neuropathy, which I think occurs probably earlier. So ATPIII, I think, would be better.

DR. SINGLETON: I am certainly happy with that idea, that we would be more agnostic in the way ATPIII is agnostic about those features.

DR. RUSSELL: The other criteria is the International Diabetes Federation. Does anyone have any strong views for or against that?

(Crosstalk.)

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DR. RUSSELL: Very good.

DR. MALIK: So I guess IDF is more international and takes into account ethnicity as well. So that's the only other thing that we need to be aware of, if you're going to talk across the world, because their cutoffs for waist circumference are different for different ethnicity groups.

DR. POP-BUSUI: [Inaudible – off mic].

DR. MALIK: Are they? Okay. That's fine.

DR. SMITH: Is it necessary to select a criteria? Because I'm just thinking, what happens when the ATPIV comes out? Are we going to have to get back together?

MALE VOICE: Say what we're using for now and then we --

DR. SMITH: Yes, yes, no. I get it. But I'm just throwing out the idea as to how important is it to tie ourselves to one.

DR. SINGLETON: I just worry, if we didn't, then people would immediately say, which one.

DR. POP-BUSUI: But I still think that this

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is going to be also a fluid definition because, as long as we accumulate --

DR. SINGLETON: That's my concern.

DR. POP-BUSUI: -- more evidence, whether one or other of these risk factors may be weighing more towards the risk, then we might change it. But for the moment, we do not have.

DR. FREEMAN: That's why I suggested the possibility of looking at the individual factors, and I proposed cutoffs, because these may differ. I do think we should put a stake in the ground and say this is what we think at this point in time because obviously things are going to change. The hemoglobin A1cs that we just said previously will change. But I think we need to put our stake in the ground, but I think of course we'll change.

DR. POP-BUSUI: Because the risk for complication is not only for neuropathy at much lower level than retinopathy. It's also for cardiovascular disease and we know that, at least at this continuum, starting actually as early as 5 percent A1c.

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DR. HERRMANN: I think you had termed this, but I think it might have to be -- for the disorders we've spoken about, implicit has been, although we haven't listed them, the exclusionary criteria. But for this one in particular, in terms of being granular about defining the metabolic syndrome criteria and the neuropathy phenotype, I think particularly as investigators will be using this for research studies, you may want to list out in more granular detail what the exclusionary criteria are, including things like foot deformities. Just at least think about that, so that you increase the likelihood that what you're dealing with is a metabolic syndrome associated neuropathy.

DR. SINGLETON: I think that's something we can imagine of severity of neuropathy, in which we think it's very unlikely that you have this as the sole cause. I think that's the kind of statement I would make about it.

DR. HERRMANN: Then other laboratory tests, yes.

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DR. BENNETT: In terms of other tests, though, having an interest in genetics, I would just keep genetics out of it because you have exactly the same issue with attribution, and many of the variants that were described as pathogenic are probably risk variants. So I think you're just muddying the water further if you bring genetics into it.

DR. SINGLETON: You're probably right. I bring it up because I think that it plays an important role here, and it's something we should study.

DR. BENNETT: It's a great issue for research.

DR. SINGLETON: Yes.

DR. BENNETT: But I think it's really going to muddy the issue with diagnostic criteria at this stage.

DR. FREEMAN: So what I'd like to do is [inaudible – off mic] -- I think this is far more effective.

DR. SINGLETON: It's a bigger panel.

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DR. FREEMAN: So just [inaudible – off mic].

DR. WRIGHT: Rob, it's an opportunity to include activity as a factor. I feel like this would be a missed opportunity if that's not addressed as well. I think the animal research is really going to provide great evidence that activity, inherent activity, is a big modifier.

DR. SINGLETON: But you'd say, like, in the setting of decreased activity, this is more likely, something like that.

DR. WRIGHT: Prevalence would be high.

DR. SINGLETON: The taxonomy so far isn't really addressing the treatment so much as the diagnostic criterion, so I think that would be very reasonable to say that's a pre-supposing, pre-disposing factor, behavioral factor at the very least.

DR. SMITH: In domain 3, right?

DR. ZOCHODNE: So Rob, this isn't a chair-type question, but did you say you measured insulin levels and had been looking at those as a marker of insulin resistance?

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DR. SINGLETON: No, not really. I mean, in what study? I guess that's the question.

DR. ZOCHODNE: I think it would be pretty interesting.

DR. SINGLETON: We are doing it now -- we have done it in our bariatric surgery cohort, and we've done it in ADAPT. We're doing it in ADAPT. We haven't said we're doing it in TOPSPIN, right?

DR. SMITH: We are.

DR. SINGLETON: We are doing insulin levels?

DR. SMITH: Yes

DR. SINGLETON: Excellent.

DR. SMITH: Yes.

DR. FREEMAN: [Inaudible – off mic].

DR. ZIEGLER: I said it all. I just would add that I would never use the term "metabolic syndrome" in a patient report, so all I would do is to name the individual components and see whether those risk factors are present or not of the diagnoses.

DR. FREEMAN: Good. So now is the time [inaudible – off mic].

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

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

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

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

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series, one from 1952 with Garland and one from Stamboulis in 2005. The co-existence of peroneal nerve palsy, those who had diabetes, in the most recent study was at about 30 percent of patients with peroneal nerve palsy.

So this was a retrospective review, and that's as good as the evidence gets, of 642 patients seen in that lab between 1994 and 1999, and 7 of 23 who had peroneal nerve palsies also had diabetes. So that's pretty weak evidence if you think about it, one lab, retrospective review.

Often, these get better. They're spontaneous. They get better in diabetes or non-diabetes. If they don't get better, you usually send them to surgery for exploration and to look, or you image and you look for different things like cysts and ganglia. The management is pretty straightforward.

I forgot about the decompressive surgery group, the surgeons who are cutting the nerves at the ankles -- I mean cutting the entrapment sites at the ankles. And we should exactly think about

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it a bit, I thought, so I'm throwing it up here.

So what about entrapment of the deep peroneal nerve at the ankle? It can present as pain on the dorsum of the foot and sensory deficits in the web area between toes 1 and 2, so like a mononeuropathy. And there have been observational studies on releasing the peroneal nerve at the ankle as a treatment for diabetic neuropathy.

Of course, they don't just release the peroneal nerve. They release the posterior tibial nerve, and the peroneal nerve, and I think there's another. There's about three nerves on each foot that they release. And the studies are based on Tinel signs sites of potential entrapment, a surgeon tapping on the nerve, getting a Tinel sign. They don't do nerve conductions. And in the studies where they have done this, they operate on one foot and use the contralateral foot as their control.

I put this out because it's being done. There is even a surgeon now in northern Ontario who is doing this. The literature reviews of these

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procedures by the American Academy in 2006 and a more recent review by Tannemaat in 2016 said that there was no definitive proof.

I put it here because, if you're thinking about lower limb peripheral nerve entrapments, we have to be aware of an entire population of physicians who believe this exists and that they can treat painful diabetic neuropathy particularly by surgery. That's what I want to say about the peroneal nerve.

Would anyone like to comment at this point or should I wait until after Roy?

DR. GIBBONS: So I just want to throw in a comment. Thank you for raising this. This is so critical because you're right. We're sort of a little bit of head in the sand saying we know it doesn't really exist as a truth. But I think the question of belief by the physicians is critical because I'm not entirely sure they even believe it. Some of them are evangelical about it.

But this is a cash business. I have seen it multiple times now in airlines on the in-seat

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magazine advertisement now in this, compressive neuropathy surgery. It's a cash business. They do extremely well doing this. And they think maybe their patients get better, but they're happy to do them for them.

DR. HARATI: But do the patients get better?

DR. BRIL: Let me just answer this for a second. In painful diabetic neuropathy studies, we know the placebo response rate is a good 40 percent. So I think if someone presented with isolated pain on the dorsum of their foot and numbness in the web space, perhaps they have an entrapment. Perhaps they would benefit from release. So it's not impossible.

Tarsal tunnel syndrome, in my experience, in non-diabetes patients, is exceedingly rare. I don't know why, but it is exceedingly rare. And the patients I've sent for release haven't had very good outcomes for some reason. But we need to think about this.

DR. GIBBONS: So the local advertisements -- and Roy, you may have seen this

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as well -- in our own newspapers, they advertise as 85 to 95 percent success rate in the newspaper. I have never seen a patient get better ever.

DR. HARATI: Patients report to the surgeons that they are better, but the improvement doesn't last long enough, so when they come and see us, we don't see any improvement.

DR. RUSSELL: Vera, there is a rigorous Cochrane review of this that was sent with the first by Chowdhry [ph], that actually looks at all the research done, including all the papers published by surgeons. And actually, most of that is based on pretty broad sensory testing. So that may form a basis for your decision.

Now, I know the surgeons are trying to create a rebuttal to that Cochrane review, but so far, I haven't seen a meaningful response from them.

DR. BRIL: I wonder if that's the second. Doug?

DR. ZOCHODNE: There is this weird clinical trial that's been completed that they're really

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touting. I don't know if you mentioned this already, but we're going to have to look really carefully at that and see what they did. But they're congratulating themselves on solving the problem of diabetic neuropathy.

DR. BRIL: Any other? Sorry.

DR. HERRMANN: Yes. I think conceptually, there's a difference if you have a mononeuropathy that you believe to be compressive and you do studies on decompressing that as opposed to the Dellon procedure, where they do multiple decompression to treat underlying distal symmetric polyneuropathy.

DR. ZOCHODNE: That's what the trial is on.

DR. BRIL: In their view, that's not polyneuropathy; it's multiple compressions in the foot. So just a different view, way of looking at the same disease.

DR. FREEMAN: Do you think, Vera, that you can come up with firm diagnostic criteria for those patients who we think genuinely have, let's just pick, anterior tarsal tunnel syndrome? And that

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will include both symptoms, clinical exam, and neurophysiological criteria. And I know these exist and the AANEM has those.

DR. BRIL: They exist. No, I do think, though, yes.

DR. FREEMAN: The same thing for peroneal neuropathy -- and do you have those?

DR. BRIL: I didn't bring them with me.

DR. FREEMAN: You didn't bring those, but that would be the aim. And there's no need to reinvent the wheel because I know the AANEM has done that, and in the Preston book, I think it's covered very nicely. But that's what we want.

DR. BRIL: So there would be a role for prospective studies in this, looking forward.

DR. FREEMAN: Absolutely. And that's the goal --

DR. BRIL: There are none.

DR. FREEMAN: -- really to do exactly that, to provide the framework for future studies for these kinds of conditions.

DR. MALIK: So Vera, I had reviewed recently

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a study that was randomized as it can be, but they had matching groups from the Netherlands that showed no benefit. So I'm aware of one.

DR. BRIL: Beautiful, yes. Has it appeared already or reviewed it?

DR. MALIK: I'm not sure. It's about three months ago that I reviewed it.

DR. BRIL: Right. I didn't see it, but maybe it's out.

So the ulnar nerve, we know, is compressed at the retro epicondylar groove and at the aponeurotic arcade that joins the two heads of the flexor carpi ulnaris, or at the arcade of Struthers more proximally, or more distally, where it exits the flexor carpi ulnaris.

We know that repeated trauma at the retro epicondylar groove, or pressure in surgery if the arm's immobilized, or if there's an accessory anconeus muscle, or spontaneous hemorrhage, or gout, or low BMI, losing weight, all pre-disposed to the development of ulnar mononeuropathy. Mondelli wrote in 2005 of a standardized yearly

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

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

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

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

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

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

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

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

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tunnel, as it is at any of our clinics. And 7.7 percent had diabetes.

Then Pourmemari in 2016 did a review, and this was with case control studies, and the risk of CTS in diabetes was increased by 1.97 or 1.67 in case control studies.

DR. SMITH: Is that clinically defined?

DR. BRIL: I'm not sure that it's clinically defined, and I'd have to go back and check. But what is the diagnosis? How do we diagnose it? And this is the same with the ulnar and this. Is it a clinical diagnosis or is it electrophysiology?

Albers in '96 found that 23 percent fulfilled in the DCCT cohort criteria, or in that cohort of diabetes he was studying, for median mononeuropathy independent of diabetes. But he excluded subjects with greater

DR. POP-BUSUI: [Inaudible – off mic].

DR. BRIL: Yeah, it's too early, isn't it?

DR. POP-BUSUI: No, because [inaudible – off mic].

DR. BRIL: Yes. So we had type 2 as well as

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the type 1. Yes. He excluded people with greater than mild symptoms of carpal tunnel or those with absent lower limb or sural or peroneal responses. Mild carpal tunnel symptoms are still carpal tunnel symptoms, so I think that this is a bit of a crowded population.

So I was going a little crazy because I was getting patients referred. Do they have diabetic neuropathy? And you know our standard is upper limb, motor and sensory, lower limb, motor and sensory, for polyneuropathy. Right?

So we did the peroneal and sural, and they're normal or maybe not, and then we'd do the upper limb, and we'd find what would be classical carpal tunnel, increased distal motor latency, slowed sensory conduction velocity, I thought, but they didn't have any carpal tunnel. They don't have any carpal tunnel. But this was so frequent.

So our question was, how many of our patients had clinical carpal tunnel? And the diagnosis was based on these criteria. And you had to have 4 of the 6 criteria to establish it:

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paresthesia in the hands or marked preponderance of sensory symptoms in the hands; nocturnal hand symptoms awakening the patient; symptoms precipitated by activities such as holding a newspaper or driving a ca and relief by handshaking; predilection for the radial digits; weak thenar muscles; or upper limb sensory loss solely within the distribution of the median nerve.

So 4 of those 6 made a diagnosis, a clinical diagnosis of carpal tunnel. And we found that, in our patients, in our referenced healthy population, one patient had it. Fourteen percent of those without diabetic neuropathy defined by lower limb changes and the clinical evaluation had it, and 30 percent of those with established neuropathy had it.

So then we were thinking, can we tell the difference between those who have clinical carpal tunnel and those who don't with nerve conductions? You're going to like this, Gordon. You're going to like this so much.

So we did nerve conductions; median, ulnar,

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sural. And we did all these parameters, distal motor, median latency, distal median sensory latency, distal median motor amplitude, distal median sensory amplitude, distal median sensory conduction velocity, proximal median sensory latency, and so on. And then we also did ulnar, so beside the absolute values, we did ratios. We did distal median latency to distal ulnar motor latency. We did the amplitude, the median to the ulnar. We did median sensory amplitude to the ulnar sensory amplitude; the motors and the sensories for both the motor latency, sensory latencies; the sensory CV for median to ulnar sensory CV; the proximal sensory CV to the distal sensory; and all of this to this, finding focal slowing here; the distal median sensory latency to the sural latency; the median sensory amp to sural amp; et cetera, et cetera, et cetera.

None could distinguish clinical carpal tunnel from those who didn't have carpal tunnel. None were different, except in the one healthy volunteer, they had a --

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DR. FREEMAN: How did you look at the difference or lack thereof? When you say none were different, were these means? Were these distributions? What kind of statistics?

DR. BRIL: They were means. They were pretty much means and standard deviations, I'm pretty sure.

DR. FREEMAN: Is that the best way to look at it?

DR. BRIL: Maybe not. I don't know. We might reanalyze it if you --

DR. FREEMAN: I'm just wondering because I think this is an -- nobody criticized you for the number nerve conduction studies.

(Laughter.)

DR. FREEMAN: I'm surprised. Just you've got 20 there. I would have thought you would have found one just by coincidence.

DR. BRIL: That was in the healthy volunteer, where the median sensory amplitude was half in the ulnar sensory amplitude, but because only one patient had that. What could I tell from

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that?

So basically, we couldn't find something. And you read a paper and say, do this and it'll be more sensitive, do that and it'll be more sensitive. But in this study, nothing was more sensitive. It was just the clinical criteria. So it showed us that the median nerve, too, is sensitive to the state of diabetic neuropathy.

Basically, all of these parameters absolutely worsened with the degree of diabetic neuropathy, from no neuropathy, mild, moderate, severe. All the parameters worsened directly with how severe the underlying diffuse polyneuropathy was. So that median nerve is affected early and worsens in line with the polyneuropathy, but not with clinical carpal tunnel.

So what is carpal tunnel syndrome? It should, I think, be defined clinically. The patients were treated, the ones who had carpal tunnel, but this was a cross-sectional thing. We didn't do a prospective thing where we had diabetes and non-diabetes such as with carpal tunnel, sent

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them to surgery, and brought them back, which we would have to do in order to compare the outcome to treatments in these two groups.

The other thing we didn't do was get a larger population of healthy volunteers with carpal tunnel, non-diabetes patients with carpal tunnel, and making sure they didn't have metabolic syndrome or pre-diabetes and the rest of it. But doing that, I think that was another thing we could have done to see, in the healthy volunteers, if you have more discriminatory power from your electrophysiology, but in the diabetes subjects, you didn't.

DR. POP-BUSUI: Vera, in fact, we did assess cheiroarthropathy in the DCCT edict, and we published this data three years ago. And the way we did it, we assessed cheiro by looking at other adhesive capsulitis, and then also clinical examination for carpal tunnel and ulnar tunnel syndromes. And what we found was that carpal tunnel was by far the most prevalent, and it was prevalent in 30 percent of the cohort with a mean

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duration of about 22 years of type 1 diabetes and a mean age of about 50 to 55 years.

Then the most prevalent complication that this risk for carpal tunnel was actually confirmed clinical neuropathy because at the same time, we also had evaluated the DPN and repeated dose evaluations.

DR. BRIL: It's the same.

DR. POP-BUSUI: Yes.

DR. BRIL: It's the same, 30 percent in those with diabetes. And the risk is the severity of the neuropathy for the electrophysiological findings.

DR. POP-BUSUI: But I think that's maybe something I think we should think about because, clearly, this advanced glycation may be a reason that causes this entrapment, and in the diagnostic criteria, having other clinical manifestations of cheiroarthropathy may be pointing towards a potential entrapment in addition to just symmetrical distal.

DR. BRIL: I was very disappointed that we

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couldn't have any electrophysiology that would point out those who had the clinical syndrome properly in this population.

There you are, Gordon.

DR. SMITH: Yes. We have the same data from type 2. I can't remember. We presented this at the PNS about 10 years ago, that about a third of patients who don't have neuropathy have electrophysiologic evidence of median slowing.

Have you tried skin biopsy, though? That might be a -- or CCM as a way of --

(Laughter.)

DR. BRIL: No. This was done before the days of CCM, Gordon. We've tried ultrasound. And again, this shows different results in different studies, in showing carpal tunnel in those who have diabetes.

DR. TESFAYE: The current approach in my clinic is when patients have the symptomatic carpal tunnel syndrome, I always send them to have median latency done. If it is just mild entrapment, we go for non-surgical interventions such as injections,

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steroids, et cetera. But if there is moderate to severe, they respond very well to surgical treatment.

So I think it has a role, the nerve conduction. Am I right?

DR. BRIL: You see, my study would say that you would see that slowing in someone without any carpal tunnel symptoms just the same, at the same stage of polyneuropathy that your patient is. That's what we found, that we couldn't use it to assess the carpal tunnel, because it assessed more the severity of neuropathy. Now, I know they respond to surgery and we do it.

I have a little more studies, but Dan, you had something?

DR. ZIEGLER: Did you compare both sides? So maybe that could be a clue, to compare the damage on the side of the CTS versus the other side.

DR. BRIL: I'm not so sure, but we certainly compared to other nerves in the region that were not affected or should not have been. Yes.

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DR. ZIEGLER: But you did not do bilateral measurement?

DR. BRIL: We usually do in carpal tunnel, so I can't remember the data, but our standard in the lab is if it's abnormal on one side, we do the other, so I can't really remember.

DR. ZIEGLER: I could imagine that there could be a difference.

DR. BRIL: But we wouldn't have done it in many of these, because we would only do that in a carpal tunnel, whereas we do the standard neuropathy work-up in a patient with polyneuropathy, which is median, motor, and sensory in the upper limb, and peroneal and sural in the lower limb. I could go back and look because --

DR. ZIEGLER: It would be interesting.

DR. BRIL: -- we may still have that. And the other thing, we know the studies are pretty symmetrical from the other study we represented years ago. In Portugal, actually, we presented on symmetry of the nerve conduction studies in diabetes. That's why, in the symmetrical

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neuropathy, we only do the one. But I will go back and look.

DR. RUSSELL: Vera, how about weakness in the ABP muscle or denervation in the ABP? Does that help you at all in your diagnostic criteria?

DR. BRIL: No. I think that would help in -- I can't really answer that. I know the amplitudes were no different. It all represented the severity of the underlying diabetic neuropathy, not the presence of carpal tunnel. Many of these patients didn't have any motor weakness.

DR. TESFAYE: Vera, your center is the Center for Excellence for Neuropathy Research, so a lot of your patients have come to you. Is there a selection bias? Your control group will have sort of a neuropathy element to them, so when you compare with the other group that has carpal tunnel syndrome, maybe there isn't a difference, but actually, if you had a different cohort of diabetic people --

DR. BRIL: Absolutely

DR. TESFAYE: -- maybe there would be a

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

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

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

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

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studies, prospective studies on surgery, follow-up studies, consistent studies, standardized testing, and assessments.

DR. HARATI: How about imaging just to see the structure abnormalities?

DR. BRIL: Sometimes we have done MR neurography, particularly on an ulnar nerve that's not well localized, but not often. It's hard to get. They wait a long time. And it's expensive in our system.

DR. HERRMANN: Clearly, the clinical syndrome should be the driver of the decision making with neuropathy and carpal tunnel.

DR. BRIL: I would think so.

DR. HERRMANN: Not to dismiss electrophysiology entirely, if you had more stringent cutoffs, not the traditional --

DR. BRIL: Had more? Sorry?

DR. HERRMANN: -- stringent cutoffs for abnormality -- in other words, with just diabetic neuropathy alone, is there a range of slowing or latency prolongation if it's with diabetic

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neuropathy alone? And then if you have compression on top of that, so you have a more restrictive cutoff.

DR. BRIL: So you're talking about the distribution the way Roy was. I'd have to go back and look because I don't know. I can't answer that at the moment. But that would be a good thing to look into

DR. FREEMAN: I'm just wondering, and I know you must have looked at that. You went through your 20 studies quickly. But median on the comparison studies, radial digit 1 comparison studies, where you're looking -- so the story of if this is a generalized polyneuropathy, then you're going to see symmetry in nerves of non-compression, whereas if it's compressive neuropathy --

DR. BRIL: But that's the theory --

DR. FREEMAN: It did that.

DR. BRIL: -- and it didn't hold up. We used the sural, yes, and it didn't hold up. And that was the biggest disappointment for us because, okay, the ulnar, we've gone through now and we see

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that there's a lot of ulnar nerve dysfunction, so maybe that could explain that.

DR. FREEMAN: The digit 1 as well?

DR. BRIL: We didn't look at radial, but we looked at sural, and in the past, sural to radial amplitudes.

DR. FREEMAN: Again, not asking you to reinvent your study or repeat it, but radial would be quite important because the ulnar is another potential site of entrapment.

DR. BRIL: But the sural isn't, and that actually reflects the diffuse polyneuropathy more, so we used the sural. Yes?

DR. MALIK: So Vera, is it possible to do a Bril correction factor from your data, i.e., take into account the neuropathy that's already present and somehow work out an adjustment almost for your latencies that you see in the median nerve?

DR. BRIL: Don't know

DR. PELTIER: Basically, a higher threshold to diagnose for --

DR. MALIK: Yes, from the data set.

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DR. BRIL: This is the question about the distributions, the cutoffs, and we have to go back and look at the data. I don't know that right now because I can't -- I know we looked at distributions then, but I don't recall because it was a while ago. I don't recall any such -- I just recall a lot of disappointment because we said, all right, let's compare this, all right, let's compare that, all right, let's compare this.

We went on and on because we thought some things should differ. And the only thing -- in that one healthy person who had carpal tunnel, had a difference in one parameter. Yes?

DR. RUSSELL: So Vera, there may be two factors here, so your clinical carpal tunnel is, I agree with you, clearly you have to go there on symptoms and signs. But you've also got this issue of pre-clinical, which is sort of the median mononeuropathy at the wrist.

So I guess the question is, do you have two criteria, one clinical carpal tunnel, which will really be all the clinical measurements you've

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mentioned, and the second is this concept of the median mononeuropathy at the wrist, or do we just say that's really not important to find that?

DR. BRIL: We were trying to find something that would identify the median mononeuropathy at the wrist if you wanted to, the carpal tunnel. That's the whole purpose of the study, because at that time, I had come through a lot of diabetic neuropathy studies, and they said, if you have carpal tunnel as defined by the distal latency or whatever, you can't get in the study. And I was finding a lot of patients with that, so I was trying to find cutoffs, or parameters, or comparisons that would allow patients, but I couldn't find them.

DR. RUSSELL: So I do accept that, but in a sense, what I'm talking about is sort of pre-clinical, if you could maybe look at it that way. So in other words, these are people who would absolutely have no clinical features, but you would define what median nerve slowing across the wrist may be. I'm just saying, do you consider that

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important in any way or should we just throw all of that out?

DR. BRIL: I'd have to look at the distributions to get cutoffs because we found abnormal results, but they related to severity of the diffuse neuropathy, not to the median mononeuropathy at the wrist. They were part and parcel. So I'll look at the distributions again and see if we have cutoffs that we can find, but not at this point.

Teresa?

DR. JONES: So I'm sorry to go back to the foot with this. I know that's a problem. I get these e-mails from an investigator -- I'm sure we all do -- about how great the surgery is.

Do you think you're going to be able to get a dichotomous criteria for people who would benefit from the surgery or not? Let's say somebody is out there, a person with it, and they can see all the news. They go to their doctor and they really want to know whether it's going to help them or not.

DR. FREEMAN: Before you answer that, can I

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ask another question which is so closely related to that? My concern is how -- on the one hand, there seemed to be a consensus that in the upper extremity, classical ulnar neuropathy symptoms, classical carpal tunnel syndromes, it's acceptable to have surgery in the absence of confirmatory nerve conduction studies.

DR. BRIL: For the carpal tunnel?

DR. FREEMAN: For the carpal tunnel, not for the ulnar.

DR. BRIL: All the outcomes are so different.

DR. FREEMAN: No. And I agree, I agree. Let's just say for the carpal tunnel. For somebody who is sitting in this room from Mars, what's the difference between that and what they're doing in the lakes?

DR. BRIL: So let me just say a couple of comparisons. Carpal tunnel is extremely frequent, 10-time lifetime risk. Tarsal tunnel, which we probably have all seen, is extremely rare, like hen's teeth. Outcome of surgery for carpal tunnel

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is pretty good. I don't know what your outcomes of surgery for tarsal tunnel release have been, but mine have been not great.

The other thing is, carpal tunnel is usually asymmetrical, usually one hand, sometimes both. I haven't seen too many patients who say it started in both hands immediately and it's the same, whereas for diabetic polyneuropathy, it starts in both feet usually the same.

So you might have the argument for unilateral involvement of the foot or highly asymmetrical findings, plus evidence of focal blocks along those nerves, which when we look for them we hardly ever find, but maybe that could help you and direct you. But for a diffuse polyneuropathy, and especially one that has come above the ankle, I just don't see the value of decompression.

DR. JONES: Thanks.

DR. BRIL: I mean, do people here agree with that?

DR. BENNETT: Yes. I completely agree.

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Yes. And I think your rationale is a good one, that carpal tunnel is a well-defined syndrome, localized to one nerve. It's completely different to the idea of a more diffuse neuropathic process in the legs. So I think they're quite distinct.

DR. FREEMAN: Yes. I mean, I'm a little more hard-nosed about it, actually; I'd like to see. But I was not aware of your study, which maybe makes me a little more flexible.

So again, getting back to business, two things --

(Dr. Bril gestures to leave podium.)

DR. FREEMAN: No, not yet.

(Laughter.)

DR. FREEMAN: You can lean, though, if you want to.

DR. BRIL: I'm leaning.

DR. FREEMAN: So two things, one, you make a fairly convincing point that this is not quite as relevant in diabetes, these compression entrapment neuropathies, as one would have thought, and does this topic have a place in what we are doing. And

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I would argue, yes, it does because I think those questions are so important.

So what I'm thinking about when I think about manuscripts and how to do this is that what will be unique about what you spearhead is talking about the criteria and the assessments. And I don't think we're looking at treatments.

We're looking at the taxonomy, the criteria, and the assessments of the diabetic patient, who has a potential compression entrapment neuropathy. And a lot of it may be just as you've said, that despite what we thought, it's actually not so easy to discriminate an entrapment neuropathy in the setting of a generalized polyneuropathy. The principles that I think I at least had in my mind, without knowing the literature as well as you do, don't hold up as well in reality.

So that would be my take on it. I wonder what others think. I would hear maybe the panel, who did we decide would be on this panel? I know Doug was there.

DR. BENNETT: So I'm on the panel, and I

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agree. I think maybe it should be clinically defined, that we should target. I do think it's an important issue to cover. I think one of the challenges is we may not simply be able to just transpose the pre-existing criteria for isolated CTS in ulnar, et cetera, because that's in the context of someone that doesn't have a generalized neuropathy. And we might need to think about some comment on accentuated involvement of a particular nerve relative to others.

So we might need to go back to those criteria and just see, because that is difficult to hear, how we're pulling out more involvement of one nerve in the context of a generalized polyneuropathy. That might be a bit of a challenge when we come down to write the criteria.

DR. BRIL: I think we can alert people to the fact that you can't rely so much on the studies and the current criteria and maybe develop a way to study it further as we go, because I'm convinced there's a way for electrophysiology always, Gordon.

DR. BENNETT: I agree.

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(Laughter.)

DR. BRIL: Rayaz, too.

DR. FREEMAN: Can I ask one other very quick question before we go back to the panel? I mean, every now and again, I get sent articles to review on small fiber type assessments. Now, I know Gordon was joking -- or at least I hope he was -- when he said corneal confocal microscopy. But people have looked at laser Doppler, pseudomotor function.

Did anything emerge? You obviously didn't do that, but is it possible that the small nerve fibers might be affected first and early and could be a more sensitive way of looking at this?

DR. BRIL: Diabetes patients with and without CTS, perhaps. I don't know.

DR. FREEMAN: Comparison of the two sides, the same way one.

DR. BRIL: Yes, maybe. I don't know.

DR. FREEMAN: Maybe, yes.

DR. BRIL: I don't know. Same with ulnar, I have no idea.

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DR. BENNETT: I mean, we did a little bit of work not in the context of diabetes, but just carpal tunnel. And there is a small group of patients where they have typical symptoms of carpal tunnel and normal nerve conduction studies. And when you do a skin biopsy and median enervate the territory, the intraepidermal nerve fiber density is reduced. But I have to say that is really quite a rare occurrence. And I don't think it's going to be replacing a more traditional assessment.

DR. FREEMAN: James?

DR. RUSSELL: I think I've said most of the things I've said. And I guess at this point, really, the main thing you need to decide is are you going to go with pure clinical criteria, and it sounds like, in fact, you've presented a very good argument with that.

Do you actually then say, well, perhaps we can use some confirmatory tests or some exclusionary tests, perhaps in a subnote to your clinical criteria? And that's for further discussion.

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DR. FREEMAN: Gordon and then Amanda?

DR. SMITH: I agree. I mean, I think this is what you said. I think this is really important because it's a comment on a clinical problem. And I think the data you've summarized would come as a surprise to many people in practices. So this is going to be very valuable to the community.

DR. MALIK: Should we also take the opportunity in whatever document that comes out to address the issue with this unnecessary surgery? Because the last one was 2016, so by the time we get anything done, there will be more evidence, I guess, to address it.

DR. BRIL: Well, I'd like to see this paper. I think so. I think you can't talk about entrapments without talking about that, to be honest.

DR. FREEMAN: Obviously, it's not the focus, but it's a byproduct and I think we can.

DR. BRIL: I did want to leave it out.

DR. FREEMAN: Amanda?

DR. PELTIER: I was just going to comment

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that this might be something that could be studied further. When we did our diabetic labor skin biopsy study, we actually found that our healthy control with carpal tunnel increased incidence of segmental demyelination. So there might be a signal there that you could look at.

DR. FREEMAN: Noah, any comment?

DR. KOLB: Yes. I think one other thing that's a little bit different about this type of neuropathy than some of the others we've talked about, like for instance Rob's this morning, we talked about being a little inclusive in terms of our diagnostic criteria and the taxonomy. And I think, for these specific focal neuropathies, it's important that we be fairly tight in our definition just because it's likely going to come down to clinical diagnosis, comparing one nerve distribution of clinical symptoms to another.

So I think we just have to be careful while being pretty specific in terms of defining the criteria.

DR. FREEMAN: The other panel member?

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DR. HARATI: I have nothing to say. I agree with what Dr. Bennett mentioned. Another factor about carpal tunnel is that it is a fairly common condition. I remember years ago a pathologist at Duke decided to look at flexor retinaculum that they will cut during the surgery and blindly did the Congo red stain in all of them, and 2 of the 70 had amyloidosis.

DR. BRUEHL: Can I ask one question here before you go?

DR. BRIL: Yes, last question.

DR. BRUEHL: So back to the bigger picture again with this, so there are pre-existing carpal tunnel syndrome criteria that are accepted.

DR. BRIL: Yes.

DR. BRUEHL: The clinical challenge here in this particular diabetic context would seem to be distinguishing carpal tunnel from more generalized peripheral neuropathy.

DR. BRIL: Not clinically, but on the electrophysiology.

DR. BRUEHL: But that's the two clinical

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

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

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

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

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Chris and Jim's talk as this entity that is subacute and onset, is painful, one motor, one sensory, some overlap, or perhaps combining Jim and Vera's together. Both of them are focal segmental asymmetrical.

But to me, I think it's artificial, but I do want to hear what people think about that.

DR. TESFAYE: I'm in favor of your first option. I think you need a summary paper, which we had with the Toronto.

DR. FREEMAN: I think that very similarly that's the model.

DR. TESFAYE: We had a summary paper, which will be the main paper, because people won't read everything, but then have the groups, as you say, leading on their specific areas in more detail, which would be in the public domain as well, which would be of interest. I think that would be my preferred option.

DR. BRUEHL: So when we did the APT papers, what we did for certain conditions was a single paper devoted to describing all five dimensions for

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a given condition. There are some where multiple conditions were combined.

The challenge in writing papers like that, where you're combining, is the Dimension 1, like how we're going to diagnose this clinically, makes the most sense in context of some background literature that explains what's already out there, and what we know and don't know, and here's how we came up with this.

If you have too many conditions addressed in one paper, it gets large, unwieldy, and hard to follow unless it's broken up like, first, it's all this condition; then it's all this condition, like that. And I like the idea of a summary paper that has Dimension 1 for all the conditions covered. That would be a nice reference for people to use clinically. I would be concerned about being able to provide adequate background for all of those in the same paper unless you already had more detailed papers to refer the reader to.

DR. FREEMAN: Yes. I do think it's doable. I think it's possible.

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Any other comments? Everybody is in agreement? Can I just take it that the speakers have agreed to take the lead, and the panels have agreed to help? I'll take that as a yes.

Then I suppose we should think a little bit about journals and also whether we want to seek endorsement from other societies. Clearly, we have whatever that group is called from Sitges, and we will have the CONCEPPT ACTTION endorsement and all of that which is related.

But do we want to look for support from the American Academy of Neurology, the American Diabetes Association, and any others along the lines that John England, for example, did in his paper? Is that possible? Is it reasonable? Is it important?

DR. BENNETT: What if they said to you, Roy, yes, but we would like to now input some of our members to contribute? That might be their response. What would you say? That's fine?

DR. FREEMAN: That's against the rules.

(Laughter.)

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DR. BRIL: Roy, John England -- I was on one of those practice parameters. Those are actually sponsored by --

DR. FREEMAN: Sponsored by, yes.

DR. BRIL: -- and they're set up by their quality committees.

DR. FREEMAN: I understand it was set by -- yes.

DR. BRIL: I mean, they pick the lead author, and then they have leads, and you do everything with them.

DR. SMITH: So there is a way of doing it at the AAN, and the person who can tell you most about it is Brian because he sits on -- actually the committee is JEDI, I think, because it's an affirmation. So there's no way this is going to be an AAN practice parameter. But we review all the time other guidelines such as this from other organizations that is reviewed by the subcommittee and rolls all the way up to the board.

I don't know whether it would fare well, but Brian can explain the process and tell you whether

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

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

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

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

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DR. TESFAYE: Exactly to that point. We wanted to push everything to Diabetes Care, but what they came back and said to us is, look, we're interested in the summary paper. So we went to diabetes metabolism research reviews. We published these other five papers.

DR. FREEMAN: Yes. But I do think that some of these papers would be highly impactful in probably some major journals, one in top tier and the rest in -- I wouldn't call them obscure, but lower level journals.

So what do you think, Vera?

DR. BRIL: I was agreeing with Solomon. I think the summary paper to Diabetes Care would be great, but I think the sub-papers are a little more than perhaps they may want to read in Diabetes Care. And I would agree they should be directed into neurology literature.

I'm wondering, Gordon, if the AAN did sponsor it, would they then be more likely to publish in Neurology? Because I do think that they should be impactful, but something like Neurology

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may be where we want to get.

DR. SMITH: I think that they're not going to sponsor this. They might affirm it.

DR. BRIL: I mean affirmation.

DR. SMITH: I'm doubtful that would have an impact, but we could talk to Bob and ask him, I think. I like the idea of co-publishing the main paper in the diabetes and neurology literature. And I suspect there might be enthusiasm on Bob's part and maybe even for some of the other component papers, particularly things like the TIND and DLRPN papers.

DR. FREEMAN: David, then Jen?

DR. HERRMANN: Certainly, for the neurology practice guidelines and practice parameters, the level of evidence and the formula for which you arrive at it is -- because we were involved in the neuropathy sort of testing one -- is very, very restrictive. And I think the process will be vigorous, particularly if you have some validation in some of the data sets, but it might be hard to fit the process that you're following here into

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that model.

But they may accept it in some sort of a review as a review of some sort, as outside of the guideline type format.

DR. SMITH: This would not go in as a guideline because it's not a guideline. So the whole affirmation process through the practice committee and the academy is really separate from the publication issue and the general neurology.

DR. HERRMANN: So this could be as reviews, really.

DR. SMITH: I mean, they're just disconnected. I don't think the affirmation, which may be difficult because of the reasons you bring up, would really be connected to the publication.

DR. FREEMAN: Somewhat along the lines -- and Jen, you're going to speak now -- of the manuscript that was published on the chemotherapy peripheral neuropathy.

DR. GEWANDTER: Yes. I was just going to say, last time for that manuscript, Dr. Roche just asked me to send it to him. And obviously, he has

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to recuse himself because I'm on the paper. But he just told me yes or no, so once it's drafted, we could do the same.

But also, I will say that paper was definitely a systematic review based on data, so I'm not sure it's the same. But then I was going to say also that the way we did APT was as a supplement that everything was together. So even if the main paper was published in Neurology, I think it would be a good idea to try to put the rest together and find a journal that was interested in doing that.

DR. FREEMAN: Teresa?

DR. JONES: I think Amanda's actually been really -- you go first.

DR. PELTIER: No. I was just going to make two points. One is, I do think, taking Steven's point, that the more that we can validate these by running them through our databases, I think better because, otherwise, I think you just suffer from being the 17th set of diabetic neuropathy criteria, number one.

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Then number two, also, the better you do this, the more you can open up to other things. Like, for example, we completely left out diabetic autonomic neuropathy, even though we circled around it. And that would to me be the next item on the agenda list as far as the next ones to address.

DR. FREEMAN: No, agree. I just thought it was too challenging to do and do a session, but I agree.

DR. PELTIER: I agree. You have to limit it somewhere.

DR. FREEMAN: So Teresa, are you ready?

DR. JONES: Yes, so two things. One, we have an R21 program for secondary data analysis. R21s are hard to get, but if it came in as a group, it might be better well received and you could pay for a biostatistician and all of that.

The other thing when you're writing these papers, it's really helpful for me with initiatives if you have some specific high-priority research needs or opportunities, because then we can refer to it. But again, high priority and specific would

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be good. Thank you.

DR. FREEMAN: Great. That's really very helpful, and we should definitely consider that. Rayaz?

DR. MALIK: So I guess is it going to be a narrative review a systematic review, or a meta-analysis?

DR. FREEMAN: I think it's going to be a narrative review, expert consensus. I think it's of that ilk. It's not meta-analysis, although there should be some meta-analyses that go into the decision such as it is.

DR. MALIK: I think if you put it in as a systematic review, there is a process, and the journals are more receptive to that because they then see that it might be treatment-induced neuropathy, but you've got 4 papers or 10 papers, and this is what it shows.

DR. FREEMAN: Yes. I think, where possible, search strategies should be published, and I think we can do our best to make this a systematic review. I'm not sure it's going to be that easy.

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Vera, do you think your topic, which I think probably, is best suited to a systematic review?

DR. BRIL: No, not systematic so much, but I'm wondering, Rodica's group, our group, some of the others, whether we can put those together. I'm not sure that this is where that is. But doing the extra data analysis, I think, is important, looking at the data set, trying to find cutoffs. To get fresh data to put in might be interesting, so that's what I was thinking.

Rodica, what do you think?

DR. FREEMAN: We can talk about research agenda. My concern is the balance between having a work product and getting it out and not losing. Individual enthusiasm is easy to maintain. Group enthusiasm is substantially harder, and my concern is that this will get put on everybody's back burner. So I'm leaning towards --

DR. BRIL: Descriptive.

DR. FREEMAN: -- making do with what we have, with as much data analysis we can do quickly, and then research agenda.

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DR. POP-BUSUI: I also think that we should strive for getting something which is unique and we have chance to do so. So why not do it in the right way?

DR. BRIL: Rodica, I agree, but as I'm sitting here, what I've been thinking about is, where are those data files, what computer are they sitting on, what shape are they in, where are they stored? I'm thinking practical, retrieving it, retrieving all that, which maybe it should have it all classified and beautifully laid out, but getting exactly that data may be feasible.

DR. FREEMAN: I do think that what we're doing is unique. I think that we can argue as to how different it is, but I think it's different. And I think the more original data we can put into it, the better, but we'll talk after lunch about a research agenda. And I think that's when all of these can emerge. Doug?

DR. ZOCHODNE: Sorry. I may have missed it at the beginning of your talk. Did we cover intercostal neuropathies, meralgia paresthetica, or

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

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

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

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

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

A F T E R N O O N S E S S I O N
(1:04 p.m.)
Final Discussion
DR. FREEMAN: Two items on the agenda this afternoon or maybe three.
Do you have any diabetic neuropathy consortium business?
DR. GIBBONS: No. I'll be sending around a summary of all the things we talked about, and I'll be roping everybody into work. Thank you.
DR. PELTIER: We come up with a name yet?
DR. GIBBONS: No. We're waiting [inaudible – off mic].
DR. FREEMAN: Two pieces of the agenda, one is research agenda, and that's a big picture and small picture. Based on this meeting, I wrote down a couple of things that we thought would be good, and I just want people to throw out whatever else.
One idea was empiric validation, and that was using perhaps EDIC, DCCT, other databases, and I would hope that Rodica would help us with that.
Is there anybody else who has any other

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

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

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DR. ZIEGLER: The GDS will be difficult, I think, several hurdles. I don't know. I cannot promise whether that works, but I could have a look, whatever. If there is a need, I could do my own analyses, so with the CORA data regarding the metabolic syndrome.

DR. FREEMAN: Yes, exactly. And that's also on the list, but that would be different.

DR. BRIL: So Roy, I would have to get ethics approval before I could share data with anybody. I mean, it would be a global ethics approval for a database, but I couldn't just share it or pool it without going through my ethics committee.

DR. FREEMAN: Right, no. Of course, I understand. So I think there are two possibilities. The one possibility is that this be done at an individual level, as I guess Dan is suggesting, that he could look at his database and give us data to support whatever assertions we will make. And the other is that this be done as a group effort with people volunteering and helping.

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I'm sure we have enough work to do. Either one is fine.

Yes?

DR. MALIK: So there is NIH-funded DP3 multiple consortia data. It's about five centers where we have got very detailed phenotyping in diabetic patients, probably a cohort of around a thousand-plus patients and then follow-up data as well up to 7 to 8 years with detailed phenotyping.

Bruce Perkins, myself, and Nathan Efrom were part of the consortium, and Vera, so obviously I don't know if there are aspects that you want to interrogate, that you think are important, and then I'm sure we can consider that.

DR. BRIL: But it's the same thing. Even if I look at my own database to share outside, and if I'm doing stuff that I didn't originally have ethics approval for, I have to go get it; and I'm sure for the consortium as well.

DR. MALIK: But it's fine. You can put it in ethics --

DR. BRIL: But that's not an issue. You can

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do it, but it'll take time.

DR. FREEMAN: It's a hurdle. So the question is next steps. Okay? So we've got a couple of databases. We've got a couple of people who have either direct or partial ownership of the databases. Give me a message as to what direction or a road map as to how we can take the next step. I think it's kind of important.

It seems to me that probably we're going to be doing this based on -- and I like the idea of the Delphi method, but it would be, I think, important for us to actually have some empiric data.

DR. BRIL: If it's reanalysis of what already exists and what we did, we could just go ahead and do it. If we're going to add to our database from outside, it wouldn't matter to us. It wouldn't matter to whoever's giving it to us. But if we're just taking the existing database and looking at the distributions --

DR. FREEMAN: So that's, I think, what we're suggesting.

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DR. BRIL: -- then that's fine. We could do that.

DR. BRUEHL: That's what I was thinking, instead of trying to go out of your way to get more data at this point, is just take whatever happens to be archived, the best data sets we've got.

What I might think is, it looks like we've already got at least draft versions of most of the sets of criteria and have everybody think about, if we had a giant database, like Rayaz was just saying about diabetics with all kinds of phenotyping data, if we were to do a cluster analysis, for example, and have that divvy up the patients based on X, Y, and Z characteristics, which you have to specify, what would you expect to see if you think that the criteria are valid?

How would you expect it to break out? Because I think the strongest thing we can address with existing data is do real patients break out into categorizations that look more or less like the categories we've created.

But it's garbage in, garbage out. So we

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have to think about what do you want to go into the analysis. And looking at the list of features that we had yesterday in our group, we had a list of, I don't know, maybe eight or so features for the sensory changes, pain-related characteristics. With a large data set, you could include 15 or more variables and have it classified based on that.

DR. FREEMAN: So are you suggesting a hypothesis-driven analysis or an agnostic, hierarchical kind of analysis?

DR. BRUEHL: You could do both. I mean, the first thing I would say is, it doesn't take any more time to do it. You just include a massive set of variables you're interested in, and with enough patients, you can just do a cluster analysis on the whole thing, see how many categorizations there are, look at the patterns of signs, and symptoms, and test results within each of those, and just have everybody look at that and say, what would you call this; does this remind you of anything, some diagnostic entity.

Then the flip side is, take our individual

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criteria, include only those features we've included in our criteria, and see, if we look -- ideally it would be a group that you think would meet the criteria and another group that clearly doesn't, cluster based on the features and diagnosis you're interested in and see if it pops out as two different categories. That's more hypothesis driven.

DR. BENNETT: Anything I would say about the completely non-hypothesis driven is, all the databases all have different measures, different levels of granularity. So it might be easier actually to get the criteria first and then see how those map on because, actually, when we have that, we'll at least know what databases have the right information in them.

DR. BRUEHL: Correct, yes.

DR. BENNETT: Otherwise, we could all spend a lot of work on different databases, then find they don't map to each other all the criteria in an easy way at all.

DR. SMITH: Yes. I was going to make that

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same point, but I wonder if [inaudible – off mic]. Sorry.

So let's say that Vera's database has the right categories of symptom and sign descriptors to allow this sort of agnostic approach. One could do the agnostic approach with one database, look at the data, then do a Delphi sort of model based on that information, derive the criteria, and then validate them in a different database that also has similar granularity. And if that's plausible or attractive, then the first step would be just to know what databases are available, what the look like, and which might be useful for this.

DR. BRUEHL: I think it would be important, just based on what we've done so far, that whichever database we pick has the data elements that are in what we're considering. If there's one that's missing key features, that makes it difficult to do that validation.

DR. FREEMAN: That's not going to be key features, but I think the degree of granularity may differ among the databases.

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What I think I'd like to ask is, is there anybody who would like to spearhead that initiative by communicating with everybody? To me, it seems a great project for somebody.

DR. TESFAYE: Rodica maybe.

(Laughter.)

DR. BRUEHL: I can tell you from conversations outside the meeting she's already volunteered to do this.

DR. FREEMAN: We're talking about not only her database, but speaking to David, speaking to Vera. It's funny. I was going to have the exact same approach. I said, it seems a good approach for somebody young. And I was going to volunteer Noah to do it, but Rodica, if she's enthusiastic, that's great. Good. And who shall I say nominated her?

(Laughter.)

DR. BRUEHL: All of us. I will, and I will offer to help guide her on this.

DR. FREEMAN: Look, I think this is really, really important.

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DR. BENNETT: I do think it's much easier once we've got some idea of what the core features might be.

DR. FREEMAN: That's to come, so let me keep moving. While we're on this, then, because this seemed rather critical, Dan's database, it looked like there's the possibility of you actually enthusiastically looking at the features of the metabolic syndrome in the same fashion that you looked at impaired glucose tolerance.

I think that would really put this entity on the map or take it off the map. Do you trust Dan to do this by the way?

DR. SINGLETON: I think I'd like to talk to Dan about the phenotyping of neuropathy that you have, because as I said before, I think that's where other databases are weak.

DR. FREEMAN: Are there other databases other than --

DR. SINGLETON: Neurologists have collections of patients with impaired glucose tolerance and neuropathy, and I think that there is

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some value in aggregating those patients. Teresa Jones was suggesting to me that she would be very interested in more outcome data about those people. What happens to them? What's their fate over time? Do they go on to develop diabetes? If they don't, does their neuropathy get worse despite not going on to getting diabetes?

I think that we in this room have large collections of well-phenotyped pre-diabetic neuropathy patients, and seeing how their natural history evolves would help to answer this question as well.

DR. ZIEGLER: Actually, what we have now is 7-year prospective data, so the stuff you presented, we published. We now have the follow-ups. But of course, the neuropathy assessment is screwed [indiscernible] using the MNSI, although in the follow-up, we also have nerve conduction, but point of care with a DPN check, but there's nerve conduction data there.

Of course, we could model the role of the metabolic syndrome in the incidence progression of

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neuropathy during that 7-year prospective follow-up, which is, I think, unique. And that's population based. The only thing is, it's an elderly population, so there will be a number of deaths, of course. But that gives you also some room for mortality analyses.

DR. SINGLETON: Is Dan's database unique? Do we have other ones that we can roll together with?

DR. FREEMAN: Any other community-based anything, EURODIAB, NEURODIAB?

DR. TESFAYE: We've got access to EURODIAB data, but it depends, as David mentioned. We need to have a hypothesis as well. There's two ways of looking at these. One is to have a hypothesis-driven mining of data and being careful to make sure that there aren't major confounders, selection bias. All these needs to be done very carefully.

For instance, if you wanted to look at the severity of pain and the severity of neuropathy, you can mine any data. You're looking at two associations. Even if there is selection bias, it

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doesn't matter. You're looking at pain severity.

So you can do that, so as long as there is a good hypothesis, the data is there in London.

DR. FREEMAN: I think we're talking about the pre-diabetic, metabolic syndrome features.

DR. TESFAYE: The type 1 patients.

DR. FREEMAN: Yes.

DR. GIBBONS: Just one thing as well -- I mean, obviously we've had changing guidelines and requirements in terms of treatment care. So one of the things we'd seen in our own database was that the introduction of things like ACE inhibitors, angiotensin receptor blockers, have all of that modification of the other risk factors, does in fact modify the risk factors. So particularly statin use and everything else, when those are introduced, that does add variables that we have to think about.

DR. ZIEGLER: So we can adjust for whatever you want. So this information of course we have in CORA.

DR. SINGLETON: Maybe, Dan, you and I could

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just think about the questions we want to ask about this.

DR. ZIEGLER: We can also model the early course of neuropathy. Of course, then, if it's a GDS study, based on whatever you want, nerve conduction, thermal thresholds, vibration, QSD, it's all there. Some patients also have skin biopsy and CCM. And for those, we now have some 200 to 300 people from within the first year from diagnosis over 5 years, prospectively.

That's for type 1, type 2, so we had two groups and, for the type 2, you can model the metabolic syndrome and the questions of interest.

DR. SINGLETON: Just to be clear, are they patients with diabetes and metabolic syndrome?

DR. ZIEGLER: They're all diabetic, so those GDS-driven diabetes studies are all diabetics. So the starting point is within the first year after diagnosis, and then the first five years. So that's early neuropathy, extremely well phenotyped. By the way, they all have the glucose claims, so we have insulin sensitivity, which by the way does not

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correlate with the neuropathy. I would have published that, but it correlates with autonomic neuropathy.

So that's one part. On the other part, the CORA is -- this is not population based. So there is some kind of selection there. And CORA is population based, and most of these people actually have normal glucose tolerance as it is distributed in the population. It is population based. All have the OGGT done at baseline and after seven years.

DR. SINGLETON: It seems like the most useful would be to focus on study participants before their diagnosis of diabetes. Look for those who do or do not have other features of metabolic syndrome by ATPIII criteria.

DR. ZIEGLER: Yes. Actually, what we have of course is incident diabetes there, so the translation from pre-diabetes to diabetes. And you can see why the metabolic syndrome was a predictor of that. I'm not sure whether the groups are large enough. That needs to be seen by the statistician.

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So the group is something like 700 in total, and I guess at least one-third has died of course within seven years.

DR. FREEMAN: That's interesting. I'd be particularly interested in looking at the incidence of retinopathy and microalbuminuria. And often, when as a neurologist I talk about this entity, whatever it is, I say, what about nephropathy, what about retinopathy, why neuropathy? And I'm sure you guys may have had to answer that question as well. And I've heard Eva say, oh, it does occur, but I'm not so sure the diabetologists buy that.

DR. ZIEGLER: You mean pre-diabetes and microvascular? There's controversy there. It's not generally accepted that this really exists.

DR. FREEMAN: Yes, no, I understand. And that's an argument that is often given to counter the neuropathy story.

So the next point was, somebody raised the possibly of a vignette approach to Chris and Jim's data. I think it was Gordon who thought it was a good idea.

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Do you want to elaborate? What should Chris do? What should Jim do?

DR. SMITH: I think I was more interested in the idea of using this agnostic approach with Chris's data because you have these categories fairly well worked out and in four different groups. I'm trying to remember my comment about the vignette, and I think that was for Jim's data.

DR. FREEMAN: It was.

DR. SMITH: Yes, because I think we all think we know what it looks like.

DR. FREEMAN: Yes, no. And I think it was prompted by, I don't know, isolated peroneal neuropathies and things that we might think were something else and whether there's a gray zone on the edge in what people thought of that.

I think it would be interesting. I don't know if it's that critical. I think the database mining and the cluster analysis would be rather interesting with Chris's database as well, which it seems like there is a lot of data there, and that's something that perhaps Chris needn't put on

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

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

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

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

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DR. FREEMAN: Yes. So I think it does provide at least some sense that this was done in a, if not evidence base that was a reasonable distillation of what experts feel --

DR. BENNETT: The only thing I would say, Roy, is that the general thing would be to do the survey before the meeting, put everyone in a room, discuss, and then repeat. I don't know; it would be a very big telecom. But you'd need some kind of discussion after the initial survey; otherwise, wisdom doesn't have a chance.

DR. BRUEHL: Can I suggest an alternative here? we've biased ourselves for doing a Delphi method within the group here, but we now know what the lay of the land is, all the things that we'd be interested in looking at. Is it possible to set this up and distribute to some mailing list of diabetic researchers that weren't involved in this or neurologists that weren't involved in this a little more broadly?

DR. FREEMAN: That's an interesting idea. What do people think? Is it possible to do? Or we

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could just call it a modified Delphi approach. We're allowed to do that. But you're right. Do you think we could find 20 neurologists, diabetologists with an interest? It might be interesting to do that as well.

Anything else that emerged that others think would be worthwhile doing? I've got one or two things on my agenda, but they more relate to future activities. Any other research projects that came to mind as a consequence of this?

(No response.)

DR. FREEMAN: So I think what I'd like to do is just quickly say my view, as I said earlier, is that we do need to deconstruct everything that we've done so far, and begin again, and to think about standardization and things.

As I was discussing with James, I mentioned about my first ever assay sensitivity. We really don't know how sensitive our measures are to change to talk about placebo response, to talk about the various instruments and outcomes. All of those things, I think we need to take a long hard look at

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what we have. I know that some have done this more than others, but I think, to me, that's part of the research agenda. And I think that's something to think about. I don't know.

James, I know that you've thought about this a lot. Vera, you've thought about this a lot. Do you want to maybe just give a little discussion on that and maybe provide a framework as to where we could go next?

DR. RUSSELL: We had a careful discussion about this, and I said that I think we really need to separate what we're doing here at this meeting, which is coming up with predominantly clinical criteria, from how we're going to look at endpoints. One of the problems -- and I've looked at the various clinical scales that are being used and other measures that are being used or developed by many people, some by ourselves.

The one problem with the clinical measures is that there's a large degree of variance, and that really affects your prior analysis. So when you're looking to do a diabetic neuropathy study,

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the problem is you're always looking at the amount of funding, and therefore the amount of available patients you'll have. And unfortunately, that amount of variance that you have in many of these clinical scales -- and this is true also for outcome measures -- really is your enemy.

So we have to approach this. So you can either say we need something which has a lower variance, and therefore we would have to require much fewer patients as an outcome measure, or we can say perhaps we should go back and we should try to refine the clinical scales and come up with clinical scales that have lower variance and therefore would require a much smaller number of subjects in the ultimate study.

Now, the other thing is that many of us, when we do this, we use our own data sets, and many of those data sets have been very carefully collected. So in other words, you have someone who really is trying to be as careful as they can and reproducible as they can. If you were to use those clinical scales with centers where people are

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perhaps going to be less rigorous about applying them, you have an even bigger problem.

So all of these things have to be taken into account and I believe you really have to separate out the clinical measures as definitions of neuropathy versus using them in clinical trials. And I think, at this point, we have a real problem with that, and perhaps we should think how can we make those clinical measures a lot more refined, a lot more reproducible, and therefore have a much lower variance.

DR. FREEMAN: Vera?

DR. BRIL: I really agree with what James just said and with what you've been outlining in the meeting. I'm not sure I have much to add. You've covered an awful lot.

I would say we are defining. I mean, it's taxonomy for the definitions of these different entities. Some of the definitions include more than clinical items. I mean, we have the clinical definitions, the confirmations, so I think it's a bit more than that. But as a first step, I think

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we've made a lot of progress to a lot of these.

DR. FREEMAN: I want to view this sequentially, that if we look at the clinical trial, what we've attempted to do in these past two days is to look at inclusion and exclusion criteria. I think what we didn't do and didn't do well enough -- and this may be, to me, one of the next items on the agenda, and I have a suggestion -- is standardization, because I think standardization comes through the next step, the clinical trial itself and the outcomes, the instruments. And I think standardization is really important as well as reducing variability, which I think may be part of the same process.

But I think we need to discuss a little how to deal with standardization when we talk in just a moment. But I think let's think about that, and that would be hopefully the next meeting or the next item on the agenda.

So I want to now begin to, in the time that's remaining -- does anybody have a hard stop at 2:00?

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(No response.)

DR. FREEMAN: Yes, okay, so enough. So this is our aim. This is what we want. And when I speak about inclusion criteria/exclusion criteria, this was the aim of the meeting, I think beautifully quoted.

Next slide. This is the kind of thing we want to come up with. We haven't quite done it. The formatting looks very similar to our formatting, but this is where we want to go.

Can we see the next set of slides? And that'll be the PowerPoint one. So I don't know if you remember from yesterday.

DR. BRIL: Could you go back to that?

DR. FREEMAN: Which one?

DR. BRIL: The one you just had up.

DR. FREEMAN: The migraine one, yes.

DR. BRIL: How was TIA excluded? I'm curious.

DR. BRUEHL: [Inaudible – off mic] -- it's like, whatever you would use clinically to diagnose TIA, if they need that [inaudible – off mic].

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DR. BRIL: So clinically, but it didn't include imaging or vascular studies?

DR. BRUEHL: No. That's actually preferable for rule-outs like that since in many cases, it can be really broad; so leave it just kind of generic and say if they have this condition or other conditions, you don't get the diagnosis, and not really go into how you determine that.

DR. BRIL: So in other words, you're very specific about the elements of migraine, but how you exclude other things is very generic.

DR. BRUEHL: Very generic.

DR. FREEMAN: It's an interesting point with regard to the question that David raised this morning about the neuropathy of the Ziegler-Singleton syndrome.

(Laughter.)

DR. FREEMAN: What do you need to exclude? Do you specify as they didn't do over here or do you say B12, SBP, IP?

DR. BRIL: So when we talk confirmatory tests, do you have to list them then? Because I'm

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just curious. This is all about the clinical definition and that, and you're not being very specific. So the question is -- and this is to what we're doing here now. How specific do we have to be about confirmatory tests?

DR. BRUEHL: This is just my opinion. If having looked at all this literature, you're convinced that one test is the gold standard and the others aren't as good, it might be worth saying that to use that test. Otherwise, you could just certainly say confirmed by testing and you could just say EG in parentheses and list a couple without saying what exactly a person could do, which makes the job much easier in creating the criteria, because then you don't have to assess so much exactly about what readings on this test would mean this.

DR. FREEMAN: Let's go to the next PowerPoint. So this was the group and the small group, which was Eva and Gordon. And I just wanted to go through this and I have a couple of questions. So my red, a possible neuropathy

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symptoms or signs, one or more symptoms or signs, and the first discussion is, for possible, one set of symptoms okay and one sign okay for possible neuropathy?

I'm assuming that for possible sensitivities is what will be our goal, so it might be reasonable, but I want to hear people's thoughts. Pain, I thought we could actually go back to the Delphi manuscript that Dave and I were involved in because it actually addresses that question directly. And we could then make some kind of approach to that. And I think we came up with a menu even of that.

DR. BRUEHL: I'm sorry. Can you clarify what you're saying? Because I sat in the group that did this, and literally, if we were to use something like this, it would mean that anybody reporting pain would be considered possible neuropathy. Now, that's true in the strictest sense. It's also ridiculously broad.

Would you narrow the pain to a particular type of pain?

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DR. BRIL: Symptoms in a bilateral, symmetrical link-dependent fashion in the lower limbs. That is the first sentence. So it's not pain --

DR. BRUEHL: So it's in the context of this having pain. Gotcha.

DR. FREEMAN: I'm assuming that we're all on the same page, which we somewhat are, and we're saying neuropathic pain and these are the features of neuropathic pain.

Any comments on that? I had some questions about negative symptoms, numbness, dead, how to quite do that, how to refine that. I thought some clarification was necessary; could do it, but I wanted to -- yes?

DR. HERRMANN: I have a little topic from your questions. It says one or more symptoms or signs. Under that signs being multiple, you could have three signs. You could have loss of pinprick, vibration and that might take you out of the possibles.

DR. SMITH: It should be one symptom or

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sign.

DR. BRUEHL: Should be one symptom.

DR. HERRMANN: One symptom or one sign.

DR. SMITH: Actually one plus.

DR. BRUEHL: No. It is absolutely one plus.

DR. BRIL: Originally, we had done one symptom or one sign.

DR. FREEMAN: One sign, that's what I thought.

DR. BRIL: But then yesterday, after the discussion in the group, it came to this because everybody was talking about plantar fasciitis. There's nothing at all specific about this. This is sensitive.

DR. SMITH: Yes, no. I think this was a typographical error on the slide.

(Crosstalk.)

DR. SMITH: Yes. So it's supposed to be one symptom or sign.

DR. FREEMAN: Yes. So who's writing notes? Somebody, one of your group, please write notes as to how to change this. And we'll send it round to

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you again.
Does anybody have good wording for negative symptoms?
MALE VOICE: It's numbness or dead feeling. And I mean, we have nothing.
DR. GIBBONS: Absence of detectible sensation.
DR. FREEMAN: That's a sign.
(Crosstalk.)
DR. GIBBONS: They report that they can't feel their feet on the floor.
DR. ZIEGLER: Why don't you simply replace the wording positive neuropathic symptoms and don't do that differentiation? I mean, what is it good for?
DR. BRIL: I agree. I always thought we should take out the positive and negative.
MALE VOICE: I think it's confusing.
DR. FREEMAN: Okay, but let's have the negative. How would you put the negative in? What's that?
MALE VOICE: Make another symptom that you

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notice --
DR. ZIEGLER: No, just neuropathic symptoms and you have three symptoms there. That's it.
DR. FREEMAN: So you're saying pain, numbness.
DR. ZIEGLER: It's all symptoms. Whether it's positive or negative, who cares?
DR. FREEMAN: So we're not categorizing them, but we do have to have the absent symptoms. You've got pain.
DR. ZIEGLER: That's the signs. That's the signs.
DR. FREEMAN: No, no, no. Patients will complain of something.
(Crosstalk.)
MALE VOICE: In terms of numbness and dead feeling.
DR. SMITH: So I thought we said that there were going to be non-painful paresthesias, which could encapsulate these painful paresthesias or symptoms of sensory loss was the other, as opposed to that.

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

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

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can make sure their feet are warm and use a cool tuning fork. We've done this forever. I don't think we should eliminate it.

DR. FREEMAN: You don't want to eliminate it.

DR. BRIL: No.

DR. GIBBONS: I think the EMG labs are very good at the warming. I think the clinical situations are not, and I think there is a difference.

(Crosstalk.)

DR. BRIL: These are going to be for research. Right?

DR. FREEMAN: Exactly, with rigorous attention to ambient temperature.

DR. BRIL: Yes.

DR. FREEMAN: We'll take a look and see what's out there.

DR. PELTIER: Are we going to be putting a caveat in for age?

DR. FREEMAN: We certainly can.

DR. PELTIER: I mean, if patients are over

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the age of 75, maybe require two signs just because if you have absent ankle jerks, then you're done. Then you're just saying everybody has ankle jerks over 75.

DR. FREEMAN: The ankle jerk applicability with age. You okay with that, Gordon?

DR. SMITH: With two signs, maybe. I think all of these change with age to some extent, so I guess the question is whether you want to be definitive about what those cutoffs are or just include a qualifier.

DR. FREEMAN: Yes. I mean, in the NIS-LL plus X, they were quite clear. Over 75, ankle reflexes don't count or something like that, that kind of thing. So think we're moving along.

Here, one symptom and one sign or more than one symptom or more than one sign. I think we resolved that with the first question, are we happy with this over here?

So that is the probable, and here we are edging to greater specificity and less sensitivity, one symptom and one sign, or more than one symptom,

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or more than one sign.

DR. SMITH: So I think my recollection was that we agreed that there had to be more than one sign. If that's the case, it's really symptomatic or asymptomatic for probable neuropathy based on two signs.

DR. BRUEHL: So I'm sorry. So are you saying one symptom and one sign or multiple signs?

DR. SMITH: No. I thought two or more signs was the definition of probable and that we would sub-categorize this as symptomatic or symptomatic based on the presence of a single, one or more neuropathy signs or symptoms rather.

DR. FREEMAN: So we've gone here from a symptom-weighted assessment to moving away from symptoms to signs. And it can be asymptomatic or symptomatic. It fits quite nicely with James's approach.

DR. BENNETT: I'm really worried about small fiber neuropathy with that, if we go for that.

DR. BRIL: I was going to say you could easily envision somebody with pain and loss of pin,

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that most people would say have a probable chance of having a small fiber neuropathy.

DR. SMITH: Right. So keep in mind that we have the small fiber neuropathy criteria that the other group derived, and that was going to be an exception to this.

DR. FREEMAN: But that's a problem because you do want these to stand alone. Just say Dave is doing a trial and he doesn't care about small fiber neuropathy specifically, but he wants to include patients who have a high likelihood of having neuropathy. He would say, quite reasonably, burning pain plus one sign, pin prick -- and Chris and you guys weigh in on this -- he would say that's highly probable; in fact, that's definitive clinical diagnosis of small fiber neuropathy.

I mean, the point is reasonable. What would you say, Gordon?

DR. SMITH: I'm saying the same thing, that those would be part of the definition of probable neuropathy. So it would be A or B. A is this; B is that.

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

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

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

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

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

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

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

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

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increase it to two signs and it's 95 percent, then it's not making much difference, but it's empirical.

DR. FREEMAN: Yes. It would be nice to know.

DR. BRUEHL: I think the thing is we don't have to be perfect on the numbers we pick here. The idea is to at least get a starting point and then use that as a basis to start evaluating these questions to fine-tune it.

DR. FREEMAN: I think that should be the approach. Gordon, are you okay? You've got enough to work with yet or do you have questions?

DR. SMITH: I think we're good, yes.

DR. FREEMAN: Next slide?

DR. BRUEHL: That was it.

DR. FREEMAN: No, no, no. So this is definite, all of the above, that we discussed, plus these neurophysiologies. And this is a good time to talk about it. James's group had quantitative sensory testing and corneal confocal microscopy as their confirmatory tests.

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When I called for questions, somebody said that QST, presumably somebody from this group, and corneal confocal, the weight of evidence wasn't there for those to be called confirmatory tests. And I think we need to, on some level, initiate that discussion. This is what Gordon's group said.

DR. BRIL: This was my question. Do we have to be specific about the confirmatory tests? That was it, because the definition is clinical. We've gone through the definition. Now, how specific do we have to be about the confirmatory tests? That was the whole point.

DR. PELTIER: I would argue one confirmatory test, which should be sufficient, because the problem is that you're going to have a lot of studies that are not necessarily going to do multiple tests. Then two, I would add CCMs since there's a huge body of evidence and there's norms, but I would leave out QST because of the issues of QST is not necessarily diagnostic since we know it's more of a subjective test as opposed to all the other ones.

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DR. FREEMAN: What are the others? Any other views on this?

DR. RUSSELL: Yes. So I think this whole area is incredibly controversial. I mean, even if you look at these confirmatory tests, we've already looked at all the problems with nerve conduction studies and which ones you actually choose.

There were the skin biopsies, which I think is a great test. Again, you have to apply the criteria developed by Laura and colleagues published in PNS or the European Federation, and you've got to follow those exact criteria if you're going to get reproducibility and if you're going to use the normative data that's been published. So I mean, even with that, which is a very good test, you have to be very specific about what you're going to do.

So I think all of these tests have their caveats. And I would maybe go with Vera or whoever said it and maybe say you would use a confirmatory test.

DR. FREEMAN: I think we can't just say --

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DR. TESFAYE: Class A evidence.

DR. FREEMAN: Which are those that have class A evidence?

DR. TESFAYE: Class A evidence in my view is does a test that you do have predictive validity for the future development of peripheral neuropathy? And I think that -- we don't have prospective stuff. I think we need to be as robust as we can.

DR. ZIEGLER: So there is evidence for nerve conduction, number one, number two the monofilament, number three VPT. Those are the predictors of foot ulcers. There are studies showing evidence for that.

(Crosstalk.)

DR. ZIEGLER: We are going back. We are now going back to the monofilament bedside test. And you can also argue that QST and nothing else is more pre-sized bedside testing. That is my take. So why not use it as confirmatory if it's more pre-sized than the bedside on which we base our clinical judgment?

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DR. SINGLETON: I think the problem with QST has been that it doesn't test peripheral nerves. It's a neurophysiologic assessment, not a nerve test.

DR. BENNETT: Don't you think that's kind of theoretical rather than evidence based?

DR. SINGLETON: No. It's not. It's pretty hard. I mean, you can have a central nervous system problem that makes your vibration sense reduced.

DR. BENNETT: Yes. So you add a caveat which is -- I mean, we're pragmatic clinicians, so this is for pragmatic clinicians. So you add a caveat, which we've seen all the time in diagnostic criteria. To be honest, most of the time, when I've seen that situation, it's been pretty obvious there's a CNS problem when you put it in the context of examination of other findings on the patient. The fact that there is evidence from [indiscernible] Larrier [ph], actually, when he compared clinical examination, QST, and skin biopsy, there was a role for QST.

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So I think it's difficult just on that pragmatic level to say we're going to push this out because of the theoretical -- I agree it's a real issue, but I'm just saying that if we go on evidence, then actually there is evidence that QST is informative.

DR. BRIL: So I would just use confirmatory tests, in brackets, e.g., nerve conduction, electrophysiology, skin biopsy, QST, because you can do thermal as well, and CCM, for example, in the brackets because, I can't see doing skin biopsies on everybody. That costs a lot. It's invasive.

So maybe we'll do them in a study if the sponsor's going to pay, maybe not. They don't often want to pay in studies of pain. I mean, sometimes they will.

DR. FREEMAN: There are two or three small fiber neuropathy studies ongoing, where skin biopsy is the gold standard.

DR. BRIL: Now, but you can't say that's going to go on indefinitely, so I think you should

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have a choice of what you do.

DR. FREEMAN: No, no, no. I understand. But as long as it's on the list, that's acceptable. Gordon?

DR. SMITH: My concern isn't the repertoire of tests that we've been talking about. And you know my feelings about this. I'm not very enthusiastic about either one of these, so I think adding QST whatever, I'm fine with. It's the other kind of crazy tests that are out there.

We can't just say confirm. We could say, "confirmed with," and you couldn't really say level A evidence, but some sort of caveat about strength of evidence, and then, for example, nerve conduction studies, INFD, QST, CCM, whatever.

But I'm not worried about that. I'm worried about the people that are doing the nerve decompression surgery. Dellon's created this sort of quasi-TNL QST thing. And so if we just say confirmatory test, then who knows? They may use that.

DR. FREEMAN: How about we actually specify

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the big 4, and we actually add the caveats for all four of them.

DR. BRUEHL: But are you saying confirmed by one of the following?

DR. FREEMAN: One of the following. I think that's the consensus, but we satisfy everybody by saying whatever longitudinal data do not exist, that QST measures the entire nervous system as does the rest of the sensory exam, of course, by the way, and nerve conduction studies. So we do all of that and we had a series of provisos.

I think that takes care of this one. Let's move on to the first Word document, which is called "severity." This is James. This is the QST nerve conduction study. I think we covered that, earlier comment on class A, reduce sensory signs.

These were the questions. This is pre-clinical. And then he moves on to clinically mild. And mild has reduced sensory signs, and the question is how are we going to define reduced but not lost? And then the question was what signs and standardization? And I discussed standardization

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

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

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

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

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least one abnormal test at the 97.5th percentile. Okay? We could do that, I suppose. Again, I just don't want people to do this just on vibration perception threshold or cold because I don't think that's moderate.

DR. GIBBONS: So just say that, specify that.

DR. HOKE: Yes, but why not use two measures of nerve conductions? I mean, moderate could be somebody who has both abnormal sensory or motor evoke responses.

DR. RUSSELL: Ahmet, I agree with you. Okay? We would do that. But if we're doing an epidemiological study, and let's say all you've got there is you've got your little vibrometer methodology, or you've got some sort of machine that measures cold perception thresholds, so you're not doing the nerve conduction studies, what could you use as a confirmatory test? So that's the problem.

DR. BENNETT: This is severity. [Inaudible – off mic].

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DR. RUSSELL: Yes. So the clinical is there. I mean, in Africa, you'd use the clinical scales. So I mean, my personal preference would be to move all these confirmatory tests and say you can just do a confirmatory test if you want.

DR. BENNETT: I agree. I think the confirmatory tests are a bit of a red herring. I think they should be using --

DR. FREEMAN: You want to then, as you've done -- if we move those -- is that a general consensus? It's easier to get consensus now.

(Laughter.)

DR. BRIL: I think you have to have electrophysiology for severity myself or some test showing where it is, because then how are you going to do confirmatory tests for diagnosis?

DR. FREEMAN: Yes, no. Look, I'm sympathetic to that view.

DR. BRIL: You know what I'm saying? If these all have to align, you're going to put these as completely optional, how do they become necessary? I mean, or do they? Can you do that?

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DR. BENNETT: I mean, I'm going to do two things here, which is [inaudible – off mic]. This should just be severity.

DR. MALIK: I think that was exactly the rationale. We thought that there has to be an objective measure, small, large, or both, but there has to be a subjective way, the way you've got, a way to define severity.

DR. ZIEGLER: To delete QST again. Yes, you could argue that the other three are objective, either morphology or function and CV, therefore, there is no place for QST because this is psychophysical. Variability is higher.

DR. MALIK: Yes. That's fine.

DR. ZIEGLER: So there's a rationale for that.

DR. FREEMAN: You're okay with that?

DR. RUSSELL: Yes.

DR. ZIEGLER: It fits with your VPT problem.

DR. RUSSELL: How about we say, for moderate, then, you would have to have either an abnormal nerve conduction study value greater than

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the 97.5th percentile or two other abnormal measures that are greater than that percentile?

DR. ZIEGLER: For confirmation, you would require only one in each case of severity. You can define it by percentile. So as it stands, you can go 79.5 for the moderate and 99 for the severe.

DR. RUSSELL: Right. Yes. The only thing was, what do we do about the vibration, the cold perception?

DR. ZIEGLER: It's out now.

DR. RUSSELL: So we're taking it out completely? Okay.

DR. FREEMAN: I think you're taking it out and you put your --

(Crosstalk.)

DR. BRIL: I think there's a lot of work Andrew did about vibration with a biophysiometer. And it may not be so reproducible, but that's not what you're trying to do here. But if you have someone who's off scale on those instruments, they're at risk of foot ulceration, and you have people who are less.

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

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

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

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

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

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

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

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

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

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MALE VOICE: No, no, at least, I don't know, two or so, three.
DR. RUSSELL: So severe would now be loss of at least two.
Adjournment
DR. FREEMAN: Yes, loss of at least two. Great to see you.
(Whereupon, at 2:25 p.m., the meeting was adjourned.)

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