ACTTION - CONCEPPT MEETING ON SMALL FIBER NEUROPATHY

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ACTTION

CONCEPPT MEETING ON

SMALL FIBER NEUROPATHY

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Westin Georgetown

Washington, DC

C O N T E N T S

P R O C E E D I N G S

(8:02 a.m.)

DR. FREEMAN: Good morning, all. Welcome to day 2. I do not wish to equate being hanged with developing a consensus with the group of you, but there is a parallel. So what I want to do in this introduction is to concentrate the mind a little and get everybody right on target because come 1:00, we will be working to develop a consensus statement. And our assignment, I initially had written charge, but I thought it was a little bit too close to being hanged, is to develop a case definition, which is to say inclusion and exclusion criteria.

So we're not looking at outcomes. We're not looking at what is used in clinical practice. This is a case definition for a randomized control trial, which is to stay inclusion and exclusion criteria. And it's getting to be an enormous amount of work to do this, and I want to try and keep our eye on the ball so to speak.

Now we could use this in observational

studies, in case control studies, could be used in cohort studies, but the aim is to develop something that can be used, will be used, in randomized control trials, ideally phase 1/phase 2 trials -- sorry. I should have said phase 2/phase 3 trials, phase 2/ phase 3 trials. And if it spills over into clinical practice, so much the better, but that's not the focus.

Now, what I want to do again to get everybody focused is to present approaches that have been used to this. I have a view on this, but I'm not going to be too prescriptive at this point, but later on. But I want people to begin to think over the course of the morning in these terms. And there really are I think sets of approaches to this, one of which comes from the neuropathic pain grading system, which was redeveloped following the redefinition of what neuropathic pain in the current era is, which is a very neurologically based approach, pain being a lesion or disease affecting somatic sensory nervous system, so, a lot less tight than the previous definition, which was

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along the lines of damage or dysfunction.
Simon who spoke yesterday was part of this group as were a number of individuals involved in the neuropathic pain field. And what I want you to begin to think about is the possibility of looking at what we have been talking about over the past day in terms of history, which is to say here is the irrelevant neurological lesion or disease, pain in a neuroanatomically plausible distribution. But I think in our terms, we are thinking about what the symptoms are, what idiopathic is, so the nature of the pain, the nature of the autonomic symptoms, and of course the distribution and the duration, and that would constitute the history.
The examination over here, pain associated with sensory signs in the same neuroanatomically plausible distribution. We are thinking about things like pinprick loss, thermal sensation loss, hyperalgesia, allodynia as features of the examination. And then finally over here, the confirmatory tests, diagnostic tests confirming a lesion or disease of the somatic sensory system.

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This morning we will be talking about the diagnostic tests, which as you will hear, will be intraepidermal nerve fiber density, quantitative sensory testing, and autonomic testing now.
So we will need to come up with an approach to these, how to combine them, how to synthesize them. Again, I have some views on this, but I will want you to be focused in that direction. It is a possibility that we could use this possible probable, definite approach, but it certainly is not necessary. So that's one approach. I said I would give two approaches.
The other approach I'm going to give is a little different, and that comes from the international classification of headache disorders, which I think probably should be regarded as one of I think the best approach to classification, at least in the neurology field. Perhaps in the pain field, it's been highly successful in terms of therapeutic development, and I think we can take some points from it.
So again, I'm not suggesting that we mimic

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this, that we mirror it, but I want you to think of this in terms of an approach. And the approach is, A, this is how migraine without aura is classified, and as you know, this is I think a 400 page document or -- an 808 page document at the very least. So migraine without aura, at least 5 attacks fulfilling criteria B to D -- B to D follow headache attacks lasting 4 to 72 hours, untreated or successfully treated. And here I want to introduce the notion of a menu of possibilities.
Greater than 2 are of the following characteristics, unilateral location, pulsating quality, moderate to severe pain, intensity, aggravation, et cetera. So the menu approach greater than to 2 or 4, during headache, greater than one of the following: nausea, photophobia, phonophobia; again, the menu approach not better accounted for by other possibilities. And this is prescriptive as to what migraine without aura is. And then if less than 5 attacks, then probable migraine without aura.
Between these two extremes, I'd like us to

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come up with something at the end of the day that fits something along these lines. And having set the stage, I think we are now ready for the first talk, which will be chaired by Eva. So if you could possibly come forward and introduce the first speaker.
First, we are going to have Nurcan Uceyler, who will be talking about the sensitivity and specificity of QST, and we can be thinking how these could be incorporated in our final consensus.
Presentation - Nurcan Uceyler
DR. UCEYLER: Thank you very much. Enjoy your breakfast.
QST, I would like to give you an overview of the methodology and the work that has been done so far in this field looking at idiopathic small fiber neuropathy. This is what I have searched for and what I've prepared. Quantitative sensory testing, QST, well, in general is a method to assess different nerve fiber types. It's not just the small nerve fibers; it also contains the large nerve fibers, of course.

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It is, if you wish, the quantified version of the neurological examination that we do, actually nothing else, quantified version. We do get a thermal and mechanical perception and pain thresholds as functions of the small nerve fibers, A delta and C, plus large fiber functions and muscle nociceptor functions.

Standardization is a very big issue here. That's for the work of the German research network, neuropathic pain. DFNS is so valuable, I would say, putting together single test 13 in a very standardized manner so that we can all do our assessments in a way that we can also compare the results from different groups. Very important other points, individual comparison with normative value. So when we do the test, what is the normal? With what should we compare our results? And I will show you examples also from our group, how much the results can differ depending on with what you compare all this.

I'm not sure who of all of you has undergone QST, him or herself. It's very, very valuable to

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do this, to also understand how difficult all this is and how subjective -- and that is not a keyword -- the answers that we get from the patients are and how we should then put them in order and evaluate also. So I would like to very quickly go through the major items that are tested with QST, and I will show you how the DFNS protocol is working.

The DFNS protocol is very often cited, but what is behind it is actually that we give the patients always the same instructions. That's the major point. Everybody everywhere in each lab does give the same instruction, and how do we now get to the thresholds? The first five tests are actually for the small nerve fibers, and when we look here, for instance, for the cold detection thresholds, what do we tell the patient? This is not the validated English version. This is just the translation I made now for this presentation from the German version.

So please press the button immediately when you first feel a change. The patient should push

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the button when he or she feels the change in temperature to cold or cooler, cold or cooler. Then you press the button and have value. For warm, it's just the same. Press the button when you feel warm or warmer, and then you get one detection threshold after having repeated this three times. And the third test, which is thermal sensory limen, ask the patient to immediately press the button when feeling a change to cold or warm, and tell us, do you feel this as cold or do you feel this as warm? And this is also repeated 6 times, one after the other, and the patient has to tell you so you get several results, which is an average afterwards.

This is, I can say already, one of the tests which is most unreliable, I would say, where you get most diverse results. It is very, very difficult, even for a normal person, to really find out is this now getting colder, is it now getting warmer? This is very, very difficult to say, and that's why the TSL actually is the one that we in general do not rely so very much on. So cold and

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warm detection thresholds are much more robust, still having otherwise a range of possibilities to answer.

Paradoxical heat sensation, maybe I should also say a word on that. This is a number 4. This is not really a test. This is what the patient is telling us. When we cool down to thermode, some of these patients tell us, "Oh, it's getting hot." We're cooling down to thermode, and all of a sudden they say it's warm or even hot, painful thought. This is paradoxically heat sensation when cooling down, also as a sign of an impairment of these little fibers, PHS.

Cold pain thresholds, of course, please press the button immediately. When you feel cold, you get a second sensation, which is then pain. And for the heat pain threshold, the same thing, the other way around. So your skin will be now warmed up. At some time, there will be a second perception in addition to warm. Please press the button immediately when you perceive such a painful feeling, and this is also repeated 3 times in the

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area of interest.
These already test for the small nerve fibers when you want to check the thermal perception threshold, so CDT and WDT. The other ones I will go through quickly. This is mechanical detection threshold where we use the Von Frey here with different filament sickness and ask do you feel the touch, please say yes. And another is the mechanical pain threshold where we use dull needles and then ask, okay, do you feel a pinprick, sharp pen, and then press this to tell us.
Mechanical pain sensitivity, which is going again with these dull needles, where dull needles will be pressed on your skin with using different pressures, intensities, and also with cotton ball Q-tip and brush into immediately. And then please estimate the painfulness of each single stimulus. This is very, very difficult. Estimate the intensity of each stimulus between 0 and 100. Please keep this in mind. So this is really not easy also for the patient.
Allodynia, this is what we do in clinical

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practice as well, so we use a brush or a cotton ball, and then again, is this painful or not, again, estimate between 0 and 100. Wind-up ratio, when you repetitively stimulate a certain skin area and then ask the patient estimate in sum the painfulness of the serious between 0 and 100, you will get an idea about wind-up ratio.
Vibration detection threshold, I think this is very clear; this is what everybody is doing. And pressure pain threshold, I would please pay attention to this. This is, in my opinion, not investigating really skin nociceptors. So we are putting pressure on a muscle. This is pressure pain threshold above muscle. And I think these are different nociceptors. These should be muscle nociceptors, which are even less well investigated, as number 13 in this row.
What happens here, you get thermal perception and pain thresholds and mechanical perception and paid thresholds, paresthesia, muscle pressure pain, wind-up allodynia. All this together go into such a dead score where you have a

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zero line, which is per definition the normal group. The reference group is zero, and everything that goes on this is a loss of function, and everything that goes above zero is a gain of function. So you have hyperalgesia or hypoalgesia. This is how you read these plots as a result of your 13 tests.
It is important to remember these other tests looking at the A delta and C fibers, here you have the mechanical detection thresholds, vibration detection thresholds, et cetera, for A beta. But also a little portion I would say, C-tactile afferents, we should not forget about them. I think these are very important nerve fibers that are also assessed here and the muscle nociceptors.
What is really crucial? And I will repeat this several times. I also think this is very important when we're talking about inclusion/exclusion criteria. These results all depend on age, and they all depend on gender and body region; so hand, feet, face back, abdomen is different. And very crucial is again what do you

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compare with. There are different reference values -- I will come to that in a moment -- and it is very, very important to know what is in it, which range is really covered.
Advantages, disadvantages, I would like to put that first before I come to the study results. It is very obvious. All this is very noninvasive of course. This is attractive. It is well standardized when you use the standardized protocol so you can then really compare the results of different labs. And I would say 13 tests only one hour.
Well, the disadvantages are dependencies, and that's really a problem, the dependencies. You need an experienced and trained investigator, so you need an investigator who is trained in all this. I just read these instructions. It's more than just reading out the instruction.
You need a cooperative subject of course who understands, who has some introspect, and then can tell you really what he or she feels, and the control data used for comparison. Of course you

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can turn this argument around and say, 13 tests, test one hour. Who has one hour to do all these tests? They are much too long.

Very important, don't forget, we cannot localize the pathology with this method. When we do this, we look at all this. We look at the stimulated side up to the brain until the patient tells us something. So we do not know where the pathology really when we get a pathological result out of this.

Well, this is not very well reasonable, but that doesn't matter. I have tried to make it in a standardized way, so I have always this blue box on the side with some items I thought would be important information to get out of the papers that I found for quantitative sensory testing of a thermal threshold testing in papers that are dealing with idiopathic small fiber neuropathy.

I will start here with one paper by Periquet and colleagues, 1999. His colleagues investigated 44 patients with small fiber neuropathy, and the SFN criteria were simply clinically suspected. So

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these are patients with burning feet, toes, and dysesthesias. They used CASE IV, which I am not familiar with. Some of you will be familiar with this. I'm not. This case 4 seems to have normative values of the company. I also do not know what is in. I didn't find any data on that. And there is some thresholds determination, which is different from what I've shown here. Again, it seems to be a protocol. I'm not familiar with this.

This group did not calculate some sensitivity or specificity, but what they did is they somehow compared skin biopsy and QST and come to the conclusion that QST is less sensitive than skin biopsy making the diagnosis of these small fiber patients. And the main result, when you look at the results of this QST measurement, is 23 out of 32 patients that were investigated had somehow a pathological threshold for this thermal perception.

I would say here is a caveat. As far as I understood, the QST results do not only cover thermal perception, but there is also some

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vibration, a detection put into it. So I think this is a mixed result. One should be careful maybe with this, so one study.

The next one is 1999, Tobin and colleagues, looking at 15 patients with idiopathic small fiber neuropathy we would call it. No control group, again using the normative values of CASE IV clinically suspected, so no really criteria. They didn't do the assessment themselves. They looked into the medical records of these patients. And again, no sensitivity specificity calculation, but the conclusion that QSART in this case was most sensitive to really find all these patients. And when you look at the cohorts, 10 out of 15 with pathological thresholds. No standardized assessments, very small patient group. I think these are some of the caveats that need to be considered.

Next, Magda 2002 presents data of 14 patients; again, no control group; again, the normative values of the company, again CASE IV, clinically suspected cases. This is impressive

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when you look here, 14 out of 14 patients with a pathological threshold for thermal perception, which is quite impressive I would say. None of the other studies that I will show you will reach this high number, and very similar caveats, again, here, particularly also in a very small group, not to forget.

The next one is Scott 2003, looking at 20 patients clinically suspected. Now, they use the Medoc thermode, following the manufacturer's recommendation, and I think also using the manufacturer's control values, which is now not comparable with what we have seen up to now. They did a calculation for sensitivity and specificity, and say 78 percent of sensitivity, 46 percent of specificity for small nerve fiber impairment. Twelve out of 20 patients were pathological.

Here comes a very important study, Devigili and colleagues, 2008. This has been cited a lot, lot, lot; 42 patients having been investigated in a very standardized manner. As far as I've understood 24 additional control subjects have been

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investigated as well, and there was another database of age and gender-matched normative values that these values have been compared with.

The criteria actually came from the study, the current criteria that we are using, Devigili 2008. These are, however, based also on prior criteria from Stewart and Lacomis, looking at clinical presentation, thermal perception, and skin biopsy and using here the Medoc system, threshold determination, again, a little bit different of what we have seen; sensitivity 57 percent, 37 percent of specificity, and 38 out of 67 patients with pathological findings.

Scherens and colleagues 2009, this is not one of the DFNS centers I can say. This is the group of Christoph Maier in Bochum who investigated now with the DFNS protocols, so very correctly, 42 patients who had burning feet and toe, clinically suspected. They are using the Medoc system, and they are using the DFNS protocol: sensitivity, 38 percent, 80 percent of specificity, 5 out of 16 patients, 31 percent, pathological thresholds. So

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again, very different numbers.

Here are two studies that I only have as abstracts. Many information are missing here, but just to give you an idea, Shukla and colleagues, 2005, 25 patients clinically suspected small fiber neuropathy, 18 out of 25 with pathological thermal perception thresholds, and on the other side, Lefaucheur and colleagues, 2015, 35 patients, no control group, clinically suspected, warm detection threshold, 55 percent pathological; cold detection threshold, 32 percent.

DR. FELDMAN: And there is no indication of which devices?

DR. UCEYLER: This is, unfortunately, just the abstract that I got.

DR. FELDMAN: Oh, okay.

DR. UCEYLER: Unfortunately, I couldn't get the full paper, unfortunately.

This paper, we talked about that yesterday. This is a very large group from the Dutch cohort, deGreef and colleagues of this year, more than 900 patients, really a big, big group. Devigili, 2008

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criteria were used. QST is not so much the focus. Please correct me, Karin, when I say this. So there is not much information in the paper really in detail, but as far as I understood yesterday also from our personal communication, this is, again, a different protocol. This is Bakkers and colleagues, 2015, I think from the same group, also a modified and optimized not really QST. That's why in the paper also it says TTT, which is temperature threshold testing. And here, quite a high number, 614 out of 921, so 67 percent of patients with pathological thresholds.

So maybe I confused you a little bit, but that's good because this is the situation. So we have very diverse numbers because we have very diverse methods and devices and everything. What I would like to show you now are the results of three studies that we have performed. And where I have learned quite a lot, I think about QST and how to deal with these results, and this I would like to share with you.

This was the first study, which is published

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2010, where we were really at the beginning, and we had only 24 patients. But it is now for all these three studies the same lab, actually also the same technician who is doing this. This is the same DFNS protocol, et cetera. This is the homogeneity, and now look at the results.

We had 24 patients, and how we go ahead is that we always recruit an additional control cohort with our subjects for the group analysis to get this kind of plot. And at the same time when you're a clinician or when you're doing a study, you have to compare, of course, your results with normative values for the individual patient to find out is this now pathological, yes or no.

At that time, we had from the DFNS cohort the Rolke 2006 paper with the first normative values that we were able to compare our data. So what did we find out? We saw with the Devigili 2008 criteria the Somedic thermal tester using the DFNS protocol and now comparing our patients with a Rolke normative database, 20 out of 22 with pathological thermal perception thresholds, which

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is 91 percent. This is really high.
We compared with the control group that we collected, so 24 against 21, which were age and gender matched. We saw it fits very well, cold and warm detection thresholds with a hyposensitivity here, very interesting, MDT, mechanical detection threshold, which should be actually normal in these patients, also with a hypersensitivity, which is difficult to understand because none of these patients had any signs of polyneuropathy of large fibers, not in the history, not in the clinical examination, and also not in the nerve conduction studies, but they do have this. At that time, we couldn't interpret; we just showed and, yeah, it was like that. I hoped it would disappear when the groups get larger. Okay. So this is the first study, and this is the result.
Second one is under review at the moment. Where we collected, the focus was on large fiber neuropathy, so patients with sensory motor, axonal and demyelinating or mixed, large fiber polyneuropathy, 292, all investigated with this QST

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protocol; and in this group, 58 patients with isolated small fiber neuropathy, so idiopathic small fiber neuropathy that we have. And in the meantime, we had collected -- though this is now work of 10 years -- 273 healthy controls in our groups. So all of this has been done in the same lab where you saw the results before.
What do we see here? Again, we have this control group, which is now much bigger, and now we have also new 2010 normative values, Magerl et al., for the DFNS cohort. Rolke 2006, four years later, Magerl at 2010. Devigili criteria Somedic tester, DFNS protocol, what do we see? 28 out of our 58 patients when comparing with the current normative database of Magerl et al. have pathological thermal perception thresholds, which is less than 91 percent, which I showed you before.
DR. FREEMAN: Cold pain and heat pain, is that behind one of the --
DR. UCEYLER: Cold pain threshold, heat pain threshold, not much really happens. It doesn't show much.

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DR. FREEMAN: Really?
DR. UCEYLER: No. And when you look at this, this is also very, very interesting, I think. The blue ones are the patients with confirmed large fiber neuropathy, so large fiber neuropathy does not only affect the large fibers; it also affects of course the small fibers. So these patients are the ones that are, let's say, more ill, right? The nervous system is more ill. They have the most pathological values, and the red ones are the small fiber patients who do not have -- not for clinical presentation, not for electrophysiology -- an affection of the large fibers. They are in between controls and the large fiber patients.
Very interesting, this is mechanical detection threshold, vibration detection threshold for the large fibers. Of course, the polyneuropathy patients with large fiber neuropathy, they are very pathological here. But please look at this. This is again MDT, and it has not normalized with a larger group. It's still there. Hypersensitivity, although the patients do

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not tell us, we cannot find out in the clinical examination and nowhere else. It's interesting.
DR. FREEMAN: And these were not fibromyalgia patients, these were --
DR. UCEYLER: Oh, no, definitely. Burning feet and toes, this is not fibromyalgia. This is idiopathic small fiber neuropathy for sure, second study, so this is not yet published.
Now comes a third one, which we're currently working on the manuscript. This is another cohort, 56 patients with idiopathic small fiber neuropathy. Now I have stratified for gender, female and male. We have the large control group and still the Magerl cohorts to be compared individually. Everything else is the same in Rolke's work; nothing has changed now 14 out of 56 with pathological thresholds. So only 25 percent.
So what is with the other 75 percent of all patients who do have small fiber neuropathy? They do have this, but they have normal thresholds here. When we go ahead with this -- I'm not saying that this is all the truth.

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DR. FELDMAN: They do have it based on skin biopsy?
DR. UCEYLER: They did have a skin biopsy, all of them.
DR. FELDMAN: So this is based. So you're saying when they do have it, you're saying they do have it base on skin biopsy?
DR. UCEYLER: Be careful. For the skin biopsy, this is also not the gold standard. So Giuseppe will present the data. I don't know what he will be saying about this. There is no gold standard.
DR. FELDMAN: So when you say they definitely have disease, what is the gold standard for you to say that?
DR. UCEYLER: This is now a study. What is the gold standard? The story of the patient, I have burning feet and toes. This is the first thing.
DR. FELDMAN: So it's pain.
DR. UCEYLER: Pain, tingling, dysesthesia. Some of them will have pathological thresholds.

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Another proportion will have and/or pathological fiber density, and there will be a subset. And I don't want to go into too much detail also because of time. There will be a subset that will have all these patients underwent skin biopsy, underwent QST, underwent CCM, and underwent pain-related evoked potentials. And we do have patients with this very clear history of burning feet, nothing pathological in all of these. Some of them do have a genetic reason that we found out, a few of them.
It's very interesting. Those of these patients that got microneurography -- we had the chance to get this for some of them -- had spontaneously active fibers in the end.
DR. RUSSELL: Nurcan, can I ask of all this data, what percentile are you using as your cutoff? Are you using the 5th percentile, the 1st percentile? What's your --
DR. UCEYLER: For the thresholds here, comparing?
DR. RUSSELL: Yes, for your thresholds.
DR. UCEYLER: We are looking at the -- I

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will show this in a moment. For the individual comparison to come to this data, we are looking at the table of Magerl et al. 2010. I will show this.
DR. RUSSELL: No. What's your percentile cover?
DR. UCEYLER: Ninety-five percent of confidence interval.
DR. RUSSELL: So 30 percent/
DR. UCEYLER: Right.
DR. RUSSELL: So you went back and looked at your data at let's say the 1st percentile, presuming it's going to be even lower than this. Is that correct?
DR. UCEYLER: Yes.
DR. RUSSELL: And the second question is, the data from Magerl et al., what is the population group that was gathered in this -- this group here?
DR. UCEYLER: I'm coming to that, yes. These are Europeans.
DR. FELDMAN: We probably have maybe five more minutes to wrap up. Okay?
DR. UCEYLER: I think I'll make it.

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DR. FELDMAN: Okay, good.
DR. UCEYLER: So this is striking, right? This is important. Now we're coming to this. We have to be aware of what we're comparing with what, again. So when we compared with Rolke 2016, this is the solution. These were 18 healthy patients with a mean age of 38 years. Our patients are much older. The group is much bigger. So it is no surprise that when I compare patient group of mean age 50 with these normative values, you have to look who is in. Then you will have many, many pathological values and come up with 20 out of 22. I think this is the solution.
When you look at Magerl 2010, these are 180 controls, 180 between 20 and 70, so we have patients even up to 89 years old. We have actually per decade, when you put this into decade, 10 to 15 controls per decade. So again, this 180 is coming to a small number of 10 to 15 per decade. And with increasing age, it is even getting very difficult to become pathological, so this is a very badly readable piece of this table, so you can see

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how big this 5 to 95 confidence interval is. Until you get pathological, you really need a very, very severe impairment of your small nerve fibers until you drop out of these normative values. And of course here, this is a very, very large group also with older controls. I think that explains a lot.

A little excursion before I come to the end. Of course, 13 tests, as I said, you don't need all of this. What about bedside tests? There have been some attempts. This is just one example from the group of Rausch Perrone and Kia [ph] in Germany, where they tried to get some bedside testing for Fabry-associated small fiber neuropathy.

In addition to some questions in the questionnaire that they put together, they say apply Tip Therm in random digit order to find out cold and warm detection thresholds. This is a bedside test, of course, not the standardized protocol. If you want to look for hypoesthesia, use one von-Frey filament and ask the patient, and of course the tuning fork, which is standard for

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every neurologist.

So summing up, I was surprised actually when, again, screening that they're not so many studies actually investigating idiopathic small fiber neuropathy using quantitative sensory testing. It has its advantages, no question. There are some drawbacks that we have to keep in mind. The numbers for sensitivity and specificity are very diverse. This has its reasons I already said.

So logical QST does not exclude other differential diagnosis, and the crucial aspect aspects, in my opinion, the standardization of course, we have to have something that is really standardized with DFNS protocols since more than 10, 12 years now, I think is doing quite a good job here. Training the devices, lab certification are the major keywords here and the size and composition of the control group that we are comparing with is something to be kept in mind.

I think that's it already. Thank you for your attention.

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(Applause.)

DR. FELDMAN: I think to stay on time, we'll take the questions during the panel. So next up is Giuseppe.

Presentation - Giuseppe Lauria

DR. LAURIA: So thank you very much also for the kind invitation. I will try sharing with you some conceptual point with a critical spirit on a monster that I guess I've contributed to create, which is a skin biopsy. So it will be a little journey over the years.

So starting from this, this is where we were 20 years ago. Everything has started here in Sweden at the Karolinksa Institute, and then there were two labs, one in Minneapolis, Canada, and the other one at Hopkins with Justin and Jack Griffin. And from then to the time with younger guys, so myself and Maria Nolano went back to Milan.

This is where we are now. So the big covered countries I guess for USA -- you missed just one in Alaska. And there are some others. I know there is one which will be set up in Israel

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soon and one in Australia. So it is quite impressive how the biopsy spread out through the countries.

So the career that this little thing, this little piece of skin has done, over the year has been really great because it allowed actually the investigator to overcome the need of the sural nerve biopsy to investigate the myleinated nerve fibers, which actually, even through the biopsy, can be assessed with the electron microscope, as you see here, in the dermis and even in the epidermis. It's quite difficult to find them, but they are there.

The history, very briefly, you know first identified by Langerhans. He used to be a medical student at that time, and then 50 years later, there were great scientists who even provided the first quantification and found first it proximates to this gradient in the body. And going through these historical notes, I will put my point, which I believe are quite interesting for the discussion today. So the first availability of the antibody

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that we use against the epitope that is relevant, than the normative, the guidelines, and then the transvalues for the two methods that are used, as you know.

You know that these fibers are quite interesting because they are naked. Actually, they lose the Schwann cell ensheathment while they cross the dermis, the junction. It's quite interesting because this is what happens also for the large myleinated [ph] fibers while they approach the inner core of the mechanical receptors, so they are in close contact with cells, which role is not only structural, but might have some role also in the transmission of sensation. But you also know that these fibers undergo a strict segregation during the development. In particular it is interesting how they target the different levels, the different part of the skin based on the expression of a number of growth factors, transition [indiscernible] factors, so mainly NGS, they're running Schwann.

This is to show you the reason why for many

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years it was impossible to identify these fibers in the epidermis because the only available antibodies were against the, uh, a game dabchick epitopes. So, but the number of a peptidergic epitopes. The number of peptidergic fibers in the epidermis is low.

So what has changed has been the availability of antibodies against this protein gene product 9.5 that stains pretty well all the fibers in the superficial layers of the skin that you see here. And what is this? This is antibodies against the cytosolic enzyme that removes the ubiquitin and is transported with the slow component of the axonal transport. So it is actually an unspecific, cytoplasmic protein, and this is what we target. Since it is very abundant in nerves, it is used as a marker for the peripheral nerves as in our case.

The other interesting thing is that although, as you know, not all these small size neurons in the DRG are nociceptors, so they express the TRPV1 receptor, capsaicin receptor. All the

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fibers in the epidermis do, so it means that there should be a kind of segregation also for the expression of this. And this is a quite clear overlap with a marker stain in the cytoskeleton.

So the first point is that the fibers with the clinic that we use commonly in the labs are staying using a marker which is not specific for the fiber function. The second thing is that the fibers and epidermis are nociceptors. I think they can be defined in this way.

The second point is that -- well, actually the biopsy [indiscernible] has boosted the story of the small fiber neuropathy, clearly, because before the first studies in the mid-90's of the last century, the diagnosis was more blurred. At that time, the first studies first demonstrated that some patients with symptoms could be attributed to damage or impairment of the small nerve fibers despite a normal function of the large fibers at the nerve conduction studies, and even at the pathological level have an impairment, damage, a loss of these fibers looking at the skin, so a very

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distal neuropathy.

This has been assessed in different times. There's a nice paper that David published and sent me years ago showing the agreement between the skin biopsy and the sural biopsy. And there is about one-quarter of those patients who had the normal morphometry in the sural and impaired, and the loss of fibers in the skin. So that's a figure that we record.

But the other important thing is that at Hopkins, Justin, Jack, and all the people working at that time provided the first normative reference range that actually were adjusted by age decade; not by sex but by age decade, but with the 80th percentile interval that you see here; and providing also some diagnostic performance of the technique compared to the two different percentiles, so 10th and 5th. And looking at the 5th, you see this with this specificity and this low sensitivity, providing also positive predictive value and negative predictive value, which we will spend some words later.

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But the other important thing is that they didn't find any difference in terms of age decades since there wasn't any age related decline. So what happens is this mean plus the standard deviation of this percentile cutoff and was capped and used. And what has happened is that for more than 10 years, our lab, but older labs actually, made reports based on a mean value that was applied to both sex and any age. So the point is that more false positive or false negative all this time.

Going to the following point, in 2005 with the groups who have published or started working earlier on the biopsy, we did these guidelines that were related essentially to the standardization of the protocol for assessing the density of the intraepidermal fibers using the two techniques, which is the bright field and the immunofluorescence, and finding an agreement on the counting rules, so how do we count these fibers, otherwise.

This is what has remained since then. What has remained essentially, just to make it simpler,

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we count this fiber. We measure the length of the epidermis and we obtain this density per linear length of the epidermis. This is what is done in both the -- so the method that's been analyzed by a number of panels, of tasks, this is the AAN in 2009. Then in 2010, we revised with the former FNS and the PNS, publishing this guideline that was kind of a revision of what we had said five years before.

But the other important thing, which is a little bit far from the clinical studies, in the meanwhile, it became quite clear that the same method could be applied, those and animal models. This is just an example of a paper we published 15 years ago on the effect of EPO on diabetic neuropathy in a streptozotocin model to control the diabetes and the regeneration of the fibers that will work very well. But also it became quite clear that we can use the biopsy to analyze with different techniques of the nerves. This is just comparable with the sciatic nerve analysis. This has been used mainly in CMT models, but this is

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fine. You see here, that's a model of a CMT4 with the outfolding myelins.

Let me go on to the point. In 2005 and '10, there had been the standardization of the procedure and the country rules for both the technique with the agreement that distal leg biopsy was enough and was fine for diagnostic purposes in small fiber neuropathy, and that the preclinical model of peripheral neuropathy could be -- I mean, the biopsy was fine also for assessing them. But the other important thing is that interlab standardization on the procedure and the counting is a very relevant issue. It remains a very relevant issue.

Moving on, in 2010, we with a group of 9, 10 labs worldwide, we provided this normative reference arranged for clinical use in this quite large group of healthy controls divided by sex and age decade providing this 5th percent cutoff, which you see is not the same over the different age groups. And indeed, what we found is that there is a the decrease by more or less, less than one fiber

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per millimeter for the [indiscernible - mic fades] -- without any major influence of height, weight, and BMI.

More recently, we made an assessment to see whether it was reliable making the biopsy on the right -- or on the left side, because actually these are mainly patients targeting this examination on the patients with symmetrical polyneuropathy, that by definition it's symmetrical. And we found there was great agreement between the sites, but also, and I think it is quite important, there wasn't any variation within 3 weeks. And 3 weeks is the turnover time of the keratinocytes.

So these fibers, which enter this ecosystem, which is the epidermis crossing a very tight barrier, their density does not change while the keratinocytes make their own turnover up to the stratum corneum, which strengthens, I think, the use of the biopsy in clinical practice but also in private [indiscernible].

Then more recently also the

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immunofluorescence group provided the normative references divided again by sex and age decade, and quite interesting, they found that there wasn't any influence of the BMI and that there was a decrease of more or less a 0.5 fibers per millimeter per each decade, quite interesting because when we compare the two techniques, we found that actually there was this ratio, which is known. We find you can count many more fibers when you use the immunofluorescent technique, and the ratio was 1 to 2, so it is the same looking from another perspective with a very good diagnostic agreement if less than one fiber under 5th cutoff was tolerated.

It is another important thing that has to do with the diagnostic judgment. So when can we say if a biopsy is normal or not normal in an individual patient? Well, this agreement has to do with this very nice work that has been done at Mayo [ph] and other previous -- in which it has been suggested that the variation of less than one fiber is comparable to this 0.4 plus 1.5 magnet of

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the inter-rater variation on the same section.

So it brings to the consideration that the values, which are very close to the cutoff, just normal, must be considered with caution before providing a diagnostic judgment. And the other important thing is that this group in Germany tried to see what happened when three observers assessed the density -- I mean, they were pretty bad, although they were in the same center. And it was a disaster, but it was really great that they published it.

(Laughter.)

DR. LAURIA: It was really great because they said, well, we have trained all together. They are doing exactly the same, but why?

Well, that brings me to point number four, what we have learned and what we've got so far, that we have age and sex adjusted, the normative value for both the techniques, that we have an excellent agreement between the right and left side inpatient with symmetric neuropathy, that there's no variation at 3-week follow-up, and there is an

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exit agreement between the two techniques. But we also know that the density is just a vehicle [ph] of calculation because it's based on the technique used and on the agreement its intrinsic variability, and the fact that it is really mandatory training and also an external quality control of the skin biopsy lab.

So what is the sensitivity and specificity of this technique? Provide different results in a patient with a typical picture, distal leg or feet.

Let me show you the experience we've got in the last 20 years. So this is the number of biopsies at the distal leg we have done divided by year, so more or less 3000, and this is what has happened. So looking at the results that we have redefined using the normative that was available since 2010, what has happened in our center is that for 10 years, the number of blue is positive and red is negative. Blue is abnormal.

For quite a large number of years, the number of what we have reported as positive -- so abnormal biopsy -- was extremely higher than those

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negative. But things have changed more or a here in 2010 because now we have about 80 percent of the patients come in with an abnormal biopsy. I wondered why.

DR. FELDMAN: A similar situation, in the percent that are abnormal.

DR. LAURIA: Right. So we can share our thoughts.

So point number 5, based on the skin biopsy, for more than 10 years, our lab, and many others I think, reported what I think was a very high rate of false positives and likely a lower rate of false negatives. The figures started changing for two reasons, my understanding, the variability of the normative data and focused approach to the clinical situation of the patient, so leaving away the emotional booster that brings any new technique available in medicine, in general.

Let me go back to this paper that, actually, yes, it's been -- rough times. The point is that we thought there isn't any gold standard for that. That's a key question also for the things I will

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tell you later, very soon. When there is no gold standard, many diseases you can say a panel of expert people could set what they think is the gold standard; repeat or not, but if you have to go through this.

This is what essentially we said. Let's consider a patient with a putative disease, so with a putative small fiber neuropathy if he has 2 of 3. So clinical science, this goes in keeping with the definition of neuropathic pain that has been provided in 2008; QST abnormal threshold for the functions related to the small fibers and the reduced biopsy. In this way -- you know this -- the biopsy got this sensitivity and specificity, but this cutoff value were calculated on the ROC curve, not using the normative data, compared to 46 healthy subjects. And with this value, these are the figures that came out.

So comparing this to all the other studies, so the diagnostic efficiency across the lab, what happens? If you look at the specificity, so the true negative, it's always very, very high, since

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1998, so since the first one. Well, let's focus on the DL, on the distal leg. But if you look on the sensitivity

rate of true positive, it is ranging, in a way, very wide spectrum, and actually it remains unclear because it goes from a 0.35 to 0.90.

Again, following our experience -- Yes?

DR. FREEMAN: I'm sorry to interrupt, but can I ask, when you created your ROC curves -- and I've never really thought about this in the paper. But you said --

DR. FELDMAN: Do you want to use the microphone, Roy, so we can hear you.

DR. FREEMAN: Roy Freeman speaking. When you created your ROC curves, you used a flexible value for the intraepidermal nerve fiber density because it looked like there was a value of 7 against which you used the cutoffs as normal versus abnormal.

DR. LAURIA: Yes, because at that time, we were using the cutoff, which was a set since the 1998 paper that was 13 plus, with a 6 point

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something standard deviation. So essentially, if you look at all the papers, at that time, they reported that 7 point something was the mean cutoff used to discriminate between the negative and positive, and then the ROC could assess -- the level at which you can get the best sensitivity and the best specificity.

Clearly against the gold standard, it was an intrinsic, self-reporting.

DR. FREEMAN: But what I'm really asking, did you make that flexible or did predefine --

DR. LAURIA: No, no. We set it.

DR. FREEMAN: You set it. Okay.

DR. LAURIA: Yes.

So again, our experience, if we look at the density of the fibers in the different types of neuropathy -- this is mixed, large, and all these are pure, not much change. And what happens is if we compare the patients by pain, which is the most relevant thing, at least appears -- what happens if we compare blindly two groups of patients with this range of pain as you see here, you see the subset

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of patients may be not so large. Bu you see that the distribution of the value is pretty much the same on them.

So the point is what is the ratio with pain if you have a normal innervation or you have a decreased innervation? So essentially -- and this is the question we put 10 years to go with Clemens [indiscernible] Sommer and this paper. If the number of your fibers degrees from the normal to almost complete innervation, what happens? What is the relation with the clinics?

What we know is that, clearly, if you take a biopsy in a skin area where a patient complains of pain or sensory disturbance, as in this case of notalgia paresthetica, you clearly see that there is a loss of these fibers. So the fibers are lost, are done. There is some relations with the clinical picture. And this is what happens in small fiber neuropathy. But in a painful condition like negative erythromelalgia, it has been shown that the fibers can remain there.

So this is just to remember that they used

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to be a pre-digital [ph] area. These fibers reappear, so can regenerate why the clinical picture recovered. So this is an example. This is another example in the patient treated with steroids. So this is another example showing that the underlying disease goes better, and the pain goes away, and the regeneration of the fibers is pretty clear here. And this is the other example on the changes related to the prediabetic neuropathy patients.

So what we know essentially is that these fibers goes away. There is a relationship with the clinical picture in terms of the sensory symptoms and pain, and that the patient with painful neuropathy can still have a complete innervation of skin. Where the pain comes from here is not that clear, but keep in mind that also patient with complete insensitivity to pain can have a complete innervation of the skin.

This is clear. This is from a case with an hereditary sensory autonomic prototype 4. And this brings us to something that has been commanded

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yesterday. So what happens in patient with conditions in which essentially there is no pain? Again, some disease, yes, there might be some in ALS. We have revised our [indiscernible - off mic] with about 60 patients, and 75 per cent of these patients without pain have a complete innervation of epidermis. And there isn't any correlation with genotype; this is facial and so on [indiscernible]. But underlying this, we have used a couple of animal models, of ALS animal models, to demonstrate that also in the animal models, very early, there is a complete innervation of the skin that you see here, and that in this model, it will be attributed to a specific neurotoxic effect of a splice variant of peripherin targeting exactly the small size neurons and causing a change in the assembly of the neurofilament.

So going to the point 6, biopsy results blind to the clinical phenotype is really little informative. That's an important thing. The other point is that the availability of the cutoff value based on the 5th percentile made a skin biopsy with

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a fixed clear specificity, which is 95 percent, which is the number of true negative. But to me it is impossible intrinsically to test the sensitivity, so the number of true positives are the method because again, it is a self-reporting thing. We don't have the gold standard, so we have to decide what is the gold standard.

Again, it is impossible to define what is the positive predictive value and the negative predictive value, so the percentage of those below the cutoff will truly have a neuropathy or do not, which actually vary also with the prevalence of disease in the population. I have to tell you that we know little about that. This is what happens in terms of a change for the positive and the negative. So the high prevalence increases the positive predictive value and decreases the negative.

A few things regarding the epidemiology of the disease. To my knowledge, this is the only focused paper, my friends in Maastricht, and things they've done, which is essentially one-tenth of

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stroke, 11 [indiscernible] per 100,000, more or less.

So what is the conclusion, my conclusion? The strength. We have sex and adjusted normative value, which is tailored to patient. It's a good agreement within the two methods. We can use either, and that's fine. It's a very good method, which is reliable also from the animal models. In humans, there is a high reliability between sites and 3 weeks. Also, there isn't any influence, any biological influence for the [indiscernible - off mic], and there's a high specificity.

So it is a reliable, confirmatory tool in candidate patients. This is what we want in a randomized clinical trial, I think. We want to know the number of true negative. The limitation, there is a poor interlab agreement without the quality program, so it is mandatory for a multicenter because we don't know the sensitivity. We don't know what is the positive and the negative predictive value, so it is useless as a screening tool, simply.

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Finally to me, it should not be used as a unique tool to determine the patient, the subgroups, and it opens a number of issues related to a number of other pain syndromes. So there is another number of other issues, but I don't have time. One is the morphology of the fibers; another one, what I think would be interesting, the measurement of the dermal nerve fiber length, this was an unbiased assessment that we did in which we found a very nice correlation with the dermal nerve fiber density, but maybe we can discuss it later. Thank you.

DR. FELDMAN: Perfect.

(Applause.)

DR. FELDMAN: I think again with the idea of staying on time because we have such a long time for discussion also, we'll just keep moving forward. So next is Rayaz and CCM.

Presentation - Rayaz Malik

DR. MALIK: Thank you, Roy.

The question is, to the audience, is corneal confocal microscopy ready for prime time? And I'm

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sure you're all saying no. So here's my next 20 minutes or 25 minutes to try and convince you otherwise.

This is the technique, corneal confocal microscopy. It's relatively rapid in expert hands, non-invasive, it's repetitive, and it images corneal nerves. These are nerves and cells that we can image in the cornea patients, whether it's in the clinic or whether for cohort studies, or for clinical trials.

Corneal nerves, while they are derived from the ophthalmic division of the trigeminal nerve in the skin, we know there are 200 nociceptors per millimeter squared, but the cornea is actually claimed to be the most density innovative tissue in the body. Dominantly it is sensory nerves, probably in humans, actually. In animal models, there is debate as to the proportion of sensory sympathetic, parasympathetic, but in humans, it is predominantly sensory nerves with the cell body in the trigeminal ganglion, and they express substance, BCGRP, so neuropeptides. And there is a

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small proportion which are sympathetic, which again expressed the usual propeptides.

Corneal nerves, what are they? Well, you can scan through the different layers of the cornea and capture the layer that you need to capture, which is the subbasal nerve plexus. This is what we're interested in or we can image readily. We can't actually image these nerves very well, and these are I guess equivalent to the intraepidermal nerve fibers. So what we're really looking at is the dermal or the subbasal plexus. And if you look at electron microscopy, what you see is very similar to the skin, these are the bundles of nerve fibers. And in cross-section, you can see these are the unmyelinated axons.

So what we have done -- actually, I can't remember, Giuseppe, when INF started or really hit prime time; probably a long time before. But the first study, actually, that was done for CCM is 2000, and it was a lady called Maria Rosenberg who's an ophthalmologist in Finland, who described the potential for looking at the corneal nerves and

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relating it to MNSI.

Around about that time, we actually started a study, which is funded by the JDRF, and we set up a protocol, which allows you to capture 6 images per patient. This is a typical or very good example of corneal nerves, you can see. And essentially what we've done is set up a protocol which allows you to quantify this in an objective way. So one of the key parameters is corneal nerve fiber density, which is the large nerve fibers that run at least 75 percent of the image, and we calculate, really 1, 2, 3, 4, five, no, 5 nerve fibers, and then you calculate the density.

The other additional parameter, which I think is important, is corneal nerve fiber length, which is the total length of nerve fibers present in a given image, and then corneal nerve branch density, which is the number of branches. And more recently actually, we've looked at the area of these nerves as well and we believe that that is probably the best way of looking at nerve repair. So essentially, these are the parameters that we

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measure.
To take away the subjectivity that is always present when you take one person who thinks there's an INF there or There's a corneal nerves there, We've actually got an automated system that we developed with image analysis engineers, whereby you can take an image and instead of measuring it and taking 30 minutes and not really being sure whether this is a nerve fiber or isn't, automated image analysis takes about 25 seconds, and you can see that there's a very good correlation between automated and manual assessment. So that's actually freely available to anybody who wants to use it.
So what we've set about doing is to convince people in the audience or other people whether or not this is worthy of becoming an FDA endpoint. And really, if you go to the FDA website, they say to you that you need to fulfill certain criteria. So is it a biomarker? Is it a physical sign or laboratory measurement that occurs in association with a pathological process, and does it most

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importantly have diagnostic or prognostic utility?
In terms of diagnostic, this is the first study we did from actually an innovative grant from the JDRF for $53,000, and what we showed in that particular study using the old corneal confocal microscope, which is this is actually from the new HRT III, but this was from the old one, which weren't as good, the images, that compared to healthy controls subjects, you could see diabetic patients with mild moderate and severe neuropathy, there was a progressive reduction in corneal nerve fiber length.
Subsequently -- and actually meta-analysis was done in 2016, but there are many more studies now. There've been other centers, including our own, which were included in this meta-analysis where there were over 1600 patients that compared 550 with diabetic neuropathy, 590 without diabetic neuropathy, and 500 healthy controls. And you can see that they actually more or less show that corneal nerve fiber density, branch density, and length differentiates controls from those with

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neuropathy, and also actually detects an early deficit even in those considered to have no diabetic neuropathy because the diagnostic criteria that were used were symptoms and signs in neurophysiology. So this is showing you that corneal confocal microscopy is detecting early small fiber neuropathy with good p-values in terms of significance.
Also have a normative data set. This particular one we published is 343, but we now have in excess of 700 healthy subjects. But what you see here is this is very similar to the INFD. There is progressive reduction with age, not as marked actually as the INFD. You can see the IFND starting around 10 and it gets down to 1 by the time you get above 70. But there is nevertheless a progressive fall in the different parameters that you see, and this is age related. Again, similar to INFD, actually there is no effect of weight, BMI, and sex.
The other measure that we think may be a better measure is corneal nerve fiber size, which

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actually is not looking at individual nerve fibers, but looking at the area of these corneal nerves. And what you see here is this is corneal nerve fiber density. You see progressive fallout for the increasing severity of neuropathy, and this is nerve fiber; again, progressive fallout with increasing severity of diabetic neuropathy.
In addition, if you look at the area itself, if you look at the size frequency distribution, you can see these are healthy controls and these are diabetic patients with increasing severity of neuropathy. And you can see again. So this is showing you that there's a difference between diabetic patients with progressively increasing neuropathy severity and healthy control subjects.
In addition, if you look at the sensitivity and specificity, or the AUC, the area under the curve, for these different measures, nerve fiber density, nerve [indiscernible], nerve fiber length, nerve fiber area, what you see is that even in people with relatively early or minimal diabetic neuropathy, there is actually an AUC which is

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approximately 0.8, and this gets much better the more severe your neuropathy, which is what you would expect in terms of a diagnostic measure.

There is now, hopefully impressed, because he's just gone back with the second review, pooled multinational consortium study, which was done with 998 participants from five different centers, which included 516 people with type 1, 484 with type diabetes. And in this particular study, despite the fact that we had different diagnostic tests that were used to define neuropathy, despite the fact that we had different protocols that were used to actually undertake the CCM from using 1 image to 8 images, we still get an AUC which is comparable between the automated and the manual system for corneal nerve fiber length, which is around 0.71, and the sensitivity and specificity was around 68 and 66 percent, which, again, fares reasonably well compared to QST.

A big question always that I'm asked is, CCM, how does it compare to intraepidermal nerve fiber density, which is the gold standard. And to

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address this, we did a study of about 80 patients and healthy controls subjects, and essentially what we did is we compared skin biopsy in the dorsum of the foot with corneal confocal microscopy. And we looked and essentially asked how good was each test for identifying diabetic patients with neuropathy based on symptoms, signs, neurophysiology. What you see actually is that the sensitivity for corneal nerve fiber density was better than intraepidermal nerve fiber density, and the specificity was comparable.

In a further study we've just published, we again recapitulate that with a larger cohort where we've compared skin biopsy with corneal confocal microscopy. So this is the ROC curve for corneal nerve fiber density, length density actually, and this is intraepidermal nerve fiber density. And you see here using the optimal cutoff, so CNFD, INFD, that the AUC actually for corneal confocal microscopy is 0.81 compared to 0.73, and the sensitivity 0.77 for CNFD compared to 0.61 for INFD, 0.79 and 0.8.

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The other question that is always asked is, well, you know, corneal nerves, they're short nerves, they're up there. They don't really have this dying back process. So in order to address this, actually, what we've done is looked at the cornea itself and looked at more proximal central parts of the nerve compared to the more distal inferior wall. So we've compared changes in the same patients proximally and distally.

This is a map of a cornea. You can see here, this is the central bit and then you have the inferior wall down here. And what you see actually is if you look at the length of nerves in the inferior wall compared to the central more proximal bit, there's actually greater damage in the more distal inferior wall compared to the central part. So you can see here, this is diabetic patients with diabetic neuropathy. Without diabetic neuropathy, the gradient is much greater than the central corneal nerves.

Prognostic utility, there are actually three independent studies, but this is two independent

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studies published 156 patients recruited with type 1 diabetes. At recruitment, 101 had no neuropathy. They underwent assessment to exclude neuropathy or include neuropathy based on nerve conduction symptoms and signs, and they underwent baseline examination for neuropathy measures and ophthalmic measures.

Ninety patients were reexamined after 47 months and 18 percent then developed neuropathy according to this criteria. We then went back and looked at what measures, in terms of demographics, lifestyle, neuropathy measures, ophthalmic measures, were different in this group who developed neuropathy compared to those who didn't develop neuropathy. And what we show is that the retinopathy stages according to ETRS criteria was different. So if you developed diabetic neuropathy, then you had a higher neuropathy score, but corneal nerve fiber length you can see was significantly lower in those who develop diabetic neuropathy compared to those who didn't develop diabetic neuropathy.

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Another study from Canada from Bruce Perkins group, 65 type 1 diabetic patients followed over three years. You can see very similar incidence of diabetic neuropathy based again on the same criteria; 17 percent developed diabetic neuropathy. They actually exhaustedly looked at risk factors for developing diabetic neuropathy, and in addition undertook very detailed neurophysiological examination, quantitative sensory testing, LDI flare, and corneal confocal microscopy.

When you compared those with new onset diabetic neuropathy with those who didn't get diabetic neuropathy, you see that there is no difference for TCNS, neurophysiology, abrasion [ph] perception, and autonomic function or LDI flare. But you can see corneal nerve fiber length significantly reduced in those who develop neuropathy compared to those who didn't.

Is it clinically meaningful as a measure of how the patient feels, functions or survives? Well, for IFSN, we did a study now almost eight years ago where we showed that in patients with

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idiopathic small fiber, 25 patients referred by the neurologists exhaustively excluded all of the causes. ISFN, we showed that in fact there is a reduction in corneal nerve fiber density, nerve fiber length, and nerve branch density in patients with ISFH. Furthermore, these parameters correlate with the neuropathy symptom profile, neuropathy deficit score, and even the sural nerve conduction velocity.

Autonomic neuropathy is something that we believe is -- although the corneal nerves are predominantly sensory, we do find that in this particular cohort of patients -- so these are patients who had antidiabetic gastroparesis and severe diabetic autonomic neuropathy. You could see they had a significant reduction in corneal nerve fiber length, compared to healthy controls, compared to diabetic patients without gastroparesis. And you can see the AUC is actually spectacular in terms of nerve fiber density, nerve fiber length, nerve branch density, and very high sensitivities and specificities for these

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parameters for patients with autonomic neuropathy.

In a smaller cohort of people with idiopathic small fiber neuropathy, only 15. We've now looked and showed that 6 actually of these had autonomic symptoms. And what we now show is that corneal nerve fiber length was actually more significantly reduced in those with painful ISFN and also autonomic symptoms compared to painful symptoms alone, whereas skin biopsy didn't really differentiate the two. Although it was reduced in both groups, it wasn't different. Here you can see that it was reduced in both groups, but more so in those with autonomic symptoms. We've also got data on diabetic patients, painful and painless neuropathy, and we show actually that there is a reduction in those with painful neuropathy compared to those with painless neuropathy.

Other neuropathies, chemotherapy induced peripheral neuropathy is something that we've looked at in a small cohort of patients with esophageal and gastric carcinoma. And what you see is that, actually, even before they got

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chemotherapy, there's already a reduction in corneal nerve fiber length. And in fact what happens here is not that there is further reduction in corneal nerves, but in fact there is an increase in the number of nerves, which is consistent with on the third cycle, there is actually new sprouts or n regeneration going on. But this is actually related to pain, so much like Giuseppe has said, looking at actual nerve fiber numbers maybe is not that meaningful. You need to take the patient as a whole and you need to look at what's going on in terms of nerve fiber, not only damage but repair, in relation to pain.

Other conditions where we've looked at this CIDP. This is wit Mark Stettner from Germany and other inflammatory neuropathies. So you can see typically people would say, well this should be a large fiber neuropathy, but you can see corneal nerve fiber density, nerve branch density, nerve fiber length consistently reduced in all three conditions. And in addition, there are actually some cells, that you can see the Langerhans cells

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in here, which we've looked at, and you can see there is increased expression of these immune cells in this inflammatory neuropathy.

We also looked at people with HIV, so this is in collaboration with people in Imperial, Prof Rice [ph], where we've taken healthy control subjects, patients with HIV without sensory neuropathy according to the sensory score that they use in HIV, and patients with HIV sensory neuropathy. And you see here that there is a progressive fallout of nerve fibers more so in those with sensory neuropathy compared to those without.

In New York with a group in genetics, we've actually looked at patients with Friedreich's ataxia where we have again shown that patients with Friedreich's ataxia were significantly low accordingly on nerve fiber density, branch intensity, and length compared to healthy control subjects. In addition, we've also shown that the DAA triplet repeats, which are characteristic of Friedreich's ataxia, in terms of the frataxin gene,

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correlates highly significantly with the CCM values.

So in terms of CCM and other peripheral neuropathies, you can see that there's a whole host of conditions, peripheral neuropathies actually, that have been shown to have involvement of corneal nerves, including Fabry's disease, ISFN, hereditary neuropathies, CIDP, Wilson's disease, Graves' disease, amyloid neuropathy, and HIV neuropathy.

Is it a surrogate endpoint? Does it change in a clinical trial? The proof of principle study that we did many years ago -- the first one was 2007, subsequently in 2013, was diabetic patients undergoing pancreas and kidney transplantation. And we simply measured neurological exam, nerve conduction, skin biopsy and corneal confocal microscopy. And what we showed actually over 12 months is that nothing happened in terms of symptoms and signs, nothing happened in terms of neurophysiology, and although there was a trend for INF to increase, this wasn't significant.

What did improve at 6 months and at 12

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months in all three parameters was corneal confocal microscopy. And at that time, we were left with questions, which were, what does it mean if nothing else improves in terms of symptoms and signs in neurophysiology if these nerves are improving at 12 months? So we've now got much longer -- in 36 patients followed up for 3 years, what we see is that there is this continuous but progressive increase in corneal nerve fiber density, corneal nerve fiber length, and corneal nerve fiber area. But in addition, what we're now seeing at three years is an improvement in small fiber neuropathy symptom profile, an improvement in peroneal nerve conduction, and an improvement in sural nerve amplitude, which is at three years. And in addition in skin biopsies, intraepidermal nerve fiber density actually didn't really change and then had started to go up at 36 months, but isn't significant. But we've looked at an additional metric, which is mean dendrite length, which is the length of the intraepidermal nerve as it comes through the dermal/epidermal junction into the

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epidermis itself, so the mean dendrite length.

Here you see a significant increase at 12 months but also 36 months suggesting that perhaps intraepidermal nerve fiber density is good as a diagnostic, but perhaps not so good in a therapeutic trial.

ARA 290 is exploratory. I suppose it's a drug which has been suggested to have a particular impact on inflammation and tissue injury and tissue repair. So we've done, in conjunction with RM [ph] several studies now, ARA 290 in patients with type 2 diabetes, where we showed that nerve fiber density actually didn't -- it says 28 days dosing by the way -- didn't really improve much, but in nerve fiber length, you could see significantly did increase. In particular, nerve fiber area was increased as was nerve branch density.

Sarcoid neuropathy, we have shown similar changes, 28 days dosing increases in nerve fiber area at the lower dose and the higher dose. But in particular we also show in skin biopsies, there is a relationship between the improvement in corneal

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nerve fiber area and the expression of GAP-43, which is supposed to represent regenerating no fibers. And clinically relevant is the 6-minute walk test in sarcoidosis. We see a correlation with improvement in the 6-minute walk test and improvement in the corneal nerve fiber area.

An independent study by Vera Bril's group looked at omega-3 supplementation in neuropathy in type 1 diabetes published in Neurology this year, where they looked at changes over 12 months in terms of neurophysiology, quantitative sensory testing, and autonomic function. What they found actually, over 12 months, there was no significant improvement apart from a borderline improvement in peroneal F wave and I think vibration, with heart rate variability going down actually at 12 months. Corneal confocal microscopy, you can see here that there was actually a significant improvement in corneal nerve fiber length. Baseline 8.1 increased to 12 months to 10.1. There was also significant increase in corneal nerve branch density.

We have also got data in patients undergoing

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bariatric surgery. This is a cohort of about 40 patients with type 2 diabetes, and you see here over 12 months that there is actually an improvement in corneal nerve fiber density, corneal nerve branch density, and corneal nerve fiber length.

There are now 8 interventional studies. This is the SBK data, which is the longest, which is 36 months, but you can see this is the omega-3. This is cibinetide ARA in type 2 diabetes, in sarcoidosis, bariatric surgery, and you could see all consistently show that corneal confocal microscopy actually is able to show a change within 12 months and then progresses out to 36 months.

So we believe that we've kind of ticked most of the boxes. We need to do bigger studies and these are currently ongoing, particularly in terms of cohort studies for diagnosis; and started as kind of almost a single man operation in Manchester, then my collaborator moved to Brisbane in Australia and has now grown with many more centers that are doing corneal confocal microscopy

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across Europe, predominantly North America, South America, Middle East, China.

In fact, I'll read this out to you, but there are now 582 HRT III across the world of which there's about 18 in the US. But in the last two years, they've sold 160 to China. So you can expect some big studies that are going to come out of China very soon.

There are 562 HRT IIIs across the world, and there are actually 2100 HRT III machines which can be modified to become like the corneal confocal microscopes that we use. Thank you.

(Applause.)

DR. FELDMAN: We do have time for a couple of questions. I'd like to just make one comment, and that is you showed the Perkins study where 65 type 1 diabetics at nerve conduction studies were not a good marker of developing neuropathy. If you look at the DCCTE, [indiscernible], Jim Albers, published a paper of what was a 1,500 type 1 diabetics and showed that nerve conduction studies, particularly the sural amplitude and the peroneal

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motor conduction velocity was a very robust marker of developing neuropathy in that particular cohort over a five-year period.

How about questions? We have time for a few. Yes?

DR. STEINER: This morning, the discussions were great. The discussions today and yesterday were fabulous, so thank you. I'm coming at this from the industry perspective and looking at this -- for example, if your target is painful small fiber neuropathy, which is what we're interested in, how do you approach this with some type of an algorithm? Which is how Roy started out this morning, because if pain doesn't correlate typically well with IENFD counts, and the positive and negative predictive values aren't that good, and also if the IENFD counts are not as reliable, and mixed sensory neuropathies, QST with lower specificity would concern me to enroll those patients in a trial, and with low sensitivity we're not going to be able to enroll patients --

So basically, how do you screen for the

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target population that you want? And I'm also wondering in the context of how important the clinical judgment is, should we be considering something such as independent review boards, which we use in MS trials to confirm definite relapsed. So that's all.

DR. FELDMAN: So that's a fairly broad question for the two minutes he has, so why don't I ask you, Rayaz, just maybe to comment on your opinion on using CCM, where she has said -- she discussed skin biopsy, QST. Maybe you could just comment on CCM, and then that fairly broad question we can address during the discussion.

DR. MALIK: I don't think if you've got a trial where you believe that it's going to affect pain, you need -- it's not CCM or INFD, or even QST. I think they are to look at disease modification. That's where you've got to -- in terms of using these particular tests, whether it's INFD, CCM, or QST as entry criteria, I think we need to wait for the definition as to what we are going to propose as an inclusion for somebody who's

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got small fiber neuropathy.

DR. FELDMAN: Yeah, that's very reasonable. I think, again, to stay on time, then, we'll go to our final talk of the morning, and that's from David.

Presentation - David Herrmann

DR. HERRMANN: Just a couple of disclaimers before I start. I have no disclosures relevant to this talk. I'm not an expert in autonomic function testing. I have an interest in small fiber neuropathy and have been involved more on the sensory side of things. But because one of my former fellows got interested in autonomic testing, I'm speaking here today. So most of the work I'll review, people in the audience have contributed to.

I want to go back to this question -- as we think about autonomic testing in the context of small fiber neuropathy, I want to go back to what we're thinking about clinically because I find the term "small fiber neuropathy" to be too broad and not very useful for our purposes. They're clearly well-defined clinical subtypes or clinical

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syndromes that we can recognize. They may have different etiologies, they may be idiopathic, but we can recognize different clinical syndromes within this broad umbrella of small fiber neuropathy.

The one I'm going to be focusing on exclusively today in a laser-like fashion will be the distal small fiber neuropathy syndrome. I won't be talking about autonomic subtypes of small fiber neuropathy because the use of autonomic testing modalities in a syndrome that presents with dysautonomia is intuitive. I'll be looking at the data in distal small fiber neuropathies. I will not be looking at the data in non-length-dependent small fiber sensory neuropathy or neuropathies because there's relatively little systematic data of diagnostic testing and autonomic testing in those syndromes. So that's what I'm going to be focusing on.

With that in mind, I want to go back again to working definitions of distal small fiber neuropathy, and what you'll notice across most

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studies that have been discussed yesterday and across the studies I'll review, there are some cardinal features that allow you to enter a study or a coupled study. These include distal paresthesias or neuropathic pain, usually pain, but some are paresthesias. You need to have normal strength clinically. You have to have an absence of upper motor neuron signs. And in a qualified sense, you have to have an absence of significant large fiber sensory dysfunction. You also have to have normal nerve conduction studies.

Two qualifications, there's discussion about what absence of large fiber signs means. This can be a complete absence of large fiber science, which may be necessary to identify enriched cohorts that may have a sodium channelopathy, for example, but in most of the studies, trivial or mild distal large fiber sensory dysfunction has been included in this working clinical definition of what is distal small fiber neuropathy. There's also been varying rigor in what are normal nerve conduction studies. That's not my task today to discuss that,

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but there have been a range of different sets of nerve conduction studies applied.

Now you ask, why am I talking about these? Because nowhere on this slide is any mention of autonomic symptomatology, or autonomic testing, or autonomic characteristics. So the question is, in the distal small fiber neuropathy syndrome that we as clinicians recognize, dysautonomia doesn't appear as entry criterion in any of these studies. And this is for the borne out. There have been many cohorts looking at this clinically defined distal small fiber neuropathy. These are older ones. I'm aging myself. My name is on here. These are almost 16 years ago, early turn of the century.

But again, if you look at the clinical exam components of this, it's really examination of distal somatic neurologic impairment. There is no component of any autonomic testing clinically, and you'll see across different studies, some have included trivial distal large fiber sensory dysfunction.

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Others have been more restrictive.

So the question is why, again, think about autonomic testing? And the reason is across multiple studies -- and forgive me if I've included some cohorts of members of the audience who've done work in this area. But across time, across multiple studies, autonomics symptoms turn out to be relatively common in patients who present with clinically sensory dominant syndrome that I've outlined across various of these studies, and I'll highlight one study to make the point, that of Vera Novak.

So Vera looked at 92 patients who presented with painful feet felt to be neuropathic. Importantly, with respect to a question of dysautonomia, diabetic neuropathy was screened out of the cohort. She applied a systematic autonomic questionnaire to both the patients and to controls. And across the range of autonomic symptoms, some of the parasympathetic dysfunction, some of adrenergic dysfunction, the frequency of autonomic symptomatology on a standardized questionnaire was

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far higher across a range of symptoms than in control groups, suggesting that autonomic symptoms, if you inquired carefully, are relatively prevalent in the clinical syndrome of painful feet or distal small fiber neuropathy.

Now with that in mind, the question is, has autonomic testing being looked at given the relative prevalence of autonomic symptomatology across multiple cohorts? And the answer is yes. And I'll talk about a little bit of the data of some of the modalities and what modalities have been used. And again, I'm not going to cover every autonomic modality. I'm just going to pick on a couple.

Sudomotor function has been extensively interrogated, and most systematic studies in large cohorts -- and I'm going to focus on larger studies, not studies with 8, 10, 12 patients in primarily -- have involved evaluation of the sort of performance characteristics of QSART, quantitative sudomotor axon reflex testing. I will talk briefly also a about electric chemical skin

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conductance or SUDOSCAN, not because I believe the data is there in small fiber neuropathy, but we're going to be tossed with some recommendations at the end of this, and it's an evolving literature, and its use has also been expanding. So in the interest of being complete, I'll touch on that.

Thermoregulatory sweat testing has been another modality that's been evaluated. It's very sensitive, but unlike QSART it's not localizing. And I think this is important. If we want confirmatory tests or supportive tests of a distal neuropathy syndrome, we want those tests to be localizing to the peripheral nervous system. QSART is because it interrogates the postganglionic as sudomotor sympathetic fibers. Thermoregulatory sweat testing is abnormal in a high percentage of patients with distal small fiber neuropathies, but it's only available at a couple of centers, it's very tedious, and it's not applicable to multicenter studies, so I'll focus mainly on QSART.

Cardiovagal testing is widely available, and it's been looked at quite extensively in patients

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with distal small fiber neuropathy, particularly heart rate variability with deep breathing. There's been somewhat less study of adrenergic modalities, but they have also been studied in distal small fiber neuropathy, and these modalities, sudomotor testing, cardiovagal testing, and testing of adrenergic responses can be combined and have been combined in some of these cohorts in the autonomic reflex screen with calculation of a COMPASS autonomic severity scale or CAST scale. And I'll discuss this to some degree combining these modalities of testing.

Now, when autonomic function studies have been done in clinically defined distal small fiber neuropathy, the syndrome I described, it turns out they're frequently abnormal across a number of cohorts, and a pattern emerges. And the classical early study was that of Stewart, et al., who looked at 40 patients back in 1992; found they had a distal small fiber neuropathy syndrome. They were permissive of mild distal large fiber sensory dysfunction, and some 80 percent of 40 patients had

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an abnormal QSART response mostly in the distal lower extremities.

Cardiovagal testing by contrast was abnormal in only a small percentage of patients, 28 percent of patients. So Stewart, et al. back in 1992 concluded that sympathetic sudomotor fibers are frequently affected in the syndrome, and they suggested that evaluating of sweating is a useful diagnostic test. But autonomic nerve fibers controlling heart rate are less affected.

Moving forward in time to the study of Vera Novak, again, out of Ohio State, looking at 92 patients with painful feet, QSART abnormalities were again seen in 73 percent of patients. Very similar to the Stewart et al. study, the abnormalities tended to be length dependent mirroring the clinical symptomatology.

Cardiovagal tasting in their hands was also reduced in a fairly high percentage of patients, somewhat higher than the Stewart et al. paper. But in their hands, head-up tilt [indiscernible] testing, and measures of adrenergic function, they

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had no patients who had significant orthostatic hypotension or syncope in that particular cohort.

Phil Low's group from the Mayo Clinic in 2006 did a larger study, and they looked at 125 patients who again had that clinical syndrome of distal small fiber sensory neuropathy with a similar inclusion criteria to Stewart et al. in the features I outlined. And in 125 patients, basically, they changed this a little bit. They allowed patients to have trivial distal nerve conduction study abnormalities. They allowed inclusion of such patients.

So of the 125 patients, 78 had normal nerve conduction studies mirroring the typical distal small fiber neuropathy cohorts we've discussed; 47 had abnormal nerve conduction studies. And they arrived at the same result, 77 percent of patients had a distal QSART abnormality. And whether you had normal or abnormal nerve conduction studies, that percentage didn't change. Cardiovagal abnormalities and adrenergic abnormalities were also present in a significant percentage of

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patients, but again in a significantly lower percentage of patients than sudomotor abnormalities.

So I've gone through a range of studies here across time that suggest a high frequency of abnormality of QSART in the syndrome, less so of cardiovagal testing.

DR. RUSSELL: David, in that paper, how did they really define small fiber neuropathy?

DR. HERRMANN: So each of these -- and I'm getting to Giuseppe's work now because this was the first real attempt to define it. All of these --

DR. RUSSELL: In that paper they didn't do intraepidermal nerve fiber.

DR. HERRMANN: No. So all of these, whether it be Stewart in 1992 before skin biopsy, this is a clinical case definition, some with no large fiber signs, some with mild large fiber signs. But it was a clinical symptom and sign definition.

Now I come to the seminal paper of Devigili et al. and Giuseppe Lauria's group that really transformed the field from thinking about

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sort of clinically suspected or a clinical syndrome of distal small fiber neuropathy to say can we integrate these tests, these adjunctive measures, supportive measures, objective measures, or standardized measures into some set of actual diagnostic criteria that we could use going forward. And we've heard a lot about this.

I'm going to speak a little bit more on this topic, but I want to make one point. In Dr. Lauria's cohort, almost 50 percent of patients had sudomotor or vasomotor symptoms that were not included in the diagnostic or inclusion criteria, and a high percentage had the abnormality of laser Doppler flowmetry. So again, autonomic dysfunction was fairly prevalent in this cohort.

So in reading this, one of my former fellows who's now the head of neuromuscular at University of Nebraska, Parawat Thaisetthawatkul, who I think was a fellow at Rochester in 2001, he went on to do a peripheral nerve fellowship with the Jim Dyck and then an autonomic fellowship with Low. So he basically felt well qualified to maybe look at this

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question. He said, "David, with all this data on QSART, can we add autonomic testing to the criteria of Devigili et al?"

So he looked at patients who had sensory symptoms, most head pain without muscle weakness or upper motor neuron dysfunction. And they had very strictly normal nerve conduction studies, including either a medial plantar being normal or peroneus tertius, or EHL, in addition to standard distal nerve conduction studies. They underwent QSART sought with a Q-Sweat device; turns out to be relevant. QST skin biopsy, which was read in a moss [ph] fashion in our laboratory to look for evidence to support small fiber neuropathy.

In his clinic, about 1200 patients had been referred during the accrual time; 535 patients had clinically defined peripheral neuropathy or suspected peripheral neuropathy. Over 400 had large fiber features and were excluded because they didn't meet these inclusion criteria, but 101 had clinically suspected small fiber neuropathy, sort of fitting prior cohorts. The characteristics of

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these patients I won't go through, but we heard yesterday talks from Gordon and Rob Singleton and others relating to risk factors and testing across this disorder.

Diabetes was somewhat underrepresented in the cohort, and alcoholism had high representation. I wonder about alcohol, whether it depends on how systematically you ask about it. But leaving that aside, what he did was he took those 101 patients and he said how would Devigili criteria perform in this sort of validation cohort if you'd like in identifying or supporting small fiber neuropathy in a clinically suspected cohort.

Just to go over the Devigili criteria, you needed symptoms of sensory neuropathy, normal nerve conduction studies, which perfectly mirrored Parawat's inclusion criteria, but then you need abnormalities on 2 or more among small fiber examination, QST, which was just elevated thermal thresholds, and IEFND distally. And in this cohort, about 38 percent of patients met the Devigili criteria of patients who had a clinically

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suspected small fiber neuropathy syndrome.

Then Parawat said can we integrate autonomic testing and how does that modify the diagnostic yield, if you will? So what he said as a hypothetical criteria, he said in these patients let's set as a criterion that patients need to have two or more abnormalities of QST. There was one difference which may be relevant, is he added in heat-pain threshold testing, and this was all done on a CASE IV device, and QSART, INFD.

If you did that, you had a diagnostic yield of 56 percent, but you needed abnormalities on two or more of these three modalities. But we realize in practice that not every center test has INFD, QSART, and a CASE IV QST machine, but that may be feasible in a trial, but clinically not. So he said can we have a more relaxed set of criteria, and he did that with what Gordon Smith talked about yesterday in mind.

Because we know in the clinic, our pretest probability of neuropathy is not universal, so recognizing that not every center may have

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this -- and from prior data, we know that if you have an abnormal pin exam, so you don't just have symptoms of small fiber neuropathy, but you have signs that are supportive, your pretest probability of a definable neuropathy on some confirmed interest such as intraepidermal nerve fiber density, is higher.

So he said if you have an abnormal clinical exam, can we relax those criteria by just requiring one or more abnormalities of either QSART, INFD, or both? We didn't include QST as a confirmatory test for the following reason. There was a 2003 AAN guideline, including Peter Dyck as one of the co-authors that said that because QST is non-localizing to the peripheral nervous system, a psychophysical test, it shouldn't be used as a sole diagnostic criteria and confirmed presence of neuropathy. And so using that, they've had a normal pin exam where the pretest probability of neuropathy was lower because all you had was symptoms, and he still required the stringent criteria of 2 or more abnormalities among these

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three. And it really didn't change by relaxing the criteria. It really didn't change the diagnostic yield much.

I won't go into the individual sensitivity and specificity if you use these as the gold standard of QSART, QST, and skin biopsy. But just to make the point, in this cohort, QST was quite sensitive, but it had quite poor specificity if you used these criteria as a gold standard.

Yes?

DR. HAROUTOUNIAN: Just a quick question maybe. Are those the same patients, the 56 versus 57 percent, or as a Venn diagram, there are some patients who fell out of those --

DR. HERRMANN: Same patients, just different set of -- you're changing the criteria slightly. But when we looked at whether you could just use QSART alone using this is the gold standard, or the reference standard, or QST alone, or skin biopsy alone, these were fairly sensitive QSART and skin biopsy performed relatively well and had reasonable specificity and positive predictive value. But QST

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was quite sensitive but had poor specificity.

So really what Parawat concluded was that assessment of both somatic and peripheral autonomic fibers does enhance diagnostic criteria for small fiber neuropathy, and then he wanted to know why. And just very briefly, in a follow on study with patients with similar clinical features, what he did was he did more comprehensive autonomic testing with autonomic reflex screening test and computer, the CAST. So this included cardiovagal testing and adrenergic testing as well to QST again and skin biopsy.

Just by way of brief conclusions, there was no association between ankle INFD, any QST measure, and the CAST QSAR subscore, the CAST vagal [indiscernible] score, the CAST adrenergic score, or total CAST. So his conclusion was that, really, in this population of patients, the involvement of different populations of small fibers can be relatively variable, and therefore the autonomic evaluation does give an independent look, really. It's not duplicative of somatic

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evaluation.

DR. SMITH: Sorry to interrupt, David. My curiosity got the better of me. Was there a phenotypic difference between the 56 or 57 percent who met his updated criteria versus those who did not? Did they look the same or did they look different, from just a clinical perspective?

DR. HERRMANN: So I don't have a perfect answer because we didn't look at those patients at that granular level. I think we should go back and look at that. In terms of the broad inclusion features, distal sensory symptoms and pain, normal nerve conduction studies, normal strength, et cetera, they were the same. But I think going back and looking again in more granular detail at those who met or did not meet the criteria I think is a good question, and can't answer that now.

So there was no correlation between these measures, and that's why he concluded that looking at both autonomic function and somatic function may potentially be synergistic. But there's a cautionary note in all of this, and that comes from

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Amanda Peltier and many in this room, that really the reliability QSART is questionable. This was a small test/retest reliability study, but when you Q-Sweat, WR Electronics version, was performed on consecutive days, it had a poor rate cross-correlation coefficient from one day to the next of 0.52 at the foot; so if you just looked at the foot alone.

If you go back and look, if you look at Phil Low's work, he said QSART's highly reproducible. But if you go back -- first of all, it's a different set of equipment, and if you go back and look at the statistical methods used in those early 1980's papers, it's, it's hard to know what statistics were used, whether it was an intra cross-correlation coefficient or a PCN correlation coefficient, it was not well defined.

So I think this is a cautionary study. And again, this has been followed up by additional test/retest reliability testing that raises the same concerns.

Amanda?

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DR. PELTIER: Can I make one point?

DR. HERRMANN: Yes.

DR. PELTIER: So we are in the process of publishing -- we did a repeat reliability study, and one of the things that we found was that temperature, skin temperature was a very important factor. So if you made sure that their limbs were warm and that they were warmed to at least 31 degrees Celsius, that that significantly improved their reliability.

But if you don't do that -- and we did not do that in the first study because we didn't realize that it was an issue. So when we did the second study and we talked about David's slide [indiscernible] and the Mayo group, we did that, and it does significantly improve the reliability.

DR. HERRMANN: So that actually is a little reassuring because there is this question of what device, because what's available is Q-Sweat that you can buy from WR Electronics. But in the older Mayo studies, they used their homegrown device.

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And it turns out that the relationship of Q-Sweat to QSART is very poor. From their own data, Q-Sweat volumes are lower than Mayo QSART at for 4 skin sites. QSART and Q-Sweat volumes have poor correlation, and Q-Sweat results in a less efficient acetylcholine iontophoresis.

So I will have a couple of summary slides on my thoughts in just a moment, but I would say that this test looks sensitive. It adds to what we can achieve with just somatic testing. Whether it can be extended across multiple sites and multiple time points in centers is something to be discussed.

Very briefly --

DR. RUSSELL: David, sorry. Can I just make a point here?

DR. HERRMANN: Yes.

DR. RUSSELL: When you're looking at reproducibility, if you measure the sweat volume, that's the problem, so the actual volume. If you say to yourself, I'm going to define this by normal versus abnormal, or I'm going to define it by a percentile, then reproducibility may be much

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better.

DR. HERRMANN: Okay. So briefly, SUDOSCAN, and then I'll have two slides where I just summarize my thoughts.

DR. FELDMAN: You're fine on time.

DR. HERRMANN: Okay. So SUDOSCAN, there's been a proliferation of use of this. Many in this room now, or several, have done studies of it. And I think what's been attractive is that it's simple, and it doesn't have some of the administration issues that Amanda and James and others have pointed to with QSART.

So most of the studies of this have been in diabetic peripheral neuropathy, and that's important here. But it's been marketed -- I say marketed -- as a biomarker of sweat gland or sudomotor function. And it's very simple. You apply your hands and feet to stainless steel platforms shown here. And by the way, there are many, many studies that are literature.

I focused on ones of experienced investigators that we know. This is a study from

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Solomon Tesfaye's group, and how this works is a direct current, less than 4 volts, is applied to the platforms which function as electrodes, and there's a reaction, as I understand it, between nickel in the electrodes and chloride in sweat, resulting in a reverse iontophoresis. So you get chloride conductance. And then this gets quantified as the ratio between the observed current that's generated and the applied voltage, and the units are microsiemens or ESC. And it takes just 3 minutes, and it doesn't require special expertise, at least to cut conduct the test.

In Solomon Tesfaye's diabetic neuropathy study, he showed a marked difference between those with DPN and no DPN when using a cutoff of 77 microsiemens at the foot with lower conductance in those with diabetic neuropathy. But this was severe diabetic neuropathy. These surals were absent on average. The peroneal velocity was 32 meters per second. The peroneal EDB amplitude was 0.3 millivolts.

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In this cohort, the performance characteristics were relatively good. Area under the ROC curve was 0.85, very high sensitivity. But specificity is a diagnostic test of 76.2, I think, but lacking. But anyway, it looked promising in his hands.

Gordon did a study, and Rob Singleton, in a predominantly diabetic cohort with 42 controls, and they were diagnosed based on the Utah Early Neuropathy Scale, and they used a slightly lower ESC at the foot of 70. And they got performance characteristics that were as good as skin biopsy in this cohort; sensitivity 77 percent, but specificity relatively poor at 67 percent; positive predictive value poor at 59 percent, but similar, identical virtually to skin biopsy.

I would argue that for these tests, we would want to see ROC curves where the inflection point is more defined in the upper left-hand corner for really tests that have rigorous performance characteristics. But the point was this looked similar to prior skin biopsy.

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It turns out that Dr. Vinik is very positive about this technique. In his study, he got remarkable performance characteristics of SUDOSCAN in 83 patients with diabetes, with at the foot; a sensitivity of 78 percent; 92 percent specificity; positive predictive value of 74 percent; very strong negative predictive value box. But there are some cautionary tales, and they come from Brian Callaghan and others from the Michigan group who looked at accuracy of neuropathy, not in diabetics but in individuals with obesity, a new challenge for neurologists and sort of pertinent to what we're talking about today. And they looked at a wide range of measures.

I'm not going to go through this, but in their 120 patients, 18 of them had clinical SFN defined by symptoms and an abnormal exam; so a small number of patients, but really the preceding cohorts of Solomon Tesfaye -- I'm not sure too much about your cohort, Gordon -- they were more DPN cohorts as opposed to a nondiabetic predominantly small fiber neuropathy cohort.

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But in any event, SUDOSCAN performed moderately with AUCs in 0.7 range. QSART performed poorly here, but I'm not sure whether some of the temperature issues and other issues were addressed.

DR. FELDMAN: We did [indiscernible] go over temperature.

DR. HERRMANN: You did?

DR. FELDMAN: Yes.

DR. HERRMANN: So basically, sudomotor function testing was not particularly promising in this cohort, but a relatively small number of small fiber neuropathy patients. And very similar, Rodica's cohort, again, from University of Michigan. Another cautionary note, 37 patients with type 1 diabetes, 40 controls underwent SUDOSCAN and cardiovascular tests, autonomic reflex testing. There was no difference in SUDOSCAN measurements at the foot or hand in type 1 diabetics and 40 controls and no relationship between SUDOSCAN and cardiovascular autonomic reflex tests.

So I think there are some interest here, but

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there's a lack of data in larger, well-defined small fiber neuropathy cohorts, so we're not at a point where this can really be recommended, in my view, as part of diagnostic criteria.

So just to summarize, I have two slides left. One is what guidelines are there on how we should be using autonomic testing in distal small fiber neuropathy at this point, and they come from the 2010 AAN and AANEM guidelines. Many of us were authors on these but did not write the autonomic section of these. That was sort of led by Phil Low.

Really, I'd say that autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies. We know that, but the evidence rating and the recommendation was weak in distal small fiber sensory neuropathy. They felt that it would be better if you used a combination of sudomotor testing, cardiovagal testing, and adrenergic testing to get a higher degree of accuracy, but I think it's not practical across multiple centers,

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multiple sites, multiple time points to do a full cast or even a modified cast.

So I think while doing one autonomic test such as QSART with the standardization that Amanda and James and others have report to may be feasible and well trained investigators, just like you need training for QST or skin biopsy, you need this for QSART. But I think a full cast while may be dealing with some of the issues with single strategy testing is probably not feasible in a clinical trial setting, at least multicenter trial setting.

So to summarize, symptoms of dysautonomia and sudomotor dysfunction are common as far as we know from the published literature across multiple codes, including cohorts that have a high number of idiopathic patients. Sudomotor testing, I do feel, as diagnostic sensitivity and distal SFN, based on the work of Parawat, afferent and efferent C fibers are variably involved.

Another cautionary note there's going to be another big series that hopefully will be developed

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through Peter Dyck senior who's looked at this independently. So I think there's some question about the older normative data of Q-Sweat and maybe some new and normative data. And I think that the conclusions will be similar, that autonomic testing and somatic testing test independent aspects of the syndrome and are likely additive. But I think the rates of autonomic function abnormalities in fact are likely to be lower in that cohort.

QSART is most studied, but uncertain reliability or suitability for multicenter use. But I think Amanda answered some of those questions. Then there's this question of which device, and if everyone's using the Q-Sweat, we have to make sure that normative data is standardized to the use of that.

But I will make this point to this question of pretest probability of disease and some of the comments Gordon made, is I think if we're going for specificity and we want to make sure people truly have the disorder at entry, we should think about having to confirmatory or supportive measures,

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especially if we're going to allow patients in who only have symptoms but no clinical signs because I think that's a patient with lower pretest probability.

I think it's something for us to discuss. Do we allow patients into trials who have symptoms because this is a symptom dominant disorder, or do we require that they have abnormal pin exam? And I think that can be a point of discussion, but if you're going to just have symptoms alone, I think you need two supportive tests. And one of those could be QST and a localizing study such as a QSART or skin biopsy.

Then finally, SUDOSCAN not ready for prime time in my view just yet, but assessing both somatic and autonomic small fibers may also be relevant to measure differential treatment effects on populations of small fibers. So to the points of Professor Malik and others, some of these measures may be more amenable to change and fiber, and have a different sort of dynamic turnover, and may respond to treatment in different time frames.

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So there is an added value of having a multidimensional assessment of the patient, and I'll stop there.

(Applause.)

DR. FELDMAN: We have time for a few comments or questions.

DR. HERRMANN: Chris?

DR. GIBBONS: I think you did an excellent job considering you're not a self-proclaimed autonomic neurologist, but I think I just want to echo your points on the SUDOSCAN, and I know we've talked about this before.

I think this is sort of a unique situation actually in science where there's been sort of a systemic pervasive publication bias with significant modification of data by the company that seems to have been across the publications. Certainly there are many lower-tier publications that came first, that really escalated the quality suggestion of this device, and I think we just have to be exceedingly cautious about that.

DR. HERRMANN: Gordon?

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DR. FELDMAN: Gordon?

DR. SMITH: Yes. I agree with that. Our study was in just free-range patients with I'd say probable neuropathy, so they had to have signs and symptoms, and I think that explains why skin biopsy didn't perform very well. And SUDOSCAN didn't perform very well either, yet the company hijacked what I think was a precautionary publication and turned it into a marketing ploy. And we've been looking at this in CIPN, and it looks completely useless.

DR. FREEMAN: What Chris didn't say is we have data, which I think does not support the use of this device.

DR. HERRMANN: My own clinical use of it, we did not enter into any studies. But early on, we tested it clinically and stopped testing it clinically. So I'll just leave it at that.

DR. FELDMAN: So I guess I'll echo in. Brian and I just published a paper where we actually looked at 4,000 Chinese patients. And what we did is over a three year period, we did a

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study in Pinggu, which is a suburb north of Beijing. We just published this paper last week, where we hired a group of people -- it's very interesting what you can do there that we could actually not do here. And every third door, they would knock on the door and ask if the patient would like to come and be completely phenotyped metabolically, all demographics, and then a careful phenotype for neuropathy.

So the results were actually extremely interesting and to be expected in terms of how many people had IGT, prediabetes with neuropathy, frank diabetes with neuropathy previously undiagnosed. We did SUDOSCAN on all of those patients, and it was not particularly useful, less useful than we found in the obesity population where it wasn't that useful.

DR. HERRMANN: Anne Louise?

DR. FELDMAN: Anne Louise.

DR. OAKLANDER: I just want to add that we've been looking at SUDOSCAN in children because we have a particular interest in seeing if there

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are surrogate tests that could avoid skin biopsy in children as well. And while it's actually feasible to do SUDOSCAN down to as young as age 2, data from both normal children and children with neuropathy are really not impressive.

I think it's kind of hard to submit your papers for publication when you don't have -- it's hard to -- you know what I'm trying to say. But I guess what this goes to highlight is that we should try and get our studies out even if they do not show good diagnostic performance.

DR. FELDMAN: So we will continue this discussion, I think. Roy is going to make a few comments, and then what we'll do is we'll adjourn for a break, which will be around 10:30, and then we'll reconvene at 11:00 on the nose. And if I could ask all panel members to be sitting at the panel by 11:00.

Roy?

DR. FREEMAN: I want to do two things. One is if we could show the -- we do have the housekeeping slide, so now the checkout time, I

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would suggest you do it now rather than at 12 noon. You see the usual kind of stuff, lunch in the usual place, internet access as it was.

The other point I want to make now is that the Europeans are going to need to take an early flight. So what we thought, just because the essence of this meeting really is the consensus building, that we would take a working lunch. So we'll make the announcement after the panel, but grab your lunch and just bring it back, and we can get going on that.

We do have a panel now. We've given it an hour and a half or so. I want to eat into that just a little bit, again, continuing the theme of focusing the mind on the consensus building. So if you could maybe bring the next slide.

What I want to do in the next couple of minutes is give you a taste, a smattering of diagnostic criteria, case definitions that have been used in the literature. Some of these are courtesy of Simon and also I think -- I just want to say I thought David did a remarkable job of

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synthesizing many of the issues. But I want to use what I'm going to say in the next five minutes to synthesize where I think we should be going in the consensus building.

Now these are the Milan, Italian, Devigili et al. criteria, and as you see, there's a menu, at least two of the following. Now, one of the points -- and it may have been -- this was a single-center study. It may have been explicit in the study, but missing from the criteria are actually symptoms, and I think that's going to be an area to discuss.

Giuseppe, you may want to weigh in on this at some point, but I would prefer not now. But as we heard even in David's talk, we have been a little vague on the symptoms, and the symptoms may be neuropathic pain symptoms. They may be non-pain symptoms. They may be autonomic symptoms. They may be some combination of both. But that's something we are going to need to address, and we're also going to need to address what combination of symptoms, what's the menu, 2 of 5, 2 of 6, 3 of 2.

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Clinical signs of small fiber impairment, and this has been discussed as well. But he had pinprick, thermosensory loss, allodynia, hyperalgesia with distribution consistent with peripheral neuropathy, and in his criteria length-dependent or non-length dependent. This also will be a focus of discussion.

Then finally, we have symptoms, we have signs, the clinical examination. He did not specify how that clinical examination needs to be done. Was this structured? What kind of instrument? Where exactly was the testing done? It will be something to think about.

Then finally, the special investigations -- and this will be the focus of the discussion -- he had a QST and intraepidermal nerve fiber density as part of his criteria. You heard Nurcan give her talk. He only used warm and cooling threshold, not heat pain and not cold pain, and this too will be a focus of discussion.

The background to this, before I forget,

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should be that you should bear in mind what I think we heard Deb Steiner of Biogen say, and I'm sure the other members of industry are thinking this as well, which falls under the heading of what is a poor drug company to do when they have a hundred sites that they need to recruit for a small fiber neuropathy study and maybe five of them have QSARTs and three of them are able to do it with suitable interrater reliability.

So this is an inherent problem, that we will need in some way to come up with a working solution to. Now, David used the term "varying degrees of permissivity." With respect to the exclusions, we will need to think about that. Any sign of large fiber impairments, Giuseppe, as I said, was hard-nosed. He was rigid. He was totally non-permissive, nothing in the large fiber domain --

(Laughter.)

DR. FREEMAN: -- no major impairment and no abnormality on sensory nerve conductions. We will need to come up with a stance on how permissive we

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are going to be. And my mind does harken back to the immunomodulating talk on pornography.

(Laughter.)

DR. FREEMAN: All right. Then we have Karin's approach, which in some way really I think is a variation on Giuseppe's theme. However, she includes the hard-nosed approach presence. Here we have a menu, two of the following, a little more specific as far as the symptoms are concerned: burning feet, allodynia, diminished pain, temperature sensation, and how she begins to introduce the autonomic aspects. And we are going to need to work on how we are going to incorporate autonomic features in this.

Are we going to use some of these structured questionnaires? Are we going to be vague about this? When I use vague in the best sense of the word, are we going to leave it in the hands of the investigator or are we going to have specific structured questions? And she has an array of autonomic symptoms, and one of the possibilities, which I will float this afternoon, is that we need

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to think of this disorder as having really three components: pure sensory, pure autonomic, and mixed sensory autonomic, and come up with a way to deal with this.

So here we have a variety of autonomic plus sensory symptoms, and here we have some fairly rigid exclusions as well, very similar to Giuseppe, and also the illnesses, history, alcoholism, and a variety of disorders, which require laboratory testing. So again, giving some structure to this, begin to think along these lines.

A number of us were at the Toronto neurodiab meeting, and I think several in the audience over here. And we at that meeting developed small fiber neuropathy criteria within DPN, but often used outside. And we then put together what we call possible, probable and definite. I've never liked the word "definite." I have much prefer "clinically confirmed," but we can call it as we will if we go there.

And here, length-dependent symptoms, length dependent, not ganglionopathy, not proximal as a

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Giuseppe allowed, with clinical signs where were possible, so a combination of symptoms and signs. And bear in mind the point that David made so well in his talk about in the absence of signs, what we need, probable normal nerve conduction studies, symptoms, signs, and normal nerve conduction studies. And then definite, big spiel, normal plus altered intraepidermal fiber density and abnormal quantitative sensory testing thermal thresholds, thresholds not paying, at the foot; so another approach to this, not dissimilar, but taking a slightly different stance, looking at it in terms of possible, probable, and definite.

Of note is at that same meeting -- and I've never quite understood how this happened, and perhaps Rayaz will be able to explain, but Rayaz wrote a -- there were a number of different papers that came out of this, the autonomic paper, and Rayaz wrote a paper, which was also a consequence of that meeting, but took a fairly permissive stance with respect to nerve conduction studies. So even at the same meeting, there was clearly some

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divergence of views on how hard-nosed to be about large fiber function.

Then finally, one of the older papers -- again, thanks, Simon, for pulling this out -- from Lacomis, and his was a modification of John Stewart's, which David mentioned in his talk, small fiber neuropathy, sensory neuropathy manifest by paresthesias that are typically painful, so defining no menu, but just one specific approach. And this was in the age of the burning feet, tingling toes, age, with abnormal findings of small fiber function on at least one neurological examination, specialized electronic diagnostic testing, or pathological studies; so a kind of a menu but a little looser than developed in the ensuing years, and then for research, he got more specific, and then have the usual array of exclusions.

Okay. That's all I have to say. With that, do check out to come back -- come back at 11:00, I think. And remember, we are on a really tight schedule.

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DR. FELDMAN: Roy, should I ask, should we do the regular panel at 11:00 or do you just want to start the consensus building? What do you want to do?

DR. FREEMAN: I think we should do -- my preference would be to do a brief regular panel just because I think there's some areas to flush out, but maybe let's -- I think that's a great idea.

DR. FELDMAN: So maybe 30 minutes of a panel.

(Crosstalk.)

DR. FREEMAN: Exactly. I think that would be great. Thanks.

(Whereupon, at 10:33 a.m., a recess was taken.)

Q & A and Panel Discussion

DR. FELDMAN: Giuseppe? Let us go ahead and begin without him. I'm going to try to go up some tree branch like Bob did yesterday and actually be fairly definitive, and ask the following question of the panel.

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So let's assume, which may or may not happen. But let's assume that a couple of hours from now we've said that possible neuropathy are positive symptoms; probable neuropathy are positive symptoms and positive clinical signs; and clinically definite neuropathy requires a confirmatory test.

Among the tests that you have each discussed today, what I'd like to hear from each of you really are the pros and cons for the individual. So yes, why, for example, we should use QST, or no, why it should not be one of the confirmatory tests; and if you believe it should be the only confirmatory tests or if you believe it should come from a menu of confirmatory tests.

So it'd be really nice at the end of 30 minutes for all of us to have a clear understanding of your opinions. And why don't I start with you, Rayaz?

DR. MALIK: So should CCM be used as a confirmatory test, I would say the data, if we compare to the INFD, is sufficient for me to now

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say that we should be using it. Now, I'm happy to hear from the audience whether there are deficiencies which need to be addressed, but I think equally they ought to address if the same deficiencies apply to any of the other endpoints and what needs to be addressed for those. But for CCM, I believe that we have enough data now to use it.

DR. FELDMAN: So let me throw that piece open to the audience. Any comments? As the moderator, I'm not going to take an opinion, yay or nay, on any of these particular tests. So I'd like to throw it up to the audience.

Rob?

DR. SINGLETON: So we have been collecting data from very well phenotyped patients with diabetes either with or without neuropathy. And like Dr. Malik's group, ours has been under the auspices of a DP3 three grant through NIH. And our focus has been on looking at the correlation of CCM and other confirmatory measures of neuropathy with clinical features and then progression over time.

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And I have to say our data is quite different from the Malik group in that we find in these phenotype patients that other confirmatory measures -- skin biopsy, sural amplitude for instance -- correspond very -- they correlate very well with the severity of neuropathy that patients with diabetes have, but we've not found that same correlation with confocal corneal microscopy, and not with really any of the different types of measures of confocal corneal microscopy, and that's left us unsure about whether this is really a measure that can be used as a confirmatory test.

I think that a lot of the data for CCM looks at -- Rayaz, I haven't seen that you've looked at the severity of neuropathy in the patients that you've diagnosed, and I worry that this is not looking at subtle neuropathy, but looking at very severe neuropathy. And I think it would be useful to see from your data if there is more about that severity spectrum about how this works as a diagnostic test.

DR. FELDMAN: Rayaz, do you want to comment?

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And then we're going to move on to each of the other --

DR. MALIK: Sure. I think in the most recent paper where we've looked at the different parameters, in the severe groups, it's very clear that it's very good, but in the less severe groups, the early neuropathy groups, it doesn't perform as well. It still has a reasonable AUC, reasonable sensitivity/specificity, but it's not as well.

That I think actually highlights a common problem, whether it's INFD, whether it's QST, whether it's CCM, whether it's any test you want, it's the operative definition that you use to diagnose a condition, which will define, determine, what your sensitivity/specificity is going to be, and that often we forget. If you hear Nurcan's work, you look at that and you think, well, 25 percent or 50 percent sensitivity is terrible, but it's what's the operative definition; how stringent you've been to define that condition that will determine.

Often as investigators, actually we do play

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games, and we move the curve up and down to make it the most optimal sensitivity and specificity. So I'm happy to see your data, but data is data.

DR. FELDMAN: Yes?

DR. HAROUTOUNIAN: Can I make a brief comment just based on the systematic review? As I showed you yesterday, the data on the CCM, all the studies that we looked at showed CCM actually differentiates well between patients with idiopathic small fiber neuropathy versus controls. But I think one concern, our thought is that there were five CCM studies in the whole cohort compared to, for example, 58 QST studies. So I think although the data, at least just by looking at the literature, looked quite promising in terms of the number of studies published on the area, they are somewhat low compared to the other parameters, for instance.

DR. FELDMAN: And maybe last comment on CCM, and then we'll move to the next

Yeah, Gordon?

DR. SMITH: Yes. I just want to expand a

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little bit on our data and then kind of go over and talk a little bit about skin biopsy. The diagnostic performance is actually pretty similar to skin biopsy and the diabetic cohort, but to emphasize Rob's point, there are much more robust correlations between INFD and actually sensory electrophysiology and pain and functional outcomes, so timed up and go and measures of balance.

But the areas under the curve are a 0.6, 0.7 type level. What really performs well are clinical measures, UENS or NTSS-6. We've actually looked at, not for CCM but for nerve conduction studies and INFD across a very large group, I think probably upwards of 400 patients with diabetes, and looked at diagnostic performance. And it turns out -- and we've modeled this in a Bayesian way; we presented this data a couple of years ago -- that the positive predictive value of both nerve conduction studies and in particular skin biopsy is terrible because of the frequency with which in diabetes, patients have completely asymptomatic reductions. And then when you start to model what

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would happen in a higher prevalent condition, the predictable sorts of things happen.

So I guess the point is it's really important to consider the populations in which we're examining these tests and really think in terms of predictive values because when you translate it into the positive and negative predictive values, it's not very good at ruling things in. It's actually quite good at ruling neuropathy out.

DR. FELDMAN: Well, that's actually helpful.

One quick point, and then we're going to turn -- I've got to let Giuseppe know, what we're doing is just talking about each of these individual modalities and asking the opinion of the panel of whether or not they could be used as a confirmatory clinical test.

So go ahead, Chris.

DR. GIBBONS: So just one quick question. I'm not familiar with the data on this. Is there information on non-length-dependent small fiber neuropathies in CCM?

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DR. MALIK: No. You'll have to do that study.
(Laughter.)
DR. FELDMAN: So let's just go to the next. I don't think we'll reach any firm conclusions with this discussion, but it's gonna raise the key points for each of the potential confirmatory tests. And I think what we'll do now is a natural segue, based on what Gordon has discussed, to talk about intraepidermal nerve fiber density.
So what I said prior to you entering the room is let's just assume, may or may not happen, that possible neuropathy is a patient with positive symptoms problem. Probable neuropathy is a patient with positive symptoms and positive clinical signs, and then clinically definite neuropathy is a patient who has symptoms, signs, and a one or more confirmatory test.
Do you think intraepidermal nerve fiber density should be one of those confirmatory tests, yes or no? And if you'd like to defend whichever way you feel.

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Giuseppe?
DR. LAURIA: Yes.
(Laughter.)
DR. LAURIA: To the second, what I would like to point out is that if you have seen -- I mean, this is what happens in new tests, increases strength. All the other tests refer to skin biopsy to set the sensitivity and the specificity, which is what we want in a clinical to see whether we are accepting our true negative or not. It's clearly set by definition, based on the normative data --
DR. FELDMAN: Right.
DR. LAURIA: -- and whatever is the [indiscernible].
So I think that the -- I mean, what I'm very close to is the conceptual point that you use a tool to define whether the patient, the condition, your hypothesis -- depending on what the setting in a trial, you will have the patient in a clinical practice, if the right path is correct or not. So you have to apply the test that must have enough specificity and eventually sensitivity.

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DR. FELDMAN: Todd?
DR. LEVINE: Also just to state what's obviously inherently clear to everyone in the room, with the CCM and with the autonomic test is a tremendous variability just in the experts that we have here within the room. The skin biopsy has the obvious advantage that it can be shipped to one lab, easily, cheaply, and then you have reproducible, reliable results.
DR. LAURIA: But let me add one thing about the autonomic test and the sudomotor assessment. And I'm pretty sure that if you want to dig -- the deeper you dig, the more you get, of course. And in many cases mainly -- I don't know, in some [indiscernible] genetic patients or whatever, we want to see whether there is an impairment.
The reason why we didn't put that in the criteria is because it's a matter of 75 percent. And in at that time, what we wanted to say in this precise condition that was not a first step, but it was a step -- in this condition where we have patients with a possible -- based on the clinical

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symptoms, a possible condition of SFN, what will we need to get closer to the best clinically defined condition?
Of course, the autonomic testing is relevant, but the fact that they are positive in 75 percent means that you are leaving out 25, and it could be -- unless you use different -- no?
DR. FELDMAN: Are there any other comments on skin biopsy? Gordon?
DR. SMITH: I just have a comment for Giuseppe. We've noticed over time increasing fiber densities I think just due to enhancement and technique, the recent issue in terms of going from the polyclonal to the monoclonal. And I'm just concerned that the I think very helpful, extremely helpful normative data that you led collection, of which several years ago are now out of date. And we've been quite interested in trying to gather new normative data. This is germane to diagnostic cutoffs, less to progression.
But I'm just curious what your thoughts are on that and whether you'd be willing to do it

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again.
DR. LAURIA: This is something that we have thought about also some years ago because of many things. When you refer to a healthy population, like in genetics, you know something, but you can go even deeper. If you change from a monoclonal to a polyclonal, you might have different. So, yes.
DR. FELDMAN: So the answer's yes.
David, I saw you shaking your head also.
DR. HERRMANN: We've got an identical trend that in our lab -- well, I want to just bifurcate this a little bit. I think there are problems with many, many, many false positive skin biopsies. In our laboratory, all the time we have patients who diagnosed based on a skin biopsy with uncertain clinical history. When we repeat it in our lab, it's normal; and it's not just borderline; it's normal.
So that's one aspect of the spectrum. And I think what's driving that is as much as we try to standardize the technique and send it to a central lab, I think it can be problems in the harvesting,

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in the fixation, in the crowd protection, and in the staining. And sometimes those are obvious by way of seeing obvious crush. There are other times when you look at the biopsy and they may be mischief, but it's not that easy to tell that there's been mischief except for the fact that there's understanding of fibers [indiscernible].
So just like we see a lot of absent surals out in the community, you can get a lot of low ENF densities. So that remains a problem, but it can be dealt with if you really standardize interlaboratory quality assurance. But then we've had the flip side of the problem where in our laboratory we're getting fewer and fewer abnormal studies. And I think what it is, is over time we've become more and more fastidious about trying to detect problems, improve quality assurance, changes in antibodies.
So I think the normative data that we now use, the work that you and multiple labs did, is probably meaning that many people who fall in the low normal range, if we re-did the normative data

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with the new antibodies and sort of rigorous testing, I think we might find that the cutoffs are a bit higher. That's just my experience.
DR. FELDMAN: I actually think that's a very important point.
Anne Louise? Into the microphone, please.
DR. OAKLANDER: [Inaudible - off mic].
DR. FELDMAN: And turn it on, please.
DR. OAKLANDER: We grew these labs ourselves in different places. Many of us had trained with Jack of course. But I think this has become so much more mature a technique that maybe the time is right in a different setting for some kind of a consensus statement or meeting about the various technical parameters and quality control to improve --
DR. LAURIA: Maybe we can re-emphasize this, that this is what we are saying for more than 10 years. And listen, we have this experience, which is a daily one because we are working with our Dutch colleagues, with Michael, and we've got other experience with other labs. And listen, there must

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be an agreement which you should not consider a priori as fine.
DR. FELDMAN: So it's an agreement it sounds like.
We're going to move on to the next.
DR. LAURIA: It is in place --
DR. FELDMAN: -- okay. Two seconds, Chris.
DR. GIBBONS: Okay. Just a quick comment. One thing, we looked into why the counts might have been going up.
DR. FELDMAN: Can you turn on your microphone?
DR. GIBBONS: Sorry. We looked into why counts might also be going up, and we did find there was a change in physician perspective, and the referrals were now coming in to rule out some small fiber neuropathy in nebulous cases, which is probably one of the reasons why we were seeing a higher count, but at least in our own referrals.
DR. FELDMAN: So let us move now, just because we want to keep moving forward, to QST. And I'm going to ask Amanda, as the panelist who

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did not speak on any of the four, to give her opinion on, if she had to say choose two of the four, which she would choose. But first, let's hear QST, yay or nay.

DR. UCEYLER: Well, the QST, I presented the pros and the cons. It is a tool that is used now for such a long time. There's lots of experience with it. We have some items that obviously do reflect small fiber function better than the others. So if I would have to choose, I would say the perception threshold is cold and warm, and pinprick I'd say cold and pain. Heat pain thresholds seem not to be that helpful.

It has its problems, no question. If you use it, you should be very careful with the controls that you are comparing with, but if I would have to answer should it be included, yes or no, it would be a yes.

DR. FELDMAN: I would ask Amanda to comment now, and then I'm actually -- is James here?

DR. RUSSELL: Yes.

DR. FELDMAN: I'm going to actually ask

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James to comment on QST and the different modalities in QST also because he's done some work on it that I think is very informative and interesting.

Amanda?

DR. PELTIER: So I guess I would say that there should be first tier and second tier tests, and I'm still divided as to whether QST should be in the first tier simply because it is very subjective, and the problem with it is that if you have somebody who really thinks they have fiber loss, as Roy showed, you can fool the test. So using that as a sole diagnostic criteria would not be ideal, but I think using as a confirmatory test I think would be very reasonable.

The same thing I would do with QSART because I think QSART can be very helpful, but I would never rely on QSART as a sole diagnostic tests simply because it's very hard to make sure that everybody's doing it correctly, to make sure they're off all their medications, and to make sure that they're warm, et cetera. So I would say I'd

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have kind of a first tier and second tier test.

Rayaz, I don't see confocal well enough to know at this point to have an opinion on whether it should be in the first tier or the second tier. So that would be my comment.

DR. FELDMAN: James, would you like to just -- couple comments on QST.

DR. PELTIER: And I would not include cardiac autonomic testing at all.

DR. FELDMAN: Yeah, I'm going to talk about autonomic testing separately I think because I thought Roy made the great point of pure autonomic, pure small fiber, and then mixed.

So James.

DR. RUSSELL: For QST, the most widely used devices are those devised by Somedic, which dates from about 35 years ago initially and has been developed since that time; the Medoc and the CASE IV. And each of them has potential issues not only with the intrinsic device but also the interpretation. I would say in terms of bulk of data, the bulk of data really is with the Medoc and

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the QST.

The problem with these devices -- and it's less a problem with the CASE IV than it is with the MEDOC -- is that many of them use methods of limits. And the problems with the methods of limits are that they can be highly inaccurate in determining the actual threshold, the perception threshold at the time the person perceives that stimulus.

So I don't want to spend a lot of time going into all the technical details, but I would say that you have to be aware that the person using the device really needs to understand the limitations.

Now the CASE IV has been shown to be very reproducible provided that the technicians are highly trained at a central center and follow the instructions exactly. You also do have to warm the limb, so the limb has to be warmed to 31.5 I think were the original instructions or higher. So you have to bear all those things in mind.

I would say, bearing in mind that the overwhelming amount of data, whether you're using

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the Medoc or the CASE IV or the Somedic, shows relatively low levels of sensitivity and, depending on your normative data and your methodology, somewhat better measures of specificity. I would say overall, this is probably not a very good measure if you want a rigorous definition for small fiber neuropathy.

DR. FELDMAN: Roy, did you have a comment?

DR. FREEMAN: Yes, just a very quick comment. First of all, I'm not sure if we want to do the positive, possible possible/probable, definite or clinically confirmed, but I want to raise a question about confirmed, and we use these tests not just in small fiber neuropathy, but in a number of other classifications along similar lines.

We say that these tests confirm the diagnosis as if they were the objective tests, that the symptoms are subjective, the exam is pretty useless, and then we come in with the heavy guns, the confirmatory tests, the MRI scan.

First of all, I want to commend all of the

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speakers for a remarkable degree of I think forthrightness and honesty in portraying the strengths and weaknesses of their tests, which most times -- and I sit in a number of these kinds of meetings -- does not often happen.

But having said all of that, how do we want to think of this group of tests, the panelists? Are these confirmatory, are these the true objective tests, or are these along the lines of the clinical exam?

David?

DR. HERRMANN: I was actually thinking something similar. I wouldn't use the word "confirmatory." I would use the word "supportive."

DR. FELDMAN: Right. That is actually where the discussion needs to go is, the robustness of these tests. I like clinically supportive, maybe then confirmatory, but what is the robustness of these more objective measures? Not that the clinical exam isn't objective. I think we all agree symptoms aren't not necessarily objective, so what is the robustness?

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Anne Louise, and then David, I'd like you to really comment, again, summarize in just a brief minute your thoughts on autonomic function.

Yes?

DR. OAKLANDER: I think it goes to be what's the word we're confirming. I mean, if the word is small fiber neuropathy, then, yes, a pathology test is indeed confirmatory. If what you're trying to confirm is does the patient have neuropathic pain or are there complaints, objective versus depression, then I don't think it's confirmatory.

So what is it we're trying to confirm before we consider whether -- I do think that nerve and skin biopsy are confirmatory for the question of whether there is pathy of the nerves.

DR. FELDMAN: I think we're trying to confirm the presence or absence of small fiber neuropathy. That's at least what I'm up here on the stage trying to do.

DR. OAKLANDER: And I think it's confirmatory given the limitations of course inherent in anyone test.

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DR. FELDMAN: David?

DR. HERRMANN: So as I said, autonomic testing is not what I focus on or do specifically, but I would say with regard to QSART, I think it can be one of the options to support that definite diagnosis, as definite as we can make of distal small fiber neuropathy with the following caveats.

One, if you're going to use it, and it would have to be detailed, there has to be meticulous attention to the technical details, the training, the warming, and everything that James and Amanda said in order to make it a useful test. Any clinical trial that would use that would have to fulfill those standards and have that quality assurance.

Two, in my view, I really do think we have to suggest that its use depends on the cohort that's being enrolled. If you just enrolling patients with symptoms and not requiring signs because of the inherent limitations in these studies, I would like two modalities, so QST and QSART, QST and skin biopsy. If however you're

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enrolling people who clinically have a higher likelihood of neuropathy because you're saying in this cohort we're going to have symptoms and signs, then I think to QSART alone done appropriately or skin biopsy alone done appropriately, could be used to get you that extra piece of independent, non-subjective data.

So that's the way I would view this.

DR. FELDMAN: Are there any concluding comments here before we --

DR. SMITH: There's one comment I would really like to make, and this audience really needs to bear this in mind. And that is when you come up with criteria that you've got to have two out of the following three, or two out of the falling four, there's a problem with us because in that list, there may be things that really are not very strong markers of small fiber neuropathy.

So if we came up with a list here and said, well, okay, you need to have two out of three, and your three would be the QSART, the thermal perception threshold, and the nerve fiber density,

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then someone's got to go along and say, oh, okay, fine. The thermal threshold's is abnormal, the QSART's abnormal, but the skin biopsy is normal, but we're still going to call it small fiber neuropathy. To me, I find that problematic.

DR. FELDMAN: So you find skin biopsy the gold standard. I mean, that's the interpretation of what you're saying.

DR. SMITH: Than the other two, yes.

DR. FREEMAN: Can you clarify, listening to everything that you've heard this morning, why actually you say that?

DR. SMITH: Well, because I think, overall, the data, provided it's again done with the proper rigor, shows a high level of sensitivity and a high level of specificity. And that would be the main problem I have. There's also a problem with actually doing these things, so while it is relatively straightforward to obtain a skin biopsy in send it to a central lab to be processed, actually carting a Medicor or CASE IV machine around, or having them at several centers, or

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having the QSART and doing them as we've discussed, in other words, having the rigor during performance, is going to be problematic if you're going to do a multicenter trial.

DR. FELDMAN: Okay. Chris?

DR. GIBBONS: So I like to take the approach sometimes when getting these questions, get them in detail, if I'm seeing the patient in front of me and I have a history that I think is convinced me that they have a small fiber neuropathy --

DR. FELDMAN: So you have the symptoms.

DR. GIBBONS: -- I have the symptoms, or on my exam is a clear length-dependent pinprick loss, something I'm convinced is real --

DR. FELDMAN: So you have the signs.

DR. GIBBONS: -- then say I have these different tests, which of these will alter my decision that there's a small fiber neuropathy patient in front of me?

If QST is normal or abnormal, would it change my decision? Would sudomotor function change my decision, biopsy, CCM, what have you?

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Which of these would be powerful enough to change my decision-making process?

DR. FELDMAN: Why don't you answer that then?

DR. GIBBONS: And I would say amongst the group -- this is my own bias -- I would say biopsy would be the only thing that might switch my decision. Everything else might be confirmatory, but if I had an abnormal sudomotor function test with a normal exam, I would never be convinced.

If there's a normal length-dependent loss, say a proximal biopsy was normal, distal was abnormal, pathologically, I'd be much more convinced by that demonstration than any of the other tests.

DR. FELDMAN: Gordon?

DR. SMITH: As always, I agree with Chris.

(Laughter.)

DR. SMITH: And I just want to push back on -- I mean, the positive predictive value can be low, but in this setting, the very high negative predictive value of skin biopsy is really useful.

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I guess I disagree that abnormal skin means that there's small fiber neuropathy. But in this setting I would say normal skin basically calls into question in a trial setting whether Chris' judgment is actually sound clinically.

DR. FELDMAN: So why don't we on that fine note take a brief adjournment? Am I right, Roy? So everyone should -- so no adjournment, just everyone should get lunch or everyone should just continue? Okay. You're not eating yet. I'm sorry.

The panel can leave the stage, and you may have the microphone.

Consensus Building

DR. FREEMAN: So what I want to do is really begin the consensus a little early because I think it may not be quite as easy as it appears. Let's have some order here.

The first thing I want to do is to structure what we're going to be doing, and the way I think of this disorder, this disease, is actually having three possible components: small fiber sensory,

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small fiber autonomic, and mixed. And I think for purposes of this discussion -- when I say this, proceeding for the rest of the morning -- I want to focus predominantly on small fiber sensory with some overlap into mixed, and I'm going to leave autonomic for another date, another time just because I think that it has additional aspects to it, and I'm not sure that -- even the fabulous presentation done by David Herrmann was done with the proviso that he is not an autonomic expert, and I was not convinced by that. It was one of my favorite talks.

I suggested one possibility, we would do the possible, probable, clinically supported, and I actually like that approach. I want you to think in those terms, but we're not quite there yet. The way I want to approach this now is the gateway. How do patients come in to the clinical trial? And the factors that will bring them in will of course be the history. And the way we think the history is they will have symptoms, and these will either be length dependent or non-dependent, and they will

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have to be a duration.

Now I'm going to say that we should focus on the length dependent, but I want to try and put the low-hanging fruit away first and let's discuss very briefly one or two comments/questions about how when we are developing this consensus, when we are saying these are the criteria, how do we deal with the ganglionopathy patent, the long non-length dependent patent?

Giuseppe, for example, said that was fine. Patients could either have length dependent or non-length dependent. It's a little tricky in a clinical trial for these guys who have 100 sites and it gets a little vague, and you've got fibromyalgia patients coming into it. So my thought was perhaps is to have a little codicil, a proviso that it may be, but to focus on the length dependent, but I want to be sure that we are on the same page with this.

DR. FELDMAN: Yeah, I fully agree with you because we really want to do small fiber neuropathy, not necessarily neuronopathy. So I

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think for clarity, with a proviso possibly, but for clarity, we really ought to stick to length dependent.

DR. FREEMAN: Giuseppe, you're okay with that?

DR. LAURIA: Yes, sure.

DR. FREEMAN: Good. I like that.

So anybody who has a dissenting view? Anne Louise?

DR. OAKLANDER: No, I'm not dissenting. I agree completely, but I just want to say there's another group who had length-dependent origin but who it's not so severe that it's over most of their body or over much of their body.

DR. FREEMAN: We take that. I think we're all aware that at some point in a peripheral neuropathy, that proximal parts are involved.

DR. LEVINE: Roy, one comment. We're actually preparing a paper now. Just to clarify it as we think about it, I don't think there's a great correlation between a patient's pathology and their clinical symptoms. So I think you have to be

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careful how you define this. You put it under the history category. I think we define length dependent clinically, but you may have a patient, for example, whose predominant symptoms or in their feet. You do a cath and a thigh biopsy, and very often --

DR. FREEMAN: We're all totally aware of that. There's a difference between symptoms, pathology, physiology, structure.

So the next point is -- and again, thinking of entry criteria for a clinical trial, your trial, Biogen's trial, Kromasil's [ph] trial, how long? How long do the symptoms need to be present? The standard is six months. Some say three months. The concern of course is you make it too short, the natural history is going to be such that during the clinical trial, they improve, get better, placebo response is as good as the intervention. I would advocate six months.

Anybody wanted to dissent on that?

DR. SMITH: I agree.

(Laughter.)

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DR. FREEMAN: Gordon, now that you're chief of neurology, you need to behave, you know?

(Laughter.)

DR. FELDMAN: Maybe it's not feasible to capture them in a clinical trial, and maybe they're so rare -- there are people who just develop these roaring neuropathies and become very disabled in under six months. Not all of them are these gradually progressive. It takes years to develop.

DR. FREEMAN: Steven at the back?

DR. SAINATI: The point I wanted to make is I agree with the 6-month minimum duration; I think that's a fairly good to cutoff. But I think we should also have a maximum duration as well to --

DR. FREEMAN: Okay, good point.

DR. SAINATI: -- to rule out the burned-out, end-stage patients.

DR. FREEMAN: Good point. There's always a discussion, and maybe we should have this, as to whether symptoms that have been present for a long period of time, 5 years, 10 years, 20 years, are going to be refractory to the intervention.

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Now, I'm not sure that this is part of the inclusion/exclusion criteria and maybe it should be built into the clinical trial, but -- Chris, and then Giuseppe, and then Karin.

DR. GIBBONS: I think that's exactly the point, is I think that would be an inclusion/exclusion for a trial, not for definition though, if it's burned out.

DR. LAURIA: The other thing is that we just don't know. We don't know what happens.

DR. FABER: That's what I wanted to say. We don't know whether patients are refractory to treatment if they had symptoms for over 10 years.

DR. LAURIA: And basically a clinical trial is made to figure out whether he can respond to a new drug.

DR. FREEMAN: David, last point on this. I'm still considering this low-hanging fruit.

DR. HERRMANN: The six-month mark [inaudible - off mic]. [Indiscernible] -- it could be a recommendation rather than prescriptive so it doesn't tie a particular group doing a study into

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using six months versus eight months because it may be vagaries of the trial.

DR. FREEMAN: Yes, absolutely. Somebody may want to do a Q -- I agree. And when we speak of immunomodulating, I'm fine with that. I think perhaps the duration could have provisos, could have codicils.

DR. GEWANDTER: I feel like a couple of people said things and we kind of glossed over them. And as the person who is writing, I'd like a little clarity.

DR. FREEMAN: Sorry. Can you speak a little slower?

(Laughter.)

DR. GEWANDTER: Sorry. When Dr. Louise said how do you define length dependent, you're like, yes, yes, that's very important. So how do we define length dependent? So is it going to be symptoms and signs have to both be length dependent? Is it going to be one or the other? What do you want to say?

DR. FREEMAN: Okay.

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(Laughter.)
DR. GEWANDTER: I mean, we could maybe not -- I mean the thing is if we don't decide now, then I'm just gonna write something, and then all you guys are going to try to comment, and then I'm going to have to decide how many say one thing or other. So it'd be good if we could just decide.
DR. FREEMAN: You know, it's one of those things. I hate to make the analogy that --
(Laughter.)
DR. SMITH: [Inaudible - off mic] -- complaints. We're not talking about --
DR. GEWANDTER: Okay, so symptoms.
DR. SMITH: So here it's just symptoms.
(Crosstalk.)
DR. GEWANDTER: Perfect. Thank you. Good clarity.
DR. FREEMAN: Very precisely, what we mean by length dependent, in terms of symptoms at this point, and that's really what we are talking about.
(Crosstalk.)
DR. FREEMAN: Gordon?

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DR. SMITH: We think we know this, but when you talk to people who aren't neurologists, actually, they have a hard time wrapping their mind around this.
DR. FREEMAN: Articulate what we mean. Are we talking about -- what do we mean when we say --
DR. SMITH: Well, you're the one who recognizes it when you see it.
(Laughter.)
DR. GEWANDTER: I like below the knee.
DR. FREEMAN: No, no, no.
DR. GEWANDTER: Oh, see?
DR. FREEMAN: I think that exemplifies the problem.
DR. SMITH: Maybe distal, distal, predominant, symmetric -- symmetric, distal, predominant or something.
DR. LEVINE: And distal onset, too, because I think that's Anne Louise's point.
DR. SMITH: Yeah.
DR. LEVINE: Sometimes it's the whole body by the time we get to them, but they know it began

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in their feet.
DR. LAURIA: May I suggest to you the term polyneuropathy? That includes everything. Polyneuropathy is a length-dependent process by definition. The other one is --
DR. FREEMAN: But Jen is asking let's get rid of the jargon, and you're giving an even worse jargon in length dependent. And this is the point. I mean, we know what we are talking about, and we can word this; a peripheral neuropathy that begins in the distal part of the body and gradually or rapidly progresses more proximally. And we can deal with that.
Okay. Let's get on to what I think may be more complicated, and the symptoms are either pain or autonomic. And let's deal with a little more non- low-hanging fruit as well.
Do we want to have a discussion about non-painful sensory symptoms? Is that part of the funnel into the trial or not?
Ahmet?
DR. HOKE: I agree that it should be because

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we all see patients who have just maybe tingling and paresthesias that start in the toes, and they don't really characterize it as painful.
DR. FREEMAN: Okay. Any other comments? And then I'll move on to pain, and we can see where we go.
DR. HAROUTOUNIAN: I just have one comment. In some of the studies, patients come, and when you ask them about pain, they don't say they have pain, but they're tingling and paresthesia are severe and quite disturbing. So there's I think like semantic issues.
DR. FREEMAN: I think you and Ahmet are saying the same thing.
DR. HAROUTOUNIAN: We could say include patients who are suffering from this neuropathy, but they would not call it pain because in their head, they perceive pain as something else.
DR. FREEMAN: And at this point usually, we segue into an hour-long discussion about the nature of pain and discomfort. And I want to do my best to avoid that if we can, but we take the point.

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Chris?
DR. GIBBONS: So I guess the question also with this is not just positive, but is it adequate to include a lack of sensitivity?
DR. FREEMAN: Okay.
DR. GIBBONS: And I guess how many people would say yes.
MALE VOICE: So numbness.
(Crosstalk.)
DR. GIBBONS: So if they get into a bathtub, they put their feet in, they can no longer feel the water being hot until it goes up to the mid calf.
DR. FREEMAN: To maybe frame that -- and I do want to do that -- we're dealing with a small fiber sensory neuropathy, and to what extent the negative symptoms are large fiber is a question that I think we will need to resolve, and I think we're now entering the non low-hanging fruit.
Sorry. Gordon, you were going to say something.
DR. SMITH: I'm a little ambivalent about this decision, and I'm interested in Eva's thought.

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Eva made the point pretty strongly yesterday that pain is a defining characteristic of small fiber injury. And I worry about confusing or conflating idiopathic small fiber neuropathy from just early mixed, large and small fiber neuropathy, because nerve conduction studies are not particularly sensitive and very early, or mild neuropathy. And I think patients sometimes develop more evidence of small fiber dysfunction and evolve as a neuropathy progresses.
When I think of small fiber neuropathy, and I bet when Biogen thinks about small fiber neuropathy, they're thinking about painful neuropathy. So I think it's worth discussing this a little. I don't know the right answer. Eva always seems to know the right answer.
DR. FREEMAN: So I'm going to just frame it for Eva to answer. I think that we have to acknowledge that in some patients we are dealing with a window in time that this is going to progress from small to large, and this is a period of time; other patients, it may remain in the small

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fiber realm. And I do want to emphasize, at least from my standpoint, that we are in the realm of pain as well.
Eva comment to Gordon.
DR. FELDMAN: As you know -- and some of this is just clinical bias from my practice, is that pain clearly is the predominant symptom. In my own practice, I actually don't see individuals who complain of mild tingling or some moderate dysesthesia. They really do complain of pain.
But I think Simon makes a very good point, and he's reviewed the literature much more extensively than I have in terms of the symptomatology of small fiber neuropathy. I do think we want to probably be more inclusive than exclusive. So in the spirit of being more inclusive, I think that we need to listen to what Simon has told us and maybe include some of the non-painful sensory symptoms. Clearly in this neuropathy, I think everyone in the room would agree that pain is the predominant symptom that we see.

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DR. FREEMAN: So no doubt that pain is going to bring people into the clinic. Pain is going to bring people into the clinical trial, and I think that is where we all focusing. But there seems to be a -- I wouldn't say consensus, but at least a body of support for including non-painful symptoms.
The other point that I will make is that the way I would view this is that there is a funnel, and at each step, we are going to want to be increasing the probability of an accurate diagnosis of a small fiber neuropathy, which is to say increasing the specificity. And I think to address Eva's point, it's quite reasonable that at this point, we are inclusive with the understanding that the companies may want pain to be the predominant aspect, at least the way the field lies at the moment.
Giuseppe? Chris?
DR. LAURIA: Two different. In terms of the definition of the diagnosis, I think it makes sense, considering even -- non-painful and a

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patient with specific sensory loss, a patient with a congenital insensitivity to pain, all the fibers done is a patient with a small fiber and non-painful is small fiber neuropathy. In terms of definition of the patients for a clinical trial, considering that we are talking about clinical trials for testing the efficacy of painkillers, I agree with Eva.

DR. FREEMAN: Ahmet, Chris, and then we move on.

DR. HOKE: I just looked at the PNR data, and about close to 15 percent of our patients that are designated as small fiber that have normal nerve conduction studies but abnormal exam or abnormal skin biopsy have no pain, based on their reports. So it's a small percentage, but it's still a non-significant amount.

DR. OAKLANDER: And it chooses the others, small fiber, mediated, no sense of sensation. That's very distressing and disabling. It's a small fiber sensation, NAV 1.7 mediated as much as pain.

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We have a very strong dermatology group at MGH. Eva, you don't see those people because people with itch don't think of going to a neurologist right away.

DR. FELDMAN: Thank, God.

DR. OAKLANDER: I'm just saying, itch is very much --

DR. GIBBONS: I just want to echo Giuseppe's point, particularly the hereditary case, which are classic examples and have to be included. So can't this be the migraine with and without aura example; small fiber neuropathy with and without pain?

DR. FREEMAN: I was thinking along those lines as well.

So let's maybe move on, and I think we need to come up with a constellation of symptoms. There's not a great evidence base of what constitutes the symptoms of neuropathic pain. I and a couple of other people were part of a consensus meeting to define the symptoms of neuropathic pain suitable for genetic studies; why genetic studies, a whole other story. But I think

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the consequences of this meeting are worth just showing.

What is of interest is on the panel, there were the development of one of the neuropathic pain questionnaires and PSI and DN4, the development of the LANS, another one of the neuropathic pain screening instruments; DD [indiscernible] are both a both a screening and an outcome, and the pain detect another screening, so people who have expertise to form the basis of the way we think of neuropathic pain.

Now I'm not going to get into the difference between evidence based and consensus statements, but I think this is a reasonable rate. It was actually a fascinating process. It was a delphi method. I'll take it through the slides quickly, but basically there were 20 participants, all gave features that they thought -- symptoms that they thought were consistent with neuropathic pain. These were the major ones, and I'll take you to the slide, which I hope everybody can see even at the back.

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Is it possible or not? Can you see it? Can you read it? Okay. So round two and then round three. So with the delphi procedure, which was rather interesting, we came up and focused on round three over here.

Number one, 14 out of 15 felt that hot burning pain was the hallmark of neuropathic pain. Next was pain in a plausible anatomical distribution, which I'm thinking when I look at this and where we are, I think that's kind of taken for granted, and I don't think that need be. If we are using this to be one of a menu, 3 out of 6, 2 out of 5, I don't think that that need be, but I'm open to whatever you say.

Pain in area of numbness, and that got 10 out of 15. Then prickling, tingling, pins and needles, no mention of pain with this, so addressing Ahmet's point, addressing Anne Louise and others' points. Electric shocks and shooting, perhaps somewhat painful, got 8. And we're down to now 1, 2, 3, 4, 5, pain in an area of altered sensation, which I don't think is applicable for

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what we're doing specifically if we thinking about length dependent. And then you see a bunch of those, which I will read just in case you can't see them: numbness, non-painful; spontaneous pain; paroxysmal pain; evoked pain; painful, cold; itching. And you see these were really -- the last punch got very few votes. It wasn't termed in this way, but the hallmark of neuropathic pain.

So I think for me anyway, this conveys a reasonable constellation of features that we would think are typical of neuropathic pain.

Anybody want to add anything and anybody want to move anything up in the hierarchy? Simon?

DR. HAROUTOUNIAN: I just want to make a comment about the hot burning pain. Just by reviewing the literature on the typical symptom presentation, the burning pain is by far the most prevalent, the reported type of pain in SFN studies. And roughly it's about 50 percent. We can talk about sensitivity, but it's by far the most prevalent symptom.

DR. FREEMAN: Okay. We have one.

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Giuseppe, then Ahmet?

DR. LAURIA: We don't have any -- check on the quality of the question, whether it's used in those studies. So we don't how many questions have been done. But in general, I will support the idea to include -- I want to define spontaneous and evoked in general because it strictly depends on the number of words or number of possible items you can have.

DR. FREEMAN: So just to maybe address that because we have I think one definite. Over here we have a couple of things that cropped up, but pain evoked by light touch, and then there was just evoked pain. So the nonspecific evoked pain didn't get many votes in this, and there's no reason to say that the 15 people were correct, whereas pain evoked by light touch, by contact, by bed sheets, which was regarded as one of the hallmarks, do we want to leave it to specifically pain evoked by light touch or do we want to elaborate, pain evoked by warm water?

Any thoughts on this?

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DR. FELDMAN: I like pain evoked by light touch. That's what we see.

DR. FREEMAN: That's what we see. So consensus.

DR. SINGLETON: It has a historical detail. I think the bed sheets question, we think of as prototypic. We're not talking about exam here; we're talking about --

DR. FREEMAN: These are symptoms.

DR. SINGLETON: -- we're talking about symptoms.

DR. FREEMAN: Absolutely. We are in symptom realm. So this is a patient's daily life.

Yes?: Anne Louise?

DR. OAKLANDER: So we're talking about expert consensus, which is an absolutely valid way to do it, but we also have to look at it from the patient's perspective. So what do they think?

DR. FREEMAN: Well, not having patients here at the moment, I think we're stuck with this at the moment, but we do take your point.

Karin?

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DR. FABER: We did ask the patients this several years ago, and this was an important thing to them. So light touch or the sheet intolerant or whatever you call it, that was an important thing that patients --

DR. FREEMAN: Anything else to addresses Anne Louise's point? Anything else that they thought was important?

DR. FABER: Hot burning pain and pain during exercise.

DR. FREEMAN: And during exercise.

DR. FABER: Walking.

DR. FREEMAN: Pain during walking. That's not on the list. That's interesting. And that's also one of the things we actually --

DR. LAURIA: The feeling of constriction of the legs and feet is very usual.

DR. OAKLANDER: Deep pain and aches was slightly more prevalent than tingling or pins and needles; third was skin that has lost sensation; need to move legs. So deep pains and aches in this study of over 100 patients with confirmed was the

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most prevalent among the pain related; all these things.
DR. FREEMAN: Let's go, James and let's go, Todd.
DR. RUSSELL: So Roy, you're really looking at criteria for pain here.
DR. FREEMAN: Yes, we are.
DR. RUSSELL: If you're looking at small fiber neuropathy, I think itching and cold need to go higher.
DR. FREEMAN: Say that again.
DR. RUSSELL: If you're looking at small fiber neuropathy, I think abnormal cold percent or feeling that your feet have an abnormal cold feeling in them is actually far more common, and itching I think is far more common for small fiber neuropathy, as Anne Louise has pointed out and also Arthur Vinik has shown. But I agree with this ranking for pain, but for small fiber neuropathy, they probably need to go higher. And then the plausible anatomic distribution, we may want to define that for people who don't know what that may

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be
DR. FREEMAN: The way I'm thinking about this -- and again I open this up -- I would like to come out with maybe a menu of our top six symptoms. We can say that there may be other symptoms that are consistent with neuropathic pain in the small fiber neuropathy. So I'd like to finish before lunch, in the next five minutes, with saying which are our top six symptoms, one; and two, how many of those would be the start of the funnel, and then you can eat.
(Laughter.)
DR. FREEMAN: So Gordon?
DR. SMITH: I think the one that's missing there in my clinical practice is nocturnal pain. Maybe that's getting at evoked by light touch, but neuropathic pain is worse at rest or the night, and that allows me to distinguish it from many other causes.
DR. FREEMAN: How does fit in with what Giuseppe and those -- you're giving the standard approach, but there's more and more literature

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emerging that that standard approach that we had saying that pain is worse at night and gets better with movement, and there you have these guys saying the exact opposite.
DR. FABER: We always thought the same, that nocturnal pain is very specific, but it's very frequent. We a proper check, so we had 400 patients filling out diaries. And the difference between day and night is very little.
DR. FREEMAN: Very little.
DR. FABER: Yeah.
DR. FREEMAN: I'm aware of that, and I'm aware of what you say, and we need to somehow create emergent.
So let's maybe -- I'm going to have Giuseppe, and then I want somebody to say, okay, these are my top six and let's have -- I'm happy to do that, too, but I've kind of done it already. So let's have Giuseppe go, then Gordon, and then a volunteer to give their top six.
DR. LAURIA: Very quickly, just to say that we could stay here the entire night, and tomorrow

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morning, there will be another item within the list. So I think that -- I mean, we don't have to reinvent the wheel. There is the recommendation for the neuropathic pain assessment and definition that I suggest to follow. And I would include all the symptoms which are under the umbrella of neuropathic pain that means evoked and spontaneous pain. And I wouldn't try to define the six because there will be the seventh coming up.
DR. SMITH: Amen, brother. That's what I was going to say.
DR. FREEMAN: So be specific. Okay. How would you write this up then? What would you say as a write-up? You can't say all of the features of neuropathic pain because, as Giuseppe said, there's always one more. What do you say? I do think that we need to actually have some clarity on this. I'm happy to have the proviso in say the following features are also maybe consistent with neuropathic pain, but again, we want to be relatively specific here. As I say, we're going down the funnel, but I think we still need to be

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definitive.
DR. SMITH: I would use the NeuPSIG criteria for neuropathic pain and then say, and give examples. So I wouldn't require five or six and we each have our favorite or least favorite, I suppose, domain of neuropathic pain. But we have an operational definition that seems to work well; I would use that. And then we can give examples. You say here are six of the more common descriptors of neuropathic pain in this population.
DR. FREEMAN: So you would leave it for a clinical trial at the discretion of the investigator.
DR. SMITH: No. What I would say, I would use the operational definition of neuropathic pain --
DR. FREEMAN: This is in fact the current operational --
DR. SMITH: -- and give examples because --
DR. FREEMAN: This is the current operational definition.
DR. SMITH: Right. But let's say we use

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this ranking, and there's a patient who has distal sensory loss, distal abnormalities, or distal numbness. They say, "I've gotten numbness and I've got terrible painful itching." And on examination, they've got the appropriate length-dependent examination findings. I think we would agree that this is a patient with small fiber neuropathy, and if itches, number 7, we exclude them.
DR. FREEMAN: Okay. So I want to counter that a little. We do in a clinical trial want to be specific, and certainly in the clinical arena, there's no doubt I would say, well, that patient could have a small fiber neuropathy. But I wasn't the one that voted that itching was a symptom of neuropathic pain. I think that it is not part of my top 5. It may be number 8, 9, and 10. And I think in a clinical trial, we don't want number 10. We want -- I think when we write this up, I'm happy to say that these are also features of neuropathic pain that should be considered so that there's some flexibility, but I'd like to leave this with six.
So let's go, Eva.

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DR. FELDMAN: Well, I can give my top four. So hot burning, pain evoked by light touch, and then I actually jumped prickling, tingling, pins and needles, and electric shocks, and shooting. I mean, that is what I truly see in my clinic, so that would be my top four.
DR. GIBBONS: So I was going to throw on my top six. I was going to go burning, shooting; then tingling, pins, needles; then the bed sheet discomfort; cold; and then finally pain in the plausible distribution.
DR. FREEMAN: Okay. Let's go. Noah?
DR. KOLB: I was just going to agree with what Gordon said because being inclusive here does not mean that all those patients will get included in the trial because we're going to have examination features as well as other things to confirm that these people have neuropathy. So being inclusive in the symptoms doesn't mean that you'd be including patients in a trial necessarily, erroneously.
DR. LAURIA: Carrying [indiscernible] the

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possible group? What makes this suspicion of a SFN? The patient's symptoms, which are pain. So I don't care if a patient has a feeling of cold, although the feet are warm. This is very frequent, for instance, although he has burning feet. What I care is that he has symptoms that resemble -- that rises suspicion that there is small fiber damage, or pathology, or disease.
DR. FELDMAN: That's what he's asking for.
DR. FREEMAN: Maybe twist your mind around plantar fasciitis, metatarsalgia, calcaneal spurs, tarsal neuromas, intermittent claudications. I want to kind of --
DR. LAURIA: Yes, but we are in the same -- it's the same way because that's the first step, and then you do something, which is the clinical examination of the nerve conduction, the biopsy or whatever you want to define whether those symptoms actually represent the disease you want to study.
DR. FREEMAN: Rob, and Nurcan next.
DR. SINGLETON: I would just suggest that we

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might want to consider -- it's not really exclusionary types of pain, but things that -- as much as we think things suggest neuropathy, what you're saying is really -- you're saying there are types of pain that don't suggest peripheral neuropathy. And in Gordon's suggestion, we could serve offer those as examples in the same way.

So we say if your pain is not in a plausible distribution, if your pain is very focal and related to bone or joint, then those things are less likely to be neuropathic pain. And I think by doing so, you help to guide the investigator, but you still leave open the concept that -- I think it is appropriate to let investigator use some of their judgment in this aspect because I agree that when you get to -- you're going to do -- this is the top of the funnel still, and you're going to get to more specific things as you go forward.

DR. FREEMAN: Okay. I think now is about the right time to ask the people from industry what they would think. You guys are doing the clinical trials -- sorry. Nurcan?

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DR. UCEYLER: I'm very sorry. Just a short comment on this. I think we cannot simply pick out six items that anybody here thinks might be of interest. My sixth will be other ones, and those of the others. We have to base this on evidence, and there are obviously studies that are looking, and we have data that can tell us which are the top six in literature. If we want to give, really, single items, I think we have to base this on evidence.

DR. FREEMAN: So direct us to the evidence because the evidence is not that great.

DR. UCEYLER: But the question is -- have we asked this question? So where is the evidence? Maybe we can ask Simon. We can ask Karin, who has performed a study that's --

DR. HAROUTOUNIAN: What am I going to suggest is that maybe if we come up with a top six -- and maybe I could look again through those 70 -- 123 --

(Crosstalk.)

DR. FREEMAN: It was not that good.

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Let's hold this thought for a sec. I do want to hear from industry as to how they think this would play out in the clinical trial. You've got two choices, which I'm going to put at the extreme spectrum, into the spectrum. The one is patients who have pain, which the investigator thinks is consistent with neuropathic pain, so in the mind of the investigator; and the other, you have pain which fulfills four of the following seven, eight criteria.

DR. STEINER: From my standpoint, the more prescriptive that you can be, the better off because I keep talking about having multiple sites. So when you leave things up to the discretion of the investigator, which we do do, then you see a lot of variability. And we all talk about the importance of homogeneity and clinical trials. And if we're starting off with patients and we're targeting painful small fiber neuropathy, we know the patients are going to be coming into some type of pain, and it's working down the list to be sure that we're targeting those patients who have the

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pain due to their small fiber neuropathy.

So I guess that's why I mentioned either it has to be really prescriptive or you do need to have some type of an independent review by experts so that you say here is the entire case. Here's the history, symptoms, clinical signs, and whatever diagnostic modality is selected, because otherwise, I'm really concerned about the heterogeneous population.

DR. FREEMAN: So let me translate this. You would prefer to exclude patients rather than have a broader net that funnels down. Yes. Okay.

Steven?

DR. SAINATI: Particularly in a phase 2 trial where you're trying to get your first evidence of efficacy and you want a very well defined patient population, you want to rule out all these other masquerading disorders like intermittent claudication, plantar fasciitis, metatarsalgia, that's all very important.

As you transition into phase 3, you can afford to be maybe a little bit broader. But there

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again, if you don't find evidence of efficacy and safety, particularly efficacy, you're not going to get a product label, so then it just goes out the window.

DR. FREEMAN: Heikki?

DR. MANSIKKA: Just one quick comment. It seems like many of the items that have been brought up here in terms of how to describe the population in terms of the neuropathic pain symptoms, they are already being captured in the available instruments. So like the DN4 pretty much captures all those symptoms that were kind of touched on as a critical symptoms. So maybe there is no need to reinvent the wheel here, extensively.

DR. FREEMAN: Yeah. And the inventor of the DN4 was one of the -- unsurprising one of the participants in this consensus. However, I think it's reasonable for us to say use of one of the screening instruments is either recommended or suggested. But I think we do need to come up with our stance on this.

Anybody else? Anybody else from industry

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that I've left out? Anybody else want to comment?

(No response.)

DR. FREEMAN: Okay. So I think there is enough for us to work with. I think it's been very clear that industry would prefer to be prescriptive. I think it's very clear that for single-center investigative studies, it's in the hands of the investigator. We will express this. Simon will come up with his literature review. We have this one. Karin will send us the results of her patients.

Did it sound to me like Anne Louise had patients or you were quoting --

DR. OAKLANDER: No, we did. We have the survey.

DR. FREEMAN: You do. So you will send us that. Anne Louise will send us -- Roi will send us whatever they have. We will come up with something. It will be a menu. Let me just say, give me a sense. And this is between you and lunch, so be quick and agree with the person sitting next to you.

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If we just say, for argument sake -- we cast the net a little wide and say we have seven symptoms that we suggest helping these guys on the left-hand side of the room, skier's left, want us to be prescriptive, let's say we have seven symptoms. What do you think is reasonable? 2 out of 7; 3 out of 7; 5 out of 7?

DR. LEVINE: Roy, you had envisioned this being just yes/no, not a certain scale that they have to meet of each one.

DR. FREEMAN: Yes.

DR. LEVINE: I think if you do this, it should just be yes/no; otherwise, it gets very complicated.

DR. FELDMAN: I think 1 out of 7, because what if you just have hot burning pain?

DR. FREEMAN: One out of seven.

DR. FELDMAN: Period.

DR. FREEMAN: One of the following.

DR. FELDMAN: Because that's the most common thing.

DR. FREEMAN: One of the following.

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DR. GIBBONS: I would just like to say yes, but perhaps that has to fall into the anatomic distribution.

DR. FREEMAN: Okay. Nice point. Gordon?

DR. SMITH: That was my point, and I'm very ambivalent about counting symptoms for reasons I've already summarized. But I think the distribution is not a symptom; that's a core part of the definition of neuropathic pain. And I think the straw man you set up didn't really capture that. This isn't the investigator just does whatever they think. The other straw man is using the accepted NeuPSIG definition of neuropathic, and then you would have to have something that's said in an anatomic pattern that fits with a polyneuropathy as Giuseppe said.

I would agree with Eva. If we're going to do this, I would say one.

DR. FREEMAN: Okay. Anybody else want to comment?

(No response.)

DR. FREEMAN: Okay. So we have one out of

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the following --
DR. HAROUTOUNIAN: One or more.
DR. FREEMAN: Of course.
(Laughter.)
DR. FREEMAN: Thank you for clarification.
I think that -- operationalize, we have that. After lunch, we will deal with autonomic,, which should be a little quicker. It's now 10 past 12. Grab your lunch and let's keep going.
DR. FELDMAN: So we're bringing our lunch back here.
DR. FREEMAN: You bring your lunch here.
DR. FELDMAN: Perfect.
(Whereupon, at 12:12 p.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(12:27 p.m.)
DR. FREEMAN: I think our rapporteur has enough for the sensory. Let's move on to the autonomic. I'm going to propose that we structure this. As I said, we have sensory, which I think we've covered adequately in terms of the symptoms. And then we mixed. We're not going to go into the autonomic, but the question with respect to mixed is the following. There are two possibilities.
The one is we can say we have one set of criteria for company, the investigator, who is interested in painful small fiber neuropathy, and that is the pure sensory. And then we will have another set of criteria which we can. As Karin current has done in her criteria, you can have not only symptoms of pain but also one of the following autonomic symptoms. So we can either say that this is so tightly integrated with the painful that it is acceptable to actually get into the clinical trial if you have no painful sensory symptoms, but autonomic, or we can say, okay, we have the mixed,

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and with the mixed you can have pain plus autonomic.
Now, the pros and cons of both. So let's kind of get a sense of what people think just to let this flow a little bit, mixed versus -- what does mixed mean and could you enter the pure sensory with an autonomic symptom? Giuseppe?
DR. LAURIA: My suggestion is predominantly somatic or predominant autonomic because you can have pure autonomic neuropathy with evidence of somatic -- damage of somatic nerves, which can be --
DR. FREEMAN: So Giuseppe is saying we have the pure, painful -- let's just call it sensory, and then there is a mixed., and we can have autonomic in that. I'm assuming the mix will be what we define sensory as plus one of the following, two of the following, three of the following, and we can discuss how these questions need to be asked because if you think sensory symptoms are vague, you have not heard anything yet because most of you sitting in the audience have a

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bunch of these symptoms.
Is that an acceptable conclusion, that we will have a mixed small fiber neuropathy which will have autonomic symptoms, and we can discuss how these will be worded and how many of them we require? Consensus on that.
(Nods from participants.)
DR. FREEMAN: So I see enough nods for me to move on.
So the next question is -- and perhaps the autonomic aficionados -- I'm sorry James isn't in the audience because I think he would be very valuable -- to comment on this. But how should we deal with this bunch of autonomic symptoms? Karin can answer, Chris can answer, anybody who feels they have a stake in the autonomic field or know something about this.
How can we be relatively specific about this? Can I just while you're thinking just translate this.
We decided, James, while you were out of the room -- and I'm sure you would agree -- that we

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would have the pure sensory, and then we would have a mixed, and the mixed would have whatever we decide with pure sensory, one of the following symptoms as we decided, and we now have to decide X of Y autonomic symptoms; one, how many; and two, how we will ask for the symptoms so as to be relatively specific, which is always a challenge with autonomic symptoms.

So Chris was going to weigh in.

DR. GIBBONS: Having gone through some of the questionnaire data, I think that's probably a more appropriate approach rather than asking a few specific questions. I think for the pain, we could have gotten away with maybe six or seven of our top. Here I just don't think we can. I think we will have to be broader and use a questionnaire inclusion, whether it's a symptom of autonomic survey COMPASS, the Boston autonomic questionnaire, but a questionnaire. And probably I think we would require a minimum of two domains, if not three, within this list.

DR. FREEMAN: Just to counter what Chris is

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saying -- and I agree in broad general principles, but we certainly see patients who we all convinced have autonomic failure, who may just have orthostatic intolerance without anything else. And this is the inherent challenge, and maybe we want to be specific and maybe have two, or maybe we need to grade and say we give orthostatic intolerance 2 points and a score of 1 is insufficient, but somebody who has the full-fledge syndrome --

DR. GIBBONS: I think the counterpoint to that is are they complaining of symptoms or do they have --

DR. FREEMAN: We're still in the symptom realm.

DR. GIBBONS: On the questionnaire, frequency of bowel movements or what qualifies as constipation, maybe they don't complain of it, but they have constipation. That could be sufficient to be one of the domains like the pure autonomic failure group. There may be ways to get at that I think more clearly.

DR. FREEMAN: Chris says more than one

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domain in the autonomic realm involved, and Chris saying use one of the established questionnaires of which there are a couple.

James? I just want to make one point. Michael came up to me during lunch and he emphasized with a sensory that we should draw on what exists, pain detect LANS and DN4. And Chris is in some way echoing that.

James?

DR. RUSSELL: I would agree with that. But I think that one of the problems that we've come across is that you really have to make sure that the symptomatology is due to a likely autonomic disorder and not due to some other factor. And I'm particularly saying about the urinary problems because the trouble is that women who have had multiple children or men who may have prostate problems or whatever, clearly are going to report that as being positive, but you have to exclude those other factors. GI, there may be another factor accounting for that other than an abnormality of the autonomic nervous system.

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DR. FREEMAN: Absolutely. Men have prostate disease. Every American has reflux.

Simon?

DR. HAROUTOUNIAN: Just to clarify, are you discussing those as inclusion criteria for a study, or we're thinking about characterizing patients by their autonomic profile?

DR. FREEMAN: We are not characterizing. We not looking at phenotype. These are all inclusion criteria. This is the case definition, what constitutes an inclusion criteria or an exclusion criteria for a clinical a trials. Phenotyping is a whole other meeting.

Roi?

DR. TREISTER: We validated the COMPASS question in this population, and I don't remember all the items. There is a list of about 20 items. I would guess if we would like to be inclusive, at least one symptom of those would suggest it.

DR. FREEMAN: So we have one; Chris says two

Jen, you've got enough to work on over here?

DR. GEWANDTER: Yes.

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DR. FREEMAN: Anybody else want to comment? So the suggestion is use one of the established questionnaires. There are a couple of them. I think Chris is leaning towards --

DR. GIBBONS: Just to clarify, I think important for a writing perspective, when we say inclusionary, are we defining this as this now includes them into the mixed category from the pure sensory? They've already hit those criteria?

DR. FREEMAN: In order to be mixed, you need to --

DR. GIBBONS: You meet the first.

DR. FREEMAN: -- exactly. Maybe this is low-hanging fruit for the autonomic. Do we want to comment on what constitutes a pure autonomic small fiber neuropathy or should we leave that for another meeting?

DR. FELDMAN: I would leave that.

DR. FREEMAN: Okay. Eva is the timekeeper. I like that role. Everybody agree with Eva? Everybody always agrees with Eva. So we are operationalizing it. We've operationalized.

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So we now are on the examination, signs essentially. This is part of that consensus meeting. It's an interesting story, another day, another time. One of the important point is -- and I'm addressing something that was raised by Deb yesterday. What do the experts think with respect to it is feasible for the non-expert --

DR. FELDMAN: Talk into the mic, Roy.

DR. FREEMAN: It's hard to look at the slides and talk into the mic. What do experts think is feasible for the non-specialist to assess? This is the group that you saw, Didier [ph], and the LANS guys, and the German guys. What do they think? So they thought experts could easily assess symptoms. We decided that consensus was greater than 70 percent. They did not think that the experts were capable -- and think clinical trials over here -- of assessing signs.

DR. HAROUTOUNIAN: Non-experts, right?

DR. FREEMAN: Non-experts, non-specialists were capable. Sorry. Did I misspeak? So just give that some perspective.

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This was to me one of the more fascinating two-day meetings that I participated in. But with that perspective, I want to introduce the possible signs. What I want to have as part of the discussion is how specific do we need to be with the elicitation of these signs? And Jen and Chris are putting a lot of thought into what exists out there, but I will just touch on this.

Do you want to insist that they use the Neurotip; insist that they use a safety pin; insist that they use that $2,000 instrument that the DNS use? What about tuning forks? We all have a number of different tuning forks that we use. And then how structured is the assessment of all of these things?

Gordon structures the sensory exam very nicely. Some people use the tuning fork. I actually have gone around the room with a group of our residents and ask them how they do the sensory exam, one by one by one, and it is fascinating. Nobody does it the same way, absolutely nobody. And obviously, you are not going to get the same

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results.

So I want to -- again, just to editorialize just a little because this is going to crop up, and it's part of the same conversation, one of the strengths of QST -- and we know it's a psychophysical test, and we know it is subjectivity attached to a computer, but stimulus delivery, the algorithm for the response is in every way rigidly documented. Even taking James's point about it being time reaction time dependent, that's the strength of QST, I believe, is that everything is rigidly algorithmic.

Having put that aside, these are the possibilities, and the first question is how structured do we want to be with the way we describe these signs?

DR. FELDMAN: Can I ask a question? And that is you only have small fiber signs. In this structured exercise that we're doing, are we not going to list large fiber signs? Do we not need to examine the patient for large fiber and exclude large fiber as part of this or are we just going to

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assume we have already done that, and that we're only gonna focus on small fiber?
Could you clarify that?
DR. FREEMAN: So an important point. I thought as entry criteria, maybe going down this funnel from being relatively specific to more specific, perhaps from possible to probable, that we would only at this point focus on small five signs. I think we do want to have evidence of a neuropathy, but I think at this point we are beginning to focus on the small fiber aspects of the neuropathy.
DR. GIBBONS: I think Peter Dyck's study looking at the blinded patients, blinded examiners, should certainly give us a clue that non-experts are really going to struggle. I think we have to accept that. We have some data that we haven't published, but looking at podiatry examinations using the NIS-LL, and they vary by as much as 15 points in the same patient between 2 days.
So the non-expert can really struggle with some of these, and I think being prescriptive about

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who can do what is really required.
DR. FREEMAN: We have a vote for prescription. Any other comments?
DR. GEWANDTER: Can I ask a question about that? When you said about who can do what, do you mean be more prescriptive about the questions -- or like the exam and how people should do them?
DR. FREEMAN: No questions. This is the exam. This is [indiscernible], the pin.
DR. GIBBONS: Who might be able to do pieces of an exam? Should this be a neurologist? Should this be a neuropathy expert?
DR. GEWANDTER: I feel like that's different than what Roy is saying.
DR. FREEMAN: That wasn't my intent, actually. My intent -- because I think it's going to be quite challenging in a clinical trial to say it must be a neurologist, but that's an important point. But I think what --
DR. GIBBONS: I think we could siphon off who could do what?
DR. GEWANDTER: I have a research assistant

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who did the UENS and correlated with a neurologist, and she was able to do everything really well and correlate really well, except the reflexes.
DR. FREEMAN: Except the reflexes. Yeah, that's what Vera Bril thought as well.
David Herrmann?
DR. HERRMANN: I've always been skeptical about this, but about nine years ago, we published time vibration testing. I personally don't like [inaudible - off mic]. But we actually have a 13 year old at Stanford Medical School, but he was one examiner trained and the other was one of our neuromuscular fellows, and we trained them to develop the algorithms, the test/retest. They did equally well, and he published it in Muscle Nerve.
DR. FREEMAN: In Muscle Nerve, a very nice paper.
(Laughter.)
DR. FREEMAN: No, no. I know that paper. I thought it was a terrific paper. It's one of the few.
DR. HERRMANN: The examiner there was 13

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years of age.
DR. FREEMAN: No, I think it's a terrific paper.
DR. HERRMANN: [Inaudible - off mic].
MALE VOICE: Roy, maybe one thing to think about in terms of whether we want to be prescriptive or more vague is to look to the MS world. And if you look at what they did with the EDSS and the sensory exam, they are very discrete in terms of how many seconds with the tuning fork. And there's always going to be inter-rate variability, but if we are creating a set of criteria that's going to be used by many studies, maybe this is the time to really think about how we should define these, define them, and then that will become the gold standard.
DR. FREEMAN: So I'm not sure that we -- and Chris and Jen have been looking at this doing a systematic review on the neuropathy exam. I'm not sure that -- and correct me if I'm wrong -- that there is evidence that one approach is better than another. What is fascinating is how many times it

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actually has been prescriptive, and it is remarkably infrequently.

So I think we have two options. It seems to me that -- I don't know. This is maybe apple pie. Of course we need to be prescriptive about this. We need to define how to do it. We need to define where to do it. We need to define what instrument. And we need to define what is abnormal because this is one of the critical pieces. And I want all the neurologists, next time you're in front of your residents, ask them how they do the sensory exam. It is eye opening.

So I think we've got to get beyond that. So the question is -- and here's the question following that preamble. Do we, as Todd suggests, say this is how it's done? Do we refer to the paper that will then have been published by Jen and Chris, hopefully, saying that this is how some have done it, and we suggest that you use these measures that exist in the in the literature? And these are the two possibilities.

So I think we can on the one hand say we

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recommend that the instrument that the site and what is abnormal be prespecified and that investigators be trained in this method. And as I often say when I talk about this, there are many right ways for doing this, but for the purposes of this study, there is only one right way of doing it. So that is an approach that we can use. Variations on that theme say a lot more diplomatically than I have said it versus Todd saying that we recommend that you do it this way.

So go, Simon, and I'm going to --

DR. HAROUTOUNIAN: I just wanted to completely agree with you in terms of being prescriptive, that each study prespecifies what they test. I think in terms of what we can -- whether we should recommend specific tools and specific ways to measure, giving the data on really lack of agreement of specific changes, I wouldn't do that.

Maybe we should go with new recommendations. If you look at the 2016 paper, the science says say negative or positive neurological science upon

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sensory examination. We could go with something like that, but prescribing that in each study, the investigators will determine how they do this examination and by which tools.

DR. FREEMAN: Karin, you've got some points back there?

DR. FABER: Well, what I'm wondering is why don't we use the data that we already have. So we know for the Rydel-Seiffer tuning fork, for example, that there are perfectly normative values, and that's very easy to use bedside. And I'm quite sure that every neurologist can use that. And our residents all use that, so no differences in tuning forks because they know I will kill them.

(Laughter.)

DR. FREEMAN: Eva?

DR. FELDMAN: I'm not advocating for the scale we developed because it's inappropriate, but I do know that if you use -- we did a lot of pretesting of the MNSI, and I think if we're going to actually do this and have it be helpful, you should pick a scale that's simple to do. You can

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train other individuals, even non-physicians to do it. And it's been shown to be reproducible, reliable, and correlate highly with the disorder.

So I would actually advocate for the Utah scale and to be prescriptive. And if we want to give a scale, that seems to be the scale that's most appropriate for small fiber neuropathy.

DR. FREEMAN: I think the reviewers would tend to agree with that, wouldn't you, Chris and Jen?

DR. GEWANDTER: Me?

DR. FREEMAN: Yeah.

DR. GEWANDTER: Yeah. As far as the domains that were covered and had the most weight --

DR. FREEMAN: That certainly covers it best.

DR. GEWANDTER: -- I would say --

(Crosstalk.)

DR. FREEMAN: Chris showed 60 percent compared to everything else. How prescriptive is that scale with respect to the assessment of hyperalgesia and allodynia?

DR. GEWANDTER: Good. Well, allodynia is

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not --
DR. FREEMAN: I don't think it was that good.
DR. GEWANDTER: The pinprick is good.
DR. FREEMAN: Pinprick is good. Pinprick is very good.
Temperature?
DR. SINGLETON: Temperature is not included.
DR. FREEMAN: Not included.
DR. SINGLETON: And I think that's by design because I feel temperature is a far inferior measure to pin in terms of its reproducibility.
DR. FREEMAN: This is getting granular, and I think that's fine.
Giuseppe, do you include temperature? I know you're looking at email over there, which you should not be doing during this critical period.
(Laughter.)
DR. LAURIA: From a clinical --
DR. FREEMAN: So the question was, Rob said temperature is irreproducible.
DR. LAURIA: In a clinical setting.

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(Crosstalk.)
DR. SINGLETON: In a clinical trial --
DR. FREEMAN: In a clinical trial.
DR. LAURIA: Actually, in a clinical setting it is not. I don't think it is reliable. If you want to see whether there's a change in terms of loss of temperature, you have to do a QST I would say.
DR. FREEMAN: Okay. And maybe that's where we will come to with this, and we can quite easily say, based on data to develop into the Utah, that clinical thermal testing is not reliable. I think we have a consensus there.
What about hyperalgesia and allodynia? What did you guys find, Giuseppe, Karin? And maybe your and Gordon can talk a little bit about Utah assessment with regard to hyperalgesia and allodynia.
DR. SINGLETON: I can start with that. I think it's the weakest part of the UENS, because we didn't specify it very well and because I rarely find that patients gain points in the way that I

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check for allodynia or hyperalgesia. But I think it's good. Using a pin to look for hyperalgesia helps, and when I see patients who have increased pain sensation, they react in a way that makes it clear that they have increased pain sensation. I'll give them points for hyperalgesia for that. But it can be strengthened in our --
DR. FREEMAN: And part of it is, I mean we with our bedside QST look at mechanical and thermal hypoalgesia and allodynia, and the issue is that within the diabetic population, it is actually relatively low. And one of the issues is, well, so um, I think it's higher in this population, in the small fiber population.
Karin, any points to make?
DR. FABER: No, I agree completely. I mean this is very difficult to assess in a really reliable way. That's the big problem I think.
DR. FREEMAN: Yeah.
DR. HOKE: I was going to suggest why not just stick to pinprick, as the others don't seem to add much to the evaluation.

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DR. FREEMAN: Well, I actually think hyperalgesia and allodynia -- personally, I think when it is present, it does add, and Karin is nodding there.
Giuseppe, would you agree? I think that the pinprick certainly is bread and butter and must be done. I think the others I don't think we should omit, because I think presently are hallmarks of peripheral neuropathy, neuropathic pain.
DR. OAKLANDER: How do you assess? That's the problem. Do you require --
DR. FREEMAN: Well, I can actually -- if you leave this in my hands, I can say how it's assessed, and I'm comfortable doing that, actually been quite prescriptive on how to assess hyperalgesia and allodynia at the bedside.
DR. HOKE: But will it add to a trial? Would you use that as an outcome measure in a trial?
DR. FREEMAN: We're not talking outcome. None of this is outcome. I want to really emphasize this is inclusion criteria. We are not

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looking at outcome.
DR. HOKE: So would you enroll a patient who has normal pinprick but just has hyperalgesia?
DR. FREEMAN: Yes. Yep. I think that's one of the -- to me that's a cardinal feature of neuropathic pain. That would be my stance, that -- I don't know how often that occurs, but, I think it occurs --
Giuseppe?
DR. LAURIA: It is definitely part of the clinical picture in my experience, but how to quantify it is pretty much difficult, first. And second, what kind of allodynia because there is light-touch allodynia, but also mechanical pressure allodynia. If we stay in terms of presence of signs, which are elicited by the examiner, I think what is written in the books. So you elicit the hyperalgesia with a painful stimulus. For the quantification, you have to go to the QST, to the German part of that.
DR. FELDMAN: Although Rob did a disclaimer and said he felt that it was a weak part of his

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scales, still in the Utah scale, you do elicit hyperalgesia. I mean, again, there is no perfect clinical scale, but if we had to be prescriptive and pick a scale, it does meet -- except for the thermal impairment, it does meet all those criteria.
DR. FREEMAN: Can you remind me, Rob, how is allodynia and hyperalgesia assessed in the Utah?
DR. SINGLETON: Well, we have it as a discrete part of the test. We ask --
DR. FREEMAN: It's a question. It's not a sign.
DR. SINGLETON: No, it's a sign. Everything's a sign in the exam scale.
DR. FREEMAN: What do you use to evoke?
DR. SINGLETON: I was going to say that what the instructions say is that you should touch the patient's foot lightly and see whether they find that uncomfortable. And then I think it says that with the pin, you should see whether there is a distal predominant, uncomfortable increase in pain sensation that the patient responds to.

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DR. FREEMAN: Just by way of comparison -- and this is used for phenotyping; it's not used as an entrance criteria -- we evoke allodynia and hyperalgesia at the bedside. So pin with brush, with pressure, and thermally. And the thermal is a little complicated depending on the clinical trial, but we do have ways of doing this at the bedside without using the Medoc or the CASE IV.
DR. LAURIA: So just the thermal allodynia has to be a question in my experience because it's thermal allodynia.
DR. FREEMAN: It can be done with a stimulus and asking --
DR. LAURIA: I know, but to make it feasible --
DR. FREEMAN: No, I understand. I'm not sure that this is feasible in a clinical trial.
DR. LEVINE: So if we're going to use these as inclusion criteria, then I would say you absolutely have to include hyperalgesia and allodynia because in pure small fiber patients,

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we'll see many patients that don't really have much loss of pinprick but have severe neuropathic pain symptoms, so you're going to want to say --
DR. FREEMAN: That's Ahmet's question.
DR. LEVINE: Yeah, so I think --
DR. FREEMAN: I would tend to agree. I don't know numbers, but I would tend to agree.
Okay. So where are we with this? Simon?
DR. HAROUTOUNIAN: I just want to tell the data support that if you use only pinprick in almost 50 percent of the cases, you actually don't discriminate between healthy controls and small fiber neuropathy. So it should be some kind of composite.
DR. FREEMAN: All right. Let me just throw a balloon up in the air that you can shoot out. Allodynia assessed with pinprick, with brush, with a thermal stimulus -- allodynia or hyperalgesia assessed in one of the following ways: a pinprick, brush, and a thermal stimulus, perhaps a cold tuning fork, a cool tuning fork, a heated tuning fork.

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How would we do with that? It's a little vague, but it's better than what exists in the Utah at the time.

DR. FELDMAN: Well, the Utah is actually more prescriptive than Rob was recalling, because I just went and taught the Utah to a group of physicians in another country, and they do say to take a cotton swab, for what it's worth, in their in their instructions for allodynia.

DR. FREEMAN: I think we can come up with something. I think there's enough to work up with, between the Utah, between what we do, which is in the process of being validated. So I think we can come up with some instructions with provisos, and I want to say that ours is not -- we don't promote this as an entrance criteria for a clinical trial. We do promote it as an approach to phenotyping neuropathic pain. So we can come up with something that we will circulate, and I think flesh it out.

I suppose how specific, how structured we've agreed on. Where are we at this point? One of 3 three. We could group hyperalgesia and allodynia

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together and say 1 of 2, or 2 o 2, 2 of two teams, too stringent.

DR. LEVINE: I think you keep them separate and do 1 of 3. That's my vote.

DR. FREEMAN: You would keep allodynia and hyperalgesia. So you would say pin feels even more painful; brush fields painful, 1 of 3?

(Affirmative nods.)

DR. SINGLETON: If we're talking about the Utah as our kind of Schema for inclusion, I would recommend we actually follow the numerical entry.

DR. FELDMAN: Yean, me, too.

DR. SINGLETON: We have a qualifying score that we validated as consistent with diagnostic finds the greatest area under the curve diagnostically for the Utah Early Neuropathy Scale. One thing I would say about it is -- and I hope this is going to -- so one thing I would say about it is that it's possible to get to that score with only large fiber features.

DR. FREEMAN: That is my --

DR. SINGLETON: So I assume that your next

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slide is going to be about the inclusion of large fiber features in neuropathy on exam.

DR. FREEMAN: Well, I'm going to be talking -- at some point, and I don't know where that lies -- about the exclusions. And that's my concern about using the Utah, is that it is 60 percent but there's a 40 percent. So I'm advocating something along these lines, but with, again, lots of codicils, lots of provisos.

Chris?

DR. GIBBONS: Well, I think the exam includes what you're looking to exclude. So as a consequence, you could simply revise the output from the Utah into your separated and inclusion. So if you have absent reflexes, you're excluded. If you have weakness of the EHL, you're excluded. But that's in the exam --

DR. FREEMAN: So that's why I don't think it's a good idea to use the Utah as an entry score. I'm very happy with the Utah as far as the approach to assessing pinprick, although we can argue about what the cutoff should be in terms of distal to

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proximal. I am not -- and again, I've not looked intensely at it, but I'm not happy about its assessment of hyperalgesia and allodynia.

I think there's enough to work with, but I would like you to talk to me about the Utah, guys, to talk to me about what you think a cutoff for pinpricks should be, what's abnormal. So we define how pinprick is tested. We define where it's tested. We even define the instrument. What's normal? What's abnormal?

DR. SINGLETON: It's obviously -- it's age dependent, but I think in patients less than 60 years old, that reduced pin sensation that affects the toes and the distal dorsum of the foot is a abnormal.

DR. FREEMAN: Okay, and reduced -- again, I just want to -- and I don't mean to put you on the spot.

What's reduced?

DR. SINGLETON: Reduced is -- so you give them a normal stimulus. I usually choose the upper part of the back of the leg as my spot unless they

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tell me they have no sensation at that level. And I say this is what normal feels like, and then I go to their toe and I say, "Is it as sharp here as it is on your leg?" And if they say yes, then we're done with the pin assessment. If they say no, then we decide how much less. But I want to see that they agree that that pin sensation is less than they expect on their leg, and then I'll work up their foot, from their toe towards the dorsum of their foot to see where they find normal sensation.

So if there is decreased sensation at their toe, I want to see that by the time they get -- someplace up there leg, it becomes normal. So that confirms this idea that there's a length-dependent quality to their pain sensory loss.

DR. FREEMAN: So Todd, you've looked at the MS literature I think more so than anybody. Do they look at pinprick?

DR. LEVINE: They do. Let me think about it. I have to remember.

DR. FREEMAN: While you're thinking, Anne

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Louise? Anne Louise, you were going to say something?

DR. OAKLANDER: I was just saying I do the same as them, essentially, but I work down. I'm not saying that's better. I'm just making the comment that the devil is in the details.

DR. FREEMAN: Okay. This is --

DR. FELDMAN: Roy, can I make one comment? If we go with your idea, which I'm not saying is neither good nor bad -- of just using brush, et cetera, we just have to not have lots of gradations. It either has to be yes or no, right? Because this isn't a validated scale. So if you're going to go with a non-validated scale, you have to I think be very black and white.

DR. FREEMAN: Sorry. Which is the non-validated?

DR. FELDMAN: Well, I don't know. You're saying that maybe for hyperalgesia, we use a brush on the toe, and it's either got to be yes or no. It can't be a little bit.

DR. FREEMAN: Absolutely.

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DR. FELDMAN: So if we're going to do that, we just have to be very --

DR. FREEMAN: That's painful --

DR. FELDMAN: -- very yes or no.

DR. FREEMAN: A brush should not be painful.

DR. LEVINE: It came back to me. It took me a second. So odd sensations, paresthesias, dysesthesia, in the EDSS, it's all yes or no. Tuning fork is by seconds.

DR. FREEMAN: Let's just do pin because that's all we're using

DR. LEVINE: Pin is going to be tough for us because the first cutoff is loss of discrimination between sharp and dull. So that's the first gradation point. So it is kind of a yes or no question.

DR. FELDMAN: It just needs to be yes or no, and then that would be very appropriate.

DR. FREEMAN: How does that sound to you guys? Do you feel this is sharp as a pin or not? You don't do that, do you?

DR. SINGLETON: I think it's very reasonable

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to get a valid result when you ask people whether they have reduced pin sensation, not just absent pin sensation. I think that you lose discriminating value when you all you're trying to do is see whether they have pin sensation or not.

DR. FREEMAN: Yeah. Okay.

DR. SINGLETON: So I would argue for the idea that it's possible to say they have decreased pin sensation and still get a valid result.

DR. FREEMAN: Yeah. And I agree that hyperalgesia and allodynia are all or none. Allodynia certainly is all or none. Hyperalgesia is a little trickier, and we do have data on this.

Gordon?

DR. SMITH: I'll be uncharacteristically definitive. I think in regards to pin sensation, the way the UENS is scored, if one were to create a threshold, I would keep the threshold the same as the scale performs as a 4. And I think that also conforms to -- I've done a million UENS'S by now, and there are a fair number of people who have no other evidence of neuropathy who have a mildly

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subjectively reduced sensation to pin in their toes. It's somewhat less common to see that in both feet, so I would say a 4.

The other point to Eva is the UENS instructions actually are not prescriptive in how allodynia is assessed. I just went through the paper. It says that it's done as per a typical neurologic examination.

DR. FREEMAN: So we can be a little more prescriptive. As I say, validation presented at the APS a month or two ago.

DR. HERRMANN: One question I had, obviously if you're going to you a standardized scale [inaudible - off mic] -- you don't want to deviate from what's been validated in it. But if you are going to deviate, why not standardize the -- I mean obviously do the same approach instructions for testing on pinprick, gradations, and so forth in scoring, but why not use a more standardized instrument such as Neurotip or the Neuropin?

We use it in the CMT world, and I think it just gives you -- some parts of the world don't

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like to use a safety pin just from a hygiene standpoint. And I think it's inexpensive, it's easy, and it just gives you a little bit extra standardization. [Inaudible - off mic].

DR. FREEMAN: Neurotip is fine. Do you guys recommend Neurotip or are you specific?

DR. SINGLETON: This is real interesting because when we first validated this, we had questions about the exact size, which size of safety pin. This was something that held up provocation of our -- I think it was which size of safety pin were we talking about. Was it going to small, or large, or in the middle? And we ended up saying a size 12 safety pin because we had to do something to satisfy the reviewers.

DR. SMITH: We ordered those, too. We've stuck to that.

DR. SINGLETON: Yes, we have.

DR. SMITH: It's Office Depot.

DR. SINGLETON: They're pretty consistent. As far as we know, they are sterile.

(Laughter.)

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DR. SINGLETON: Not disease --

DR. FREEMAN: David makes a very reasonable point. In Europe, I think the UK are not happy about using safety pins in the clinical exam.

DR. SINGLETON: Not okay with it because why?

DR. FREEMAN: I'm not entirely sure.

DR. SINGLETON: A cultural difference. Safety pins have some sort of negative connotation in Europe?

DR. SMITH: They're ironically unstable [inaudible - off mic].

(Laughter.)

DR. LAURIA: [Inaudible - off mic].

(Crosstalk.)

DR. SINGLETON: That's a bizarre idea.

DR. TREISTER: I think the pins are more shaper than here. You can find here dull pins.

DR. FREEMAN: This is fascinating.

DR. LEVINE: I like the standard tool, though. I think that's a good idea.

DR. FREEMAN: What was the question? What

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was that, Todd?

DR. LEVINE: I said I think the idea of standardizing a tool is a good idea because there is variability.

DR. FREEMAN: Neurotips -- just to I think the last comment on this, do people know the sharpness of Neurotips? Is that batch to batch consistent?

DR. GIBBONS: They're not particularly expensive. I frankly hate them, but I use them. But the thing I find is that in fact they often don't work. You take the tips off and the other end comes. It just falls apart, and I don't like them.

DR. FREEMAN: All right. So let's move on. We really are moving along rather nicely.

DR. GEWANDTER: Can I ask a question, a clarifying question?

DR. FREEMAN: Do you have enough, Jen, to conclude?

DR. GEWANDTER: I have a question. We said before that it has to be distal, at least the

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history for the symptoms. Then I just heard someone say the exam should distal, but that could be someone had a distal history but not anymore. So what do we want to do about that?

MALE VOICE: Distal.

DR. FREEMAN: Distal.

DR. GEWANDTER: For the exam. So it has to be --

MALE VOICE: UENS is a distal exam.

DR. FREEMAN: It's all distal. Even if it spreads proximally, we're still interested in distal.

Anything else? Are you okay with the examination? I think there's enough to work --

DR. FELDMAN: So what did we decide, actually? I'm a little confused.

DR. FREEMAN: No, that's a very good question, what did we decide.

(Laughter.)

DR. FELDMAN: Did we decide to decide later among our choices?

DR. FREEMAN: No, no, no. We decided that

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we would use allodynia, hyperalgesia, and pinprick, and that one of those three was sufficient, and we would standardize as much as we possibly could with respect to all of those.

DR. FELDMAN: And for the pinprick, did we decide to use the UENS?

DR. FREEMAN: We decided that we would use the UENS and that we would have Gordon and Rob define exactly how we would do that, and that we would not be looking at the distribution, but we would have a dichotomous result, either positive or negative, normal or abnormal.

Is that okay?

DR. SINGLETON: Are we going to talk about large fiber exam features here or are we going to just like ignore that question?

DR. FELDMAN: And that was a question I asked earlier, too.

DR. FREEMAN: That's a question, so I guess now that two -- I obviously did not answer Eva well enough; I thought I did. So I think for the inclusion, this is my take on this, and let's float

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balloon up and see where this goes.

For the inclusion criteria for a clinical trial, I thought that we should be focusing on small fiber sensory symptoms and small fiber sensory signs and small fiber sensory investigations.

DR. SINGLETON: So are you advocating for a pure definition of small fiber neuropathy?

DR. FREEMAN: What we are going to do afterwards is -- and we do have time is to discuss whether we are getting to take the hard-nosed Italian approach, which is no large fiber aspects at all or whether we are going to take the David Herrmann permissive approach where we are going to let some patients with a little bit of large fiber stuff in.

DR. SINGLETON: I think we should talk about that now. This is where the rubber hits the road.

DR. FELDMAN: I do, too.

DR. RUSSELL: Roy, another thing that needs to be addressed in signs is when you test pinprick, are you going to test it simply on a great toe and

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determine is it painful or not painful, or are you going to do a proximal distal comparison? And the reason why I bring this up is because if you look at the MDNS, it actually asks is this painful? And whether it's because some people don't like to complain about pain or because of the different pins, people will sometimes say, normal people, that they don't feel it as painful when you touch the great toe. They are normal, so you've got to be very careful about how you define that.

DR. FREEMAN: Do you want to maybe say how should be done?

DR. SINGLETON: Well, I think I already did, how the UENS UFC is done. Whether that's how it should be done, I don't know.

(Crosstalk.)

DR. SINGLETON: But it seems like there's consensus that that concept that we're going to do something that figures out if this has a distal predominance and find it's proximal extent, that's what we're talking about, and the MDNS does not actually do that.

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DR. FELDMAN: No, it does not, because the MDNS is the broader MNS size [indiscernible].
DR. FREEMAN: So just to move the process along, can we leave this in Rob, Gordon, Jen, and my hands that we will come up with a way of doing pinprick, and we will circulate it to everybody, and we will come up with a way of testing hyperalgesia and allodynia, and we will circulate that to you. And we will say at this point, for the small fiber sensory aspect of the clinical history, the symptoms and the exam, that we have enough to at least create a preliminary draft of the paper.
Now at the request of the audience, against my better judgment --
(Laughter.)
DR. FREEMAN: -- we will move on to discuss large fiber aspects. Is that an accurate summary?
DR. FELDMAN: Yes.
DR. FREEMAN: Okay. That's where we are.
Are people comfortable? Do you need to stand up and stretch? Do you need to get some

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coffee?
DR. FELDMAN: I'm getting coffee.
DR. FREEMAN: Why don't we take a five minute break? I'll have a bite of my sandwich and get some coffee, but really just five minutes.
(Whereupon, at 1:13 p.m., a recess was taken.)
DR. FREEMAN: Bob has just walked in, and I just want to fill him in. He just had lunch with a Jake Tapper, and he could maybe fill us in about that.
DR. FELDMAN: Really?
DR. FREEMAN: Yeah. I think we've moved along incredibly well. I don't want to be too congratulatory to all of us, but I think it's been really good. At this point we have reached consensus on the approach to symptoms and on the approach to signs. What we have not done is we have not defined, done, what is idiopathic, what needs to be excluded. What we've not done is discussed genotyping and the immune trial; and what we've not done is discuss the special

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investigations. And at Rob Singleton's request, and Eva's too, we are now going to be talking about the large fiber story. And I think there are several approaches.
Is this, Rob, what you had in mind?
DR. SINGLETON: Sure, yes.
DR. FREEMAN: So I think there are several approaches to dealing with the large fiber approach. And as I said, there is a spectrum from the hard-nosed, Italian approach, nothing large fiber is allowed into the trial, to the David Herman permissive approach, where you can sneak a few large fiber findings in, and nobody's getting to know the difference. And I think the way we can approach this is -- and perhaps this is a reasonable way of doing it, and now to be quite serious, to say that the Giuseppe Lauria approach is a pure small fiber neuropathy; that the David Herrmann approach is a small fiber predominant approach. And this is where, as rob said, the rubber meets the road and how do we define predominant. And then the mixed is, on the one

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hand, on the other hand, equal.
So to me, this seems a reasonable approach. I can now elaborate a little, but since Eva and Rob wants the discussion, these are the features of large fiber listed ahead.
How would you suggest we approach this? And Karin is next, too.
DR. FELDMAN: Just the way you I thought very nicely had us talk about pure small fiber, mixed fiber, autonomic, and pure autonomic. In many ways, we could look at it this way for this entity we're now going to discuss. We keep pure small fiber. If you have pure small fiber, you cannot have any of those three, and then if you're small fiber predominant, I would suggest that you could not have motor fiber impairment. You can't have muscle. That definitely puts you into mixed axonal neuropathy. And then we could decide.
I mean there's really nice data, again, from Jim Albers showing you can have very mild abnormalities on nerve conduction studies that are abnormal and still essentially have a normal exam.

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So I don't even know if we want to go talk about nerve conduction studies here as an exclusion. I mean, maybe we don't even want to talk about electrophysiology, and just keep it to a clinical exam, and just then decide about what degree of large sensory fiber impairment we could have to be small fiber predominant. But keep those three.

DR. FREEMAN: This approach.

DR. FELDMAN: Right. Keep that approach. And you've defined pure SFN.

DR. FREEMAN: Pure is easy.

DR. FELDMAN: Right.

DR. FREEMAN: I think the decision that we have to come to is the difference between small fiber predominance and mixed, and one of the points is no motor fiber impairment at all. And I think just to make the point, and maybe it's worth discussing very briefly, somebody's talk said that they thought that the pure was 5 percent of the small fiber population. Giuseppe would say probably more. Karin would say probably more. And I think this emphasizes perhaps national

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differences, but I think it's important to bear this in mind.

So I think I'd like to focus the discussion on how do we definitely -- we have one point and I think universally agreed you cannot have any motor fiber involvement.

Anne Louise?

DR. FELDMAN: And I also don't think you should have any absent tendon reflexes. So if your ankle reflexes are gone and you have motor fiber impairment, you need to go into the mix axonal neuropathy.

DR. FREEMAN: Is everybody in agreement with the tendon reflexes?

DR. SINGLETON: Eva, if you're 70? How about that? If you're 70 years old and your reflexes are absent?

DR. LAURIA: I agree with Eva.

(Crosstalk.)

DR. FREEMAN: Eva, Rob says what about age?

DR. RUSSELL: Well, the other thing is what if you've got an L5/S1 radiculopathy? So maybe

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absent tendon reflexes --

(Crosstalk.)

DR. OAKLANDER: Let's look at the easier one first, which is weakness.

DR. FREEMAN: We've decided motor is out. That's gone. You cannot have that.

DR. OAKLANDER: What if the patient has no motor complaints and they're not weak, but when you test them, you find --

DR. FREEMAN: We're out.

DR. FELDMAN: Well, then it's not pure small fiber.

DR. FREEMAN: Karin?

DR. FABER: Well, I completely agree with Eva, I think, to have these three components, and the muscle weakness indeed is quite easy. I do agree that you should have retained reflexes because otherwise it's large fiber neuropathy. And of course we can all think of a lot of exceptions, but I think this is the general rule. I would very much like to stick to that.

Indeed, if you ask us, we say that the pure

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small fiber neuropathy is the majority, but of course it has to do with the fact that we are a tertiary referral center, so there may be bias in that.

DR. FREEMAN: Just to give Rob's counter-argument, and I don't know what the cutoffs are for the Kromasil study, for the Aptinex study, and for the Biogen study, but Rob makes the point that most -- and here we get into the discussion that Gordon raised, what is normal elderly. But many who we think of as being normal elderly may have lost ankle reflexes.

Eva?

DR. FELDMAN: So that's because they have a mixed axonal neuropathy of aging. The Scandinavians did those beautiful studies early on in the late '60's early '70's where they biopsied the elderly, the impaired nerve conduction studies, demyelinated fiber densities, and biopsied them with ankle reflexes, et cetera.

So what you see when you lose your ankle reflexes, you have a clear decrease in your

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myelinated fiber density. I mean, I really do think that if we really want to have a small fiber predominant neuropathy, you do need to have retained reflexes because those absent reflexes indicate you have a mixed axonal neuropathy due to aging. And it may be normal aging, but it's aging, so loss of myelinated fibers.

DR. FREEMAN: The question is -- so you are saying small fiber predominant. If you have lost your ankle reflexes, you are out. You are not --

DR. FELDMAN: The difference [inaudible - off mic] -- because you can have reduced --

DR. FREEMAN: We're dealing -- at this point --

(Crosstalk.

DR. FREEMAN: -- between mixed and small fiber.

Giuseppe?

DR. LAURIA: There is something that's not quite clear to me considering that the motor fiber is okay, what is the difference between the predominant and mixed?

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DR. FREEMAN: The difference between predominant and mixed is what we are discussing over here. So we are a saying mixed axonal neuropathy will be somebody who has weakness. They would be mixed. Eva is postulating that mixed axonal neuropathy is loss of reflexes. So we're trying to fill in the mixed axonal neuropathy pot, which is to say -- now we're very clear on pure.

Let me be explicit.

DR. LAURIA: I'm sorry. Maybe it's me that --

DR. FREEMAN: Let me be explicit. We're very clear on --

DR. SINGLETON: I think Giuseppe was confused. I think that we just said, Giuseppe, that no weakness can be allowed in either --

DR. FREEMAN: Yes.

DR. SINGLETON: -- small fiber predominant or mixed axonal neuropathy, or pure --

DR. FREEMAN: That's what Eva is saying. Eva is saying that you cannot be in this class over here -- this is clear. Right? This is basically

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the hard-nose criteria.

This is not so clear, and we're trying to decide what the difference is between this and this. And we have agreed that any of this bullet, the second bullet, puts you over there. What we have not agreed yet is on which aspects of these are actually permissible and are allowed to keep you in small fiber predominant.

DR. LAURIA: Any --

DR. FREEMAN: Let me just finish.

DR. LAURIA: Yes, I'm sorry.

DR. FREEMAN: Eva has suggested that reflexes would move you down to mixed.

DR. FELDMAN: Loss of reflexes.

DR. FREEMAN: Loss of reflexes. Exactly.

DR. LAURIA: I still don't understand, but --

DR. FREEMAN: Gordon?

DR. SMITH: So just a couple of points. One, in Peter Dyck's kind of dress up the patients and come to Rochester study, one of the changes we made in the second year was to agree that absent

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reflexes were acceptable in people over 70. And that was just one of the things that we agreed upon, and it improved our accuracy substantially and our reproducibility.

This is obviously not a small fiber predominant population.

DR. FREEMAN: So can I just define this accurately? And reproducibility --

DR. SMITH: Reproducibly.

DR. FREEMAN: -- would be saying somebody has a neuropathy or not.

DR. SMITH: Or not, right.

DR. FREEMAN: I just want to be clear on this --

DR. SMITH: So the reduced overdiagnosis of neuropathy.

DR. FREEMAN: -- because there are two issues over here, how easily non-neurologists can elicit reflexes, and the other is defining neuropathy based on reflexes.

DR. SMITH: So I bring that up just as a data point, not arguing one way or the other about

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reflexes. But the second I wanted to bring up is the issue of non-neurologists doing reflexes, which -- I don't know whether I've got oncology on the brain, but oncologists just seem fearful of this.

DR. FREEMAN: And that's my concern. And Vera Brill I think found that as well. I have concerns about using reflexes at all, particularly ankle reflexes, which I think most non-neurologists find challenging.

Okay. I'm going to have some closure on this quite quickly. So Nurcan, and then Bob Dworkin.

DR. UCEYLER: I wonder if the already existing criteria of Stewart 1992 and the Lacomis 2002 might be helpful in distinguishing small fiber predominant and mixed axonal. So when we look at this here, for instance, Stewart says included patients with loss of vibratory sensation at the toes absent ankle reflexes. If this is the case, still the patient can be classified as small fiber neuropathy.

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I think this is helpful; at the Lacomis site a few years later, more significant indicators of large fiber dysfunction, including decreased proprioception at the toes, vibratory loss at or above the ankles, and any distal wasting or weakness, and generalized areflexia to be exclusionary.

Is this helpful in any way? This is something that we are using, for instance, in clinical practice, and I find this very helpful because ankle reflexes, as you say, this can be lost after a certain age. Areflexia is something different. Maybe this may help.

DR. FREEMAN: So just to make sure that all of the views are on the table, there is the one view that says, well, this is normal aging and yet you can lose reflexes. Eva is saying there's nothing normal about losing reflexes. And I think we need to come to some consensus on that.

Bob? And I want to move this along because this is why I put this for last. I had concerns about this one.

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Let's go. Bob?

DR. DWORKIN: I'm sorry that I missed the last three hours, but I was in a meeting with drug company CEOs where ACTTION IMMPACT were discussed, and I obviously needed to be there.

So maybe I'm biased by the last three hours with discussions about why drug companies are leaving CNS, and in particular pain. And that was the discussion for most of the two-hour discussion of pain, which is how to get pharmaceutical companies back into pain because they've been fleeing pain because drug development is so difficult.

But in the context of that discussion, I look at this -- and maybe this is another naive question. But does this inhibit drug development? Are we slicing the pie too skinny so that if I was a CEO and looking at this and thinking, okay, I'm going to pursue Alzheimer's disease or major depression because now I've got to figure out whether my drug development program is pure SFN or small fiber predominant, and that's going to be my

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label. And of course this makes the clinical trials more difficult because, as Gordon was saying, everyone's got to be trained to do a sophisticated neurological exam.

If I'm off base here and there's no potential here for inhibiting drug development, then I retract my comments. But after my last three hours, that's a concern I have about this slight, very fine elegant slicing.

DR. FREEMAN: We have very much kept our eye on the ball, and pharma has commented, and at the end of every discussion, we've taken their views. And the last thing on our minds is to inhibit drug development. But I do take your point, and that's really my stance on reflexes. I have concerns about this.

I want to maybe just broaden this out a little and say what do we think is acceptable in the large fiber realm to create a mixed category that skiers left can include in a clinical trial?

DR. SINGLETON: I'll offer a proposal. I would say a very conservative proposal, that is

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queuing towards pure, is we would allow reduced but not absent vibration at the toe, and we would not allow reduced proprioception at the toe.
DR. FREEMAN: Reduced or absent?
DR. SINGLETON: I said we would not allow reduced proprioception at the toe.
DR. FREEMAN: You would not allow. So reduced vibration, but you would not allow any reduction in proprioception.
DR. SINGLETON: Yes. But in return --
DR. FREEMAN: As we know, proprioception can be done --
(Crosstalk.)
DR. SINGLETON: But in return for my proposal, I want to make --
(Crosstalk.)
DR. FREEMAN: -- with excursions of 90 degrees and excursions of 10 degrees.
DR. SINGLETON: Haggling here. So in return, I would say we want to either make -- I think there's a real argument for making reflexes agnostic. Like we're just going to leave them off

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of our discussion because they're hard to do.
DR. FREEMAN: I'm okay with that.
DR. SINGLETON: I think that would be a perfectly reasonable good excuse, a way to get out of this impossible debate.
DR. FREEMAN: So Rob has proposed something. We'll come to nerve conduction studies in just a second. But Rob has a proposal just talking about -- so Rob has proposed you cannot have any deficit proprioception, and he's been kind of agnostic as to the degree of excursion that the toe has made.
DR. SINGLETON: That's even more argument, of course, but --
DR. FELDMAN: I think that is actually splitting too much. I'll just say, again, having trained many people to do simple exams for large studies, to have to train someone to do proprioception I think would be difficult in any clinical trial.
DR. SINGLETON: Just not talk about it. I think vibration is more sensitive than

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proprioception, so can we just have vibration as our only large fiber sensory measure?
DR. FREEMAN: And we can say that absent vibration at the great toe moves you down to mixed, but decreased is permissible. Reflexes we don't discuss, although we know that these are large fiber, and we don't discuss a proprioception. I'm fine with that.
Anybody disagree with that, other than Anne Louise?
DR. OAKLANDER: You always assume I'm disagreeing.
DR. FREEMAN: I thought your hand was up. You have a bias.
DR. FREEMAN: Not at all. Are you guys okay with that? No? Heikki?
DR. MANSIKKA: Maybe a question triggered by Bob's comments there. So if we run a study where we actually are a little bit more permissive in terms admitting patients who have mild loss fiber involvement, would then these kinds of data actually prevent you from using the drug if we show

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it works in this more loosely defined population? Would that prevent you as a clinician to use then the drug in a more pure population? I guess that's what I'm asking --
DR. FREEMAN: I don't think so at all. There is a question I think that the regulators may wish to weigh in as to whether this would be acceptable from a regulatory perspective or at least something to think about. But let me ask -- Deb has something to say.
DR. STEINER: I was just going to say, from my standpoint, Bob, this has been incredibly helpful for me because if at the end of the day, let's say there are guidelines on small fiber neuropathy and there's the definition of pure SFN, which is a lot of what we've been talking about over the past two days. And then there's the progression towards small fiber predominant and then mixed axonal neuropathy. And if we get to the point of predominant large fiber, then that's not the patient population that we're looking for anyway.

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So I think that you could include potentially any of those patients in your study. It depends on what your target is. But this is much easier for me than just working towards what I've had to most of the time up until now, which was really idiopathic or pure SFN.

DR. FREEMAN: Okay. So I'm going to float another balloon up before people respond, and I'm going to say that we are going to say the characteristics of small fiber predominant are the following: decreased but not absent vibration. We are going to see we do not include proprioception or reflexes in this because of the fact that these are two unreliable in the hands of non-neurologists and that -- and this we haven't discussed, but I do want to move things along a little -- that absent -- and we do allow present but decreased sural sensory action potentials, but absent sural sensory action potentials will move you down into the mixed.

Can I float that up and see what people think about that? Gordon?

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DR. SMITH: I want to go back to Bob's comment and the exchange. And I said yesterday I'm ambivalent about the whole diagnostic validity of small fiber neuropathy, and that ambivalence is getting worse listening to this conversation. I worry that we could run into taxonomic chaos, because we'll have a separate taxonomy for painful peripheral neuropathy for instance. So where does our small fiber predominant neuropathy with pain differ from painful neuropathy?

I think we just need to think about the landscape in which these exist. And I think this conversation is good internally, and I think we can certainly nest this in such a way so that pure small fiber neuropathy is a subtype of small fiber neuropathy. But I just want to point out that there are these other taxonomies out there that we need to keep in mind, so that we don't end up with confusion from a regulatory or pharmaceutical development perspective.

DR. FREEMAN: I think once we start discussing idiopathic, I think it will become clearer.

DR. LAURIA: May I very quickly? Following your comment, I agree with Gordon because this is just a matter of defining the subgroup of patients, but nothing prevents in a trial dealing with the assessment of a new drug, a neuro analgesic [indiscernible], to include all of them. You will have then a more favorable postdoc analysis, for instance, by the subgroup. So I think it's

DR. STEINER: But what are you indicating, then?

DR. LAURIA: It's a painful neuropathy. If a new drug wants to reduce the pain, the neuropathic pain, do you think that it is really the core of the fact that you're taking patients with pure small fiber neuropathy or a patient with a predominantly small fiber neuropathy, that will be a never-ending discussion because pure small fiber neuropathy could get an abnormal nerve conduction study if you study the very distal nerves.

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So I think it is just a matter of defining within the group of this category of neuropathy how they subgrouped in terms of predominant impairment of the of the type of fibers.

DR. FREEMAN: I would echo that approach. That here there's no doubt that in some patients this is a moving target. They progress from pure small to mixed -- to small fiber predominant to mixed, and in other patients, they remain pure or maybe remain at small fiber predominant. There's no doubt that if you were to look at -- as David implied, if you look at plantar responses, they may be absent at some point along the way. If you were to do, as somebody showed earlier -- Giuseppe showed some sural nerve biopsies. You will see small fiber loss.

We are creating diagnostic criteria and defining the box. And I think it would be certainly acceptable from my standpoint to say that if you are looking at painful diabetic peripheral neuropathy, you are looking at the complete package, including mixed. And if you are looking

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at small fiber neuropathy, and in particular, idiopathic small fiber neuropathy, this is what we're talking about.

So that's my stance on it. Giuseppe? Karin?

DR. LAURIA: That's what I was saying.

DR. FREEMAN: I know that. I'm agreeing with you in another accent, that's all.

(Laughter.)

(Crosstalk.)

DR. RUSSELL: Roy, I agree with what you're saying, but to further define that box, you may want to recommend certain ways of actually measuring vibration. So Nurcan [indiscernible] earlier had mentioned there was a Rydel-Seiffer tuning fork that you do have normative data. And I have to tell you a lot of neurologists are very, very poor at measuring whether vibration is abnormal in older individuals.

There is also normative data as the percentiles now published for the sural sensory responses. So again, I would probably recommend we

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might want to consider using that particularly in older individuals where it's more difficult to determine cutoffs.

DR. FREEMAN: But before, Eva, I just want to make sure that we so far are on the same page with absent vibration moves you down to the mixed, and absent sural sensory action potentials moves you down to the mixed, and anything less than that keeps you in the small fiber predominant.

Eva?

DR. FELDMAN: So I'm just confused why we're even going to talk about nerve conduction studies. I mean, if you think there's variability in the ability of people to do ankle reflexes, what about getting sural nerve amplitude? So my suggestion would be if we're going to forget ankle reflexes, we should forget nerve conduction studies also. I don't think they necessarily need to be a part of this.

DR. FREEMAN: Yeah. Okay.

MALE VOICE: That's a very good point.

DR. FREEMAN: But let me say something.

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What happens if they exist? Unfortunately, particularly in the US, you cannot have a tingling toe without having nerve conduction studies done. What happens if --

DR. FELDMAN: This is in a Michigan experience. One of our fellows looked at individuals who come to us with an absent sural, and we redo the study. In almost 40 percent of the time, surals were present if there were ankle reflexes. So again, it depends, but I just don't think it should be part of this.

DR. FREEMAN: I understand. I take your point.

Rob is the one that wanted this discussion. How do you feel about Eva, that we make that agnostic as well, and all we have is vibration?

DR. SINGLETON: It's easy. We'd all agree that there are nerve conduction study abnormalities that would be exclusionary, evidence of demyelination for instance. So I think we have to --

DR. FELDMAN: But do you have to have the

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nerve conduction studies? I just think we really start getting down a slippery slide here.

DR. SMITH: Under a diabetes population, the positive predictive value of nerve conduction studies is very poor. This is the flip side of the conversation we had about skin biopsies. So I think requiring normal nerve conduction studies doesn't make sense in that context, and then it adds a great deal of complexity for something that I think has already been [indiscernible] time.

DR. FREEMAN: So we certainly are not saying normal, but we --

So Giuseppe, you've heard this discussion over here. People are saying, essentially now, small fiber predominant, all that we have left because of the complexity of the assessments, all that we have left is vibration. Karin? Giuseppe? Your experience?

DR. LAURIA: I think that the nerve conduction studies are part of the clinical examination of a patient, and I think we have to make an agreement --

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DR. FREEMAN: So you would say done by a repeatable --
DR. LAURIA: -- on what has to be measured.
DR. FREEMAN: So Giuseppe is saying done in a reputable center, these are reliable measures.
DR. HERRMANN: Nurcan?
DR. UCEYLER: I would also say we should have this in --
DR. FREEMAN: You would say? Sorry?
DR. UCEYLER: I would also say that the nerve conduction of the sural nerve should be in, should be done.
DR. FELDMAN: It will require everybody to have.
DR. FREEMAN: None of this is a requirement.
DR. GIBBONS: I think the point being that once we sort of decide that reflexes are out, I'm not sure we could include nerve conductions in. However, I do worry that if the only thing remaining now is vibratory, we're perhaps not actually looking sufficiently. I mean, maybe at the very least, we have to say normal patellar

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reflexes or something to suggest that in fact we're not missing a whole other cohort; something.
DR. FREEMAN: Any thoughts on this?
DR. HAROUTOUNIAN: Maybe this can make a difference between the probable and the confirmed.
DR. FELDMAN: Maybe we need to move on.
DR. FREEMAN: Yeah, I think so. I think so.
Bob, last word on this.
DR. DWORKIN: I need to ask Deb and Heikki a question, and then I promise I'll shut up.
Are either of you worried that if you use this kind of subtyping approach in a phase 3 trial, that someone, either at a regulatory agency like FDA or EMA, or academic experts, is going to ask you to do a subgroup analysis looking at efficacy in each of these subgroups because these sub groups have been defined by a renowned group of people sitting in a hotel room in Washington? And once you're asked to do a subgroup analysis of whether your drug has efficacy in pure versus predominant versus mixed, you're down a path you don't want to be down because, of course, what are you gonna

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find? That there is no efficacy in any of the subgroups or there's efficacy in one but not the others.
So I just want some assurance that this isn't going to be a huge problem for the people who were presumably developing these disease-modifying drugs -- and you too, Steve, I hadn't seen you back there -- developing disease-modifying or symptomatic drugs because subgroup analyses are a real problem.
So I'm not gonna say anything else.
DR. FREEMAN: Yeah. I was going to finish and ask how does this discussion sit with you guys? So Bob's question and then a more overall comment.
DR. STEINER: Yes, from the standpoint that I feel that we can better label the patients that we've been targeting to study, this is helpful. However, from the standpoint of when we get past the proof of concept and try to move into registrational studies, how we're going to navigate this and are we going to be required to look at subgroups? Absolutely. And then I could go back

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to the concerns over how we would take the possibility of having confirmed diagnosis with intraepidermal nerve fiber density to registrational studies.
So yes, it's definitely a concern. What we're just looking to see, it's pretty simplistic, is, is their efficacy in patients who have pain attributed to small fiber disease? I mean, that's really the bottom line.
DR. FREEMAN: So Deb is okay with it. Heikki, any additional comments?
DR. MANSIKKA: Yeah, I think pretty much all was already said. I think the danger is like Bob said, that if we slice the population into very small segments, then we run into problems later down the line. And therefore we should have a relatively, I don't say relaxed, but inclusive criteria how we define this population because I don't think, per se, that the treatment efficacy -- I mean, I would like to hear from the audience do you actually believe that the patient population, the pathophysiology, and the treatment

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response is somehow different in a population with pure or small fiber predominant, or if you have a little bit more, large fiber involvement.

At the end of the day, that's the most important. Do patients actually benefit from the therapy independent of their clinical phenotype?

DR. FREEMAN: I think we're going to --

DR. SMITH: That's really critical. If you want to be a lumper in this -- and we may be going down the wrong path. So far, the one argument I've heard for creating a set of criteria for pure SFN is the sodium channel narrative.

Is there another argument for a distinct pathophysiology for pure SFN? And if not, why are we spending so much time worrying on that? Because one can always create a trial specific to a group that you think is enriched with people who have a particular genotype.

DR. LEVINE: Can I just make one quick point? I know I know all the difficulties that exist in getting reliable sural responses, but I think for the pharma companies in the room, it's

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important to know that there's not a single payer in this country that will pay for small fiber testing the biopsy without normal nerve conduction studies. It is predetermined, Blue Cross, Aetna, United. I'll give you the --

DR. FELDMAN: Not Michigan.

DR. LEVINE: Really? Because the payer policies -- with our lab, we deal with all kind of people --

(Crosstalk.)

DR. LEVINE: Really? It is widespread. I will say that.

DR. FREEMAN: I'm going to go to Karin, but just to answer Gordon's question, I want to be sure that I understand what you're saying. The sodium channel hypothesis, this applies not just to patients who have polymorphisms, but the fact that a sodium channel blocker, as Karin said, would be effective in any small fiber neuropathy.

DR. SMITH: My question has to do with whether we are oversizing it and focusing on pure SFN. And it goes back to my ambivalence about the

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distinction between small fiber predominance.

DR. FREEMAN: So we know where you are.

DR. SMITH: Yeah, you know where I am. But I think it's relevant to your point.

DR. FREEMAN: I do get the point. I think we all do.

Karin?

DR. FABER: I have two points. One is also a response to Gordon, is that we would never have been able to publish sodium channels if we did not have this rigid criteria for small fiber neuropathy. So that's one. And that's also something you have to take in mind when you develop a trial.

The other thing is, if you decide which group you want to include, it also depends on the type of drug and the mode of action of the drug that you will include. If it goes for sodium channel blocker, then I don't think it makes a lot of difference whether you include the entire group or not. But for other drugs, this may be different because the genetic background may be different.

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We don't know that.

So why isn't it possible to say, okay, we have the group of small fiber neuropathy that includes pure small fiber neuropathy and small fiber predominant neuropathy? And between this, you can discriminate. You have the risk of the subgroup analysis, but on the other hand, it gives you the opportunity to select one group for a certain trial.

DR. FREEMAN: It certainly would move the field forward.

I agree with that. My sense is that the majority, if not everybody, agrees with that. Is it okay to move forward? Is the majority -- I want to see people nod or shake their heads. Eva's nodding.

Is everybody on the page that Karin so carefully -- and I know Gordon is not. But is everybody else on the page that we can move forward?

(Affirmative nods.)

DR. FREEMAN: I'm going to take that as a

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yes.
DR. FELDMAN: I think we have to move forward. People are leaving --
DR. GEWANDTER: We need to talk about the nerve conduction.
DR. FREEMAN: Yeah. I think the nerve conduction study, we were being agnostic on that and saying that all of the nerve conduction study proprioception and a nerve conduction studies we felt required people who had expertise in the area, and we thought that the results were not reproducible enough to have as part of the criteria.
Am I summarizing that correctly? Again, nod.
(Affirmative nods.)
DR. FREEMAN: Okay, good. So now because I did this last night while some of you were gallivanting, I did this before the discussion this morning, so I don't have slides for this morning. So I want to now talk about the so called supportive -- and I like that description, the

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supportive tests. And we really have intraepidermal nerve fiber density assessment with skin biopsy, which a number of people said, if not the gold standard, it should be regarded as the most objective, and the most reliable, and the strongest supporting piece of information.
We then had quantitative sensory testing, which was felt to have strengths and weaknesses. And perhaps the advantage was that it allowed us to assess thermal sensation in a way that the clinical examination did not. Then we had autonomic testing available in a few centers, increases the sensitivity without substantially reducing specificity, but required a number of criteria in order to be executed perfectly. Then we had corneal confocal microscopy, which -- well, we can discuss.
So here we are. Let me maybe introduce intraepidermal nerve fiber density first and say that here is the flow. We have patients who have passed the symptom basket, who passed the sign basket. Where does intraepidermal nerve fiber

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density fit into the menu? Is that on the same level as the clinical examination? Clearly some have said that intraepidermal nerve fiber density without symptoms is totally useless, and I think nobody would argue with that.
So if you have fulfilled first tier, second tier, where does this lie? Is this obligatory or could a patient enter the Biogen clinical trial with just symptoms and signs?
Eva?
DR. FELDMAN: Roy, can I ask one quick question? Are you under the premises that you're talking about possible, probable, and confirmed neuropathy?
DR. FREEMAN: Let's say supportive. Let's use the word "supportive."
DR. FELDMAN: Okay, supportive. So the question is to go from probable to supportive neuropathy. You don't want to call it confirmed; you want to call it supportive.
DR. FREEMAN: I think that's reasonable, but given the discussion, we can call it -- if you wish

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to call it confirmed, that's fine, too. I'm fine with that.
DR. FELDMAN: I certainly think that the consensus of this group that I heard when I was standing where you are at right now is that intraepidermal nerve fiber density should be one of the confirmatory tests, if not the primary confirmatory tests. Amanda suggested that they be in two tiers, and that this would be the number one in tier 1.
DR. FREEMAN: I heard it should be the primary.
Michael, do you want to weigh in over here? What's your take on this?
DR. POLYDEFKIS: Whether you need a skin biopsy to add to trial? Well, I look at it practically. I think you do want a more homogeneous population, and I think that helps you achieve that. So I would vote yes.
DR. FREEMAN: Giuseppe? Karin? Do you want to weigh in over here?
DR. FABER: I think we all agree with that.

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DR. FREEMAN: Anybody disagree then that in order to do a clinical trial on a small fiber neuropathy on patients who have the appropriate symptoms, the appropriate signs, we don't need a skin biopsy.

Chris?

DR. GIBBONS: I think you're sort of taking two questions there. One is, does this biopsy move you to confirmed or do you need that to enter a trial? I think those are different questions.

DR. FELDMAN: That's what I was trying to understand.

DR. FREEMAN: Let's go back a bit. For example, even with those -- I showed earlier NeuPSIG grading system, possible/probable for a neuropathic pain trial. Gordon's point, a diabetic neuropathic pain trial, probable is sufficient to enter you a clinical trial.

The question over here is, is small fiber different? Again addressing in some sense Gordon's point, that is this an entity where because of the grain greenness on the edge of the boundary, that

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we actually need to have confirmation in order to enter the clinical trial, support in order to enter the clinical trial. And that really is the question. So in my mind, they actually are quite closely connected. I accept the point that you are making, but I think with this specific entity, they actually blend into one.

DR. GIBBONS: In this case, I might disagree. I would say symptomatically I think you could absolutely enter into the probable. If you're going for a disease modifying, then I think you need confirmed.

(Voices stating agreed.)

DR. FREEMAN: Okay. This is really interesting to hear. Certain, industry is really very happy to hear this because it's a huge barrier to recruitment, patients needing to have a piece of skin removed. So Do others agree with this? I mean, I'm not sure that I do.

DR. LEVINE: Isn't post-herpetic neuralgia the analogy? We do those painful trials with --

DR. FREEMAN: No, it's not the analogy; it's

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a rash. It's a rash.

DR. LEVINE: But you may see them long after the rash.

DR. FREEMAN: There's a history of a rash. There's diabetes. There's HIV. This is my stance on this, and that's the big difference with this entity. And it really does address Gordon's point.

Yeah?

DR. SMITH: I'm curious why you're comfortable in diabetes, outside of diabetes. Over 10 percent of Americans have diabetes and only half of those have neuropathy. And I bet a lot of the millions of Americans who have diabetes without neuropathy, have metatarsalgia and plantar fasciitis, and I further would posit that they're probably more likely to have those things.

So I think it's worth being self-reflective about why. I agree with Chris. I'm a little less comfortable with it, but I think we're hiding behind diabetes to create false comfort. If we're comfortable with it and diabetic neuropathy, then I would say we probably ought to be comfortable with

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it here.

DR. FREEMAN: I'm not that comfortable in diabetic neuropathy to say how I feel, but I am more comfortable when here -- and this is just my view and I want to hear what others think. What gives me the discomfort is that you are just dealing with symptoms and signs, whereas diabetes, I would say that in a clinical assessment of the patient -- I'm just going to go clinical -- every piece of information increases the probability that you are coming to the right conclusion, and I don't want to overweight the presence of diabetes, nor the presence of HIV because there's no doubt that -- as one of my German fellows once said, you can have lice and fleas. Because you have diabetes, it doesn't mean you don't have another cause of a peripheral neuropathy. But over here, we don't have any of that stuff that increases the probability, and that's why I come down to the skin biopsy; my stance on this.

I now want to hear what others think. Eva?

DR. FELDMAN: So I would definitely share

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your concern in a pure small fiber neuropathy. I feel less so in the small fiber predominant because then we have at least two signs, a large fiber and a small fiber sign of neuropathy with decreased vibratory sensation. But thinking about it, think how many patients we have seen who we thought had pure small fiber neuropathy who we biopsied, who turned out to be at least -- their intraepidermal nerve fiber density was quite robust. And then you followed them along and realized they probably didn't have a small fiber neuropathy, although signs and symptoms were present for more than six months.

DR. FREEMAN: Although some would say they could still have it even though the intraepidermal nerve fiber density was normal. But I think that, as we discussed earlier, pharma would prefer to exclude those patients and rather have something more definitive.

David Herrmann?

DR. HERRMANN: I certainly agree that skin biopsy should be on this, would be my preference,

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the primary measure -- supportive measure. It's the way I practice, and it's the way I think these trials should be designed. But one of the questions is you're dealing with a relatively small population of patients you who can enroll in a trial, so what you want to do is avoid excluding too many people who might be eligible.

So one question is if you do have a set of tier 2 measures, let's say they are QST, let's say QSART, what happens if you have a patient whose epidermal nerve fiber density is on that 7th percentile, but the QSART's abnormal and the QST's abnormal? Those patients, I think most people feel, with signs and symptoms have small fiber neuropathy.

The point that Giuseppe made was that, really, even as good as skin biopsy is, its sensitivity is not perfect, and its specificity is better but not perfect. So it's a question, obviously you have to make some pragmatic decisions when you design trials, and we may pragmatically say, you know what, we put the QST in tier 2, we

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put QSART in tier 2, but from a practical perspective, we cannot design a multicenter trial with these kind of technologies. Then I think we have to take them out of tier 2. But if we're going to put them in tier 2, I would offer that you could back these both as an alternative. I don't know. I just put it out there.

DR. FREEMAN: We have Giuseppe, and then we have Ahmet.

DR. LAURIA: Very brief. Actually, the specificity is very high but it's by definition because of the enormity. The sensitivity is not a thing. We don't need to use the biopsy as a screening tool for the population. So we need to have that as a confirmatory test in terms of going from the probable set into the supported set, confirmed set.

DR. FREEMAN: There's a growing consensus.

DR. LAURIA: Yeah. The second point is actually, I think that we should be feasible, and we cannot exclude patients or centers dealing with patients only because one tool is not available,

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because if we put all the tools together, we see how the specificity remains high.

DR. FREEMAN: So I'm hearing so far -- and just let me synthesize -- that of the confirmatory supportive tests, we have tier 1 and tier 2 tests. Skin biopsy is tier 1, that it is a confirmatory test, and for clinical trials, we want to be careful about excluding tests that others don't have, that investigators don't have.

Eva? Sorry. Where were we? It was Ahmet?

DR. HOKE: I was going to comment to reflect on Chris' comments. I think the use of skin biopsies is gonna depend on whether you're developing symptomatic therapy, in which case you really don't care what a skin biopsy shows as long as I'm convinced the patient as neuropathy based on history and exam. But if you're doing a disease-modifying trial, I think I would like to see changes in pathology because it's something that is the most objective measure that can be quantified, whereas all the others, you'll have trouble quantifying.

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DR. FREEMAN: So why it does matter -- and maybe answer your question directly -- is that the drug developers are actually looking at an entity, looking at a disease. They are looking at small fiber neuropathy, idiopathic small fiber neuropathy. So as Gordon implied, they're not just looking at painful neuropathy. They are looking to develop a drug specifically for small fiber neuropathy. So what our goal over here is, to define the boundaries of that entity. So I think the same applies for disease modifying as it does for, and that's why I think --

DR. HOKE: But I'm not sure if that's what -- I mean, maybe the pharma people can comment. I wouldn't be trying to get a designation for idiopathic peripheral neuropathy for symptomatic treatment only because to me, you're like shoehorning yourself into a very small --

DR. FREEMAN: Let's not -- drug development is a complex business.

DR. HOKE: I would go after pain. You're making this into symptomatic.

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DR. FREEMAN: I appreciate it. I appreciate your views. You can discuss that with Deb afterwards.

DR. STEINER: But what if the target is pain in a patient population with small fiber neuropathy? There are two issues. One is that in a proof-of-concept study, we want to make sure we're enrolling the right population. The other is what are we going to get on a label, but what population are we looking at?

DR. FREEMAN: I'm going to cut this discussion.

DR. HOKE: [Indiscernible] --

DR. FREEMAN: Ahmet, let's stop. This is not why we're here. Perhaps, Deb, you can meet with Ahmet afterwards and maybe bring the CEO of Biogen in, and he can tell you how you should be running your business.

Any other comments on -- there was some stuff at the back there. Karin, any views? Anybody else want to comment?

Let me maybe outline where we stand at the

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moment, that skin biopsy is considered a confirmatory test, that this is an objective test, and that it does define the bounds of this entity. I want to get a sense as to whether this is supported by the majority, and I want to get a feeling as to where those dissenters stand on this.

(Nods from audience.)

DR. FREEMAN: So I've seen nods. Karin, nod. Eva, so you satisfied? Yeah. Rob, are you satisfied? Anne Louise? Ahmet? Not really.

(Laughter.)

DR. FREEMAN: Michael, I'm sure, yeah. He's nodding very vigorously.

Gordon?

DR. SMITH: I want to make Ahmet feel better. It's part of my conciliatory role now. To some extent, this is a paper tiger, right? So we're going to create probable criteria that are based on signs and symptoms. So for epidemiology, maybe that works, and it might be for a particular neuropathic pain agent, depending on the putative mechanism, that might work. However, in a trial

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that's targeting sodium channels where there's data from a very selective group of pure small fiber neuropathy, the company may want to go with whatever we're calling confirmed or supported.

So to some extent, this isn't our dark problem. We're creating levels of certainty that then can be deployed by pharma in a way that fits their development most appropriately.

DR. FREEMAN: I think that is actually fair. I don't think I would disagree with what you're saying. Anybody, before we take closure on this, any additional points?

Chris?

DR. GIBBONS: I wasn't sure if we actually got confirmation or disagreement on with two second tier tests.

DR. FREEMAN: No, we haven't discussed the second tier tests yet, at all.

So skin biopsy, I'm going to say we're ready to move on. I've got two additional questions with skin biopsy, and that is do we need to specify laboratories. Eva made the point about nerve

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conduction studies. I think we've all seen many skin biopsies that were misinterpreted, misread, David Herman, misperformed. And then the next point, and address both of these, is how long ago? Six months, One year, 10 years? What's acceptable? So let's open that up for discussion.

DR. LEVINE: On your first point, I was trying to do this through the AAN last year and just made no progress over the last 12 months. But a number of commercial pathology labs are now doing the 5 micron thin section through a Ventana machine and spitting it out. It's being done all across the country.

So I think there should be two issues in the first question. One is specifying the technique, so that the technique is at least consistent among labs. The second question about specifying labs is complicated. I think a central lab is always a good idea for a trial. We could recommend and, again, the drug company would choose. But I think we do need to say it needs to be the thick sections and frozen --

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DR. FELDMAN: Joint Commission accredited.

DR. LEVINE: Joint Commission accredited, yeah, exactly. So I think some basic credentials and basic techniques that we could specify would be helpful there.

DR. FREEMAN: Okay. Giuseppe?

DR. LAURIA: The number of years you're running it probably is not very useful. I would consider qualified probably or I would suggest a lab which is part of a quality control program, which is I think important, interesting, that can be created.

DR. FELDMAN: Joint Commission.

MALE VOICE: That's a U.S. based.

DR. HERRMANN: There are also different accrediting agencies. There's CAT, there's Joint Commission, so I'd just be a little broad with that, but definitely demonstrate quality assurance.

DR. FREEMAN: So I think we'll be somewhat vague as far as that is concerned. We will I think specify technique, and we will talk about cutoff values, normative data. And then we'll have to

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talk about how long ago, six months. One year, two years?

DR. OAKLANDER: One year.

DR. FREEMAN: A year from Anne Louise.

Do I hear six months? Karin, six months. Do I had three months?

DR. LEVINE: So you're saying if they've had it within the last 12 months, they don't need to --

DR. FREEMAN: That's what Anne Louise we says. Karin said six months.

DR. SMITH: We dealt with this with Topspin, and we decided not to accept outside biopsies for the various reason Todd talked about. And we talked about do we get the slides and look at them. And ultimately -- and we can all name companies, but some of the most prevalent providers of this in the United States do a terrible job. And as I think David mentioned, we routinely see people who had very abnormal biopsies at another place, and we repeat them in the lab, and it's normal.

So I wonder whether this is even a road we

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want to go down.

MALE VOICE: Quality [inaudible - off mic] with expert labs.

DR. FELDMAN: With the same [inaudible - off mic]?

DR. FABER: But I think that for me the six months is when the biopsy is done by ourselves or, for example, by Giuseppe, then it's acceptable.

DR. SMITH: Yeah, that I'm comfortable with. But the idea that we're going to create a false sense of security using any accredited laboratory value I think is a problem.

DR. FREEMAN: I think in Biogen's defense, they are taking a very rigorous -- I think it's been argued too rigorous approach to this, but I think it's perfectly appropriate in that they have readers, and then they have a central confirmatory reader. And I think that that's a very rigorous approach to this.

Chris, then Christian David Herrmann.

DR. GIBBONS: So I guess I want to step back to ask, are we defining this in a taxonomy

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standpoint? In other words, you need a biopsy every six months to maintain --
DR. FREEMAN: No, no, no, no.
DR. GIBBONS: -- to maintain your diagnosis.
DR. FREEMAN: No, no, no, no. We're not seeing that at all. We are saying somebody --
DR. GIBBONS: Just for a clinical trial standpoint, yes, but for a taxonomy standpoint --
DR. FREEMAN: We are just doing inclusion criteria, no taxonomy, no outcomes. We are just doing entrance criteria.
DR. GIBBONS: But just to play devil's advocate --
DR. FREEMAN: I just want to make sure that everybody understands. Somebody comes to James's center. He fulfills all of the criteria for a small fiber neuropathy, the signs, the symptoms, and he had a biopsy done in Anne Louise Oaklander's lab, which was done seven months ago. Does he need a repeat biopsy? That's the question, or done 13 months ago, does he need --
DR. FELDMAN: So could I suggest if the

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biopsy is abnormal, he does not; if the biopsy is normal, he does? And then you just pick --
DR. FREEMAN: But that's the question. If it's abnormal --
DR. FELDMAN: If it is abnormal, and those who are most expert can say if it's 6 months or 12 months, and we can move on because we only have about 15 minutes, and we're going to lose the Europeans who are the other tests.
DR. FREEMAN: I want to do the biopsy while the Europeans are here, but thank you.
(Laughter.)
DR. GIBBONS: I still want to clarify. So if James sees the patient a year before, fulfills everything, a year later they see me.
DR. FREEMAN: He's in front of him.
DR. GIBBONS: Right.
DR. FREEMAN: He's had a biopsy. Very simple. He's in front of him. He's had a biopsy. This is something that really is important for Biogen, for Heikki. He's in front of him. He has a small fiber neuropathy, clinically. He had a

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biopsy a year ago, Eva's point about normal/abnormal. Yes?
DR. FELDMAN: One year.
DR. FREEMAN: One year. Are we okay with one year? I think we're okay with one year.
DR. HERRMANN: Can I just make one comment?
DR. FREEMAN: Yep.
DR. HERRMANN: As much as we want to separate out for trial purposes diagnosis entry criteria, if you're going to do a skin biopsy, you're going to follow that as an outcome. And you can't take a baseline biopsy from six months ago or a year ago and substitute it for a baseline biopsy. You're going --
DR. FELDMAN: Not for baseline.
DR. RUSSELL: This is for inclusion criteria.
DR. FREEMAN: This is inclusion criteria.
(Crosstalk.)
DR. HERRMANN: Then you have to specify if it's only inclusion to make a diagnosis. But if you're going to use skin biopsy as --

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DR. FREEMAN: We are only talking about inclusion criteria.
DR. HERRMANN: But if you're going to use that biopsy as an endpoint, you're going to do --
DR. FREEMAN: We are not talking about endpoints.
DR. SMITH: The problem, Roy, is it's not Anne Louise's lab that's the issue, and you know who I'm thinking about and a few others. The problem is if we go down this route, if Biogen is going to take comfort in those biopsies, we're going to have to come up with some sort of system that I think is going to be impossible to say whose skin biopsies do we trust and not trust.
DR. FREEMAN: Well, Biogen's approach is you do the biopsy and you send it to Giuseppe, send it to Karin, and send it to Michael.
DR. SMITH: I can give you an example. I'll tell you what happened at ARUP, where the stain failed. And they reported out -- and I probably shouldn't be saying this publicly -- severely abnormal biopsies for a year. And it was only when

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we started looking at them, we realized that the stain wasn't working, and it can be hard to sort out. It's a risky thing.

DR. FREEMAN: We understand that. So I think we can word this reasonably enough.

Let's move on, and I think we now can talk about the so called tier 2 test, QST and autonomic testing. And I'm going to shelve corneal confocal microscopy for just a second. Let me hear where people stand on QST. How does this fit in?

DR. RUSSELL: Roy, the problem again here is, if you don't have to have tier 1, but you can include the patient if they're only in tier 2, then you run this problem that I mentioned earlier, that you have problems with sensitivity and reproducibility of the test.

DR. FREEMAN: So let me maybe articulate it a little differently. James is saying that tier 2 has no role in supporting the diagnosis.

DR. RUSSELL: Essentially, yes.

(Laughter.)

DR. FREEMAN: So QST is irrelevant to this.

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The other approach to this is saying that QST is actually part of the sensory examination, and could have abnormal warm and cold thresholds, and that would be equivalent to the hyperalgesia, allodynia, and pinprick that we spoke about, which would be another way of looking at QST. And we often say it is an extension of the clinical examination, and it certainly fits in.

FEMALE VOICE: It's not feasible.

DR. FREEMAN: Feasible. Where is that coming from?

FEMALE VOICE: Are we going to ask people [inaudible = off mic].

DR. FREEMAN: Okay. But we're not saying it's obligatory, but we are saying that if it is done by a reputable laboratory, that is acceptable. That's another approach to it.

So the one approach is James' approach, has no place, and we can word it politely. The other is -- this fits in as an -- there are certain tests that are extensions of the clinical examination, perhaps are better sensory tests, and this is part

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of the examination.

DR. HAROUTOUNIAN: Evidence wise, when it's done appropriately, I think the data supporting those two thresholds of warm detection and cold detection are pretty reasonable. So the question is -- again, I would generally recommend against the other things, heat pain, cold pain that is before the field. With those two thresholds, I think --

DR. FREEMAN: That was clear from the data.

DR. HAROUTOUNIAN: We can have a note that the data are pretty supportive if it's considered to be --

DR. FELDMAN: Could I ask Simon a question in case there are cases where skin biopsies are not doable? Do you believe, based on the data, that it could be a tier 1, and for a confirmatory test, it could be either skin biopsy or an abnormal QST?

DR. HAROUTOUNIAN: I think so. We should be careful in defining what the healthy controls or the normal values are. But if we define that, I think that it's -- I would vote for yes.

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DR. FREEMAN: So really there's the James' view, has no place at all. It's my suggestion that it could be an extension of the, of the exam and this Simone's view was saying that this is exam, and Simon's view is saying that this is equal weight with the pathology.

DR. HAROUTOUNIAN: I'm not saying equal, but again, if the biopsy is not available as a potentially weaker option, I think the data are pretty reasonable.

DR. RUSSELL: The one problem with this is that if you use handheld devices -- and there are several handheld devices out there. They are notoriously unreliable. So the problem I see here is that you're going to get a trial run somewhere in the world where they're going to come up with some handheld device, and they're going to say this is abnormal, and therefore this is a small fiber neuropathy.

Now, if they really did sit down and they followed all the rigorous criteria for using a sensory testing device, then one might consider

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that perhaps a little bit more useful. But if you can't actually take a skin biopsy and send it to a central lab to get it processed, then I'm not sure you're really going to have the ability to perform quantitative sensory testing using the most robust devices and in the correct way. That's my concern.

DR. FREEMAN: So these guys are going to be able to say, well, we don't want to have quantitative sensory testing. But let me just for argument's sake say that this is done with the right equipment, in the right way, done absolutely perfectly, and we will actually have to prescribe exactly how this is done.

Given that idealized circumstance, where do you think this should lie, as tier 2 or part of the examination as an extension of the examination; another point, or as tier 1? And think about that while I have Chris respond.

DR. GIBBONS: So I would support it as part of the examination. I think that could be an appropriate direction. I think another one to

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consider would be amongst tier 2, CCM, QST, and QSART; 2 of 3 abnormal would be convincing, assuming all the quality --

DR. MALIK: I think you really are missing something if you're not going to have functional assessment of the fibers because I know there are difficulties with QST and sudomotor, but it's a functional aspect. And I see patients, honestly, that have had a perfectly normal skin biopsy and yet have functional deficits. So I think it has to be in there. You can't just throw them out.

DR. FREEMAN: So Chris has made a proposal of grouping the three so called tier 2 tests, each of which requires very, very specific performance requirements, as if you have 2 of those 3, then you can move up one tier, and that is supportive, whereas skin biopsy is in and of itself an acceptable supportive or confirmatory diagnosis.

There were some other hands back over there. Gordon?

DR. SMITH: So I'm curious the frequency with which I'm QST is abnormal in an individual

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who, to use Roy's expert neurologist, finds a completely normal bedside sensory examination. And this goes to your idea of using this as an extension. And I don't know those data, and it sounds like you guys do.

DR. HAROUTOUNIAN: I think roughly 30 to 40 percent of studies didn't confirm a difference between small fiber neuropathy in healthy controls.

DR. SMITH: No. So what I'm asking is, if I see a patient who has symptoms of neuropathy, they have burning feet, yet I find a normal pin sensation or even normal bedside thermal sensation using disks, how often is QST abnormal for those domains?

DR. UCEYLER: I don't think that they are systematic.

DR. FREEMAN: So far where we are, we are not assessing thermal sensation at all.

DR. SMITH: That's right, pain sensation, yeah.

DR. FREEMAN: Bear that in mind.

So Giuseppe, you give it equal weight. You

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give QST equal weight with skin biopsy in your criteria, as do you, Karin.

DR. LAURIA: Again, if you need to define what is the condition that was the other tool -- it's a functional test, so it's different; it's not the same thing. But it is a way to define whether a class of fiber works normally or not. So if we are there, I think that we should agree on the fact that the biopsy has a higher power on that, but again, we should do so in a most feasible way. And other tools in tier 2 should be considered such as QST, CCM. I think they've shown very good results, very precise results.

So the discussion I think would be if you are going to the tier 2, since the power and actually the specificity, which is different in this case, is not that much for the QST, and you want to define the entry criteria for the trial, if the biopsy is normal, would you rely on the abnormal QST or you would need two normal examinations at tier 2?

DR. FREEMAN: I think this is where we are

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at the moment, and I want to get some consensus. So there are two options. The one is -- and this is assuming QST is available with a good instrument, perfectly performed, patient is alert, conscious, motivated, that it will be an extension of the exam. It will provide thermal assessment as part of the exam. So that will be one of the four.

That's one possibility. And the other is that it moves down to tier 2, and we have the proposal that I think came from Chris, 2 out of the 3 tier 2's need to be positive in order to give you support confirmation.

Yes, Simon?

DR. HAROUTOUNIAN: One note. So we were mentioning those 4 or 3 tier 2 criteria. There were other tests that were performed in smaller amount of studies with initially promising results.

DR. FREEMAN: There were many centers --

(Crosstalk.)

DR. HAROUTOUNIAN: My question is, if a company does a phase 2 trial, a small one, but they have ability to do LDI flare, or chips, or laser,

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is there a role to one of those indicators --

(Crosstalk.)

DR. FREEMAN: Laser disk potential is not available in the U.S., chips, almost nobody has it. And we can discuss how those should be grouped at the end, but another story. But I don't think those are part of the table.

Yep. David?

DR. HERRMANN: We have the flexibility though for the person designing the trial to say, look, we are quite interested in function without particular agent. We are less interested in an effect on epidural nerve fibers. And while we can specify that our preferred criteria include a primary, we can do Chris's option of having two of these second-tier measures that might be more of interest in a particular trial situation.

DR. FREEMAN: I like that. I like that notion, that we leave -- I'm fine with either of those two options. I want to get a majority.

So I think we really are -- we've just got to come down to a decision over here, whether it

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should be an extension of the clinical examination or whether it should be 2 of the 3. And certainly function is autonomic and function is QST, and both of them need to be performed perfectly.

DR. RUSSELL: So Roy, I guess what the issue is, the only reason why I would think you would need tier 2 criteria is if you believe that a center or a trial for some reason would not be able to use the interpretable nerve fiber density as tier 1. So in other words, this will be a substitute for tier 1.

I find that kind of hard to understand why that would be the case, but if you were to do that, then you could include the QSART. I prefer your earlier idea that the quantitative sensory testing would be one of the things that you could use to try to make your examination a little bit more accurate.

DR. FREEMAN: I'm not disagreeing with you, but I want to clarify why it might be of value. And that was the point I think made by David Herrmann, that, one, we're assessing dysfunction,

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which may be abnormal before we are assessing structure; and two, it looked like from his data we are assessing, at least with the autonomic side, a different population of fibers.

Am I articulating what you said?

DR. HERRMANN: And again, I'm a proponent of skin biopsy fundamentally, but I think they can be differentially involved in these patients. So I think that there are issues with this. I think if it's going to be used, the technical aspects and the pitfalls have to be very clearly delineated, but it may be option. And I don't think we need to be too prescriptive. It's a second tier, second-line option for certain trial designs.

DR. FREEMAN: To me, I don't have a sense of consensus at all. Two options, I need to ask for a show of hands.

Who thinks that this should be an extension of the clinical examination, that it's part of the menu, that we will have thermal thresholds as part of what we will call tier 2, perhaps possible, probable -- we're in the probable. That's the one

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possibility, so extension of the clinical exam, who thinks -- and this is purely QST, so not tier 2, but it's QST as part of an extension of the clinical exam.

Option number 1, who thinks that it should be a tier 2, and we have the 2 out of 3 menu of possibilities that is optional for the pharma. And before give this to vote, it would be helpful to hear what pharma thinks about this.

Have you understood the menu?

DR. GIBBONS: Could it be both?

DR. FREEMAN: Well, we can always -- yeah, anything can be anything I suppose.

DR. GEWANDTER: What if it's a clinical extension, is it going to be mandatory? Like is it going to be like we have to have this like as part of our [inaudible - off mic]?

DR. FREEMAN: No.

MALE VOICE: So it needs to be both.

DR. FREEMAN: Let's hear. Deb, what do you think?

DR. STEINER: I would be fine with it being

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both, and I've said that we want prescriptive guidelines. But the more flexibility there are in the guidelines so that we can make a steady work and operationalize it on a larger multicenter level, the batter. So if there were a tier 1 and tier 2 approach, that would be optimal.

DR. FREEMAN: Okay. This is like in a movie where the audience actually decides how the movies gets to end.

(Laughter.)

DR. FREEMAN: I like this; can it be both? Well, what do you think, Heikki, can it be both?

DR. MANSIKKA: Yeah. I think the previous comment -- it's good to have the flexibility, and I think there is ambiguity on the data that what is actually -- I mean data doesn't show us either way or the other, so I think therefore there should be flexibility around this.

DR. FREEMAN: Steven?

DR. SAINATI: I agree that that flexible approach makes sense.

DR. FREEMAN: Okay, flexibility. The

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Italians and the Netherlands who are about to leave, are you okay with this kind of approach? Where do you guys lie? You've thought more about this than most of us.

DR. LAURIA: I think we can support the second option.

DR. FREEMAN: Tier 2.

DR. FELDMAN: Yeah.

DR. FREEMAN: And are you okay with the 2 out of 3?

DR. FELDMAN: Yes.

DR. FREEMAN: So you would say that a positive corneal confocal microscopy result combined with, let's say, abnormal QST, one of the thermals is equivalent to a skin biopsy.

DR. LAURIA: In a patient with a probable condition, probably not.

DR. FREEMAN: So in terms of possible, probable, definitely tier 1, tier 1, tier 3, are we okay?

DR. FELDMAN: What happened to QSART?

DR. FREEMAN: Oh, okay. That was one of the

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tier 3. I thought that was included as part of tier 3, QST and CCM.

MALE VOICE: QSART.

DR. FREEMAN: Sorry. Did I say -- those three anyway. I haven't had lunch yet, unlike you guys.

So those three are okay? Are we okay with that?

Does anybody want to comment about QSART? And I think with QSART, it needs to be perfectly executed, as does QST, and I assume -- and I know least about the CCM as Rayaz leaves.

DR. MALIK: Before I go, you definitely have to include it, okay?

(Laughter.)

DR. FREEMAN: My suggestion is that you don't go yet.

DR. FELDMAN: [Inaudible - off mic].

DR. FREEMAN: Should I raise the elephant in the room about CCM?

DR. FELDMAN: No, no. As Rayaz knows, I just haven't been completely convinced as a

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clinical endpoint.
DR. FREEMAN: Eva, as an endpoint?
DR. FELDMAN: And that really is based on seeing our data. That's the data Rayaz and I have together in our NIH trial, and seeing Rob and Gordon's data. And I just think it's something that requires further exploration before we say it's a definitive trial endpoint.
DR. FREEMAN: And I have to say --
DR. FELDMAN: But it isn't fair because Rayaz is leaving. That's the reason I wanted to do this sooner.
(Crosstalk.)
DR. FREEMAN: The only negative thing I have to say about him is that he is a Manchester United supporter.
(Laughter.)
MALE VOICE: Oh, they're a great team.
DR. FREEMAN: I must say I echo Eva's point. Rayaz knows where I stand on this. I do think it might be nonspecific, but let's -- so we've said 2 out of 3. I think we do need to have this

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discussion.
DR. OAKLANDER: We submitted a clinical trial grant to NINDS [inaudible - off mic].
DR. FREEMAN: NINDS has nixed lots of grants with CCM, without CCM.
DR. FELDMAN: That has nothing to do with CCM.
DR. GIBBONS: I want to weigh in just from a slightly different perspective. I'm also not comfortable with CCM, but at the same time, I think I'm no less comfortable with it than QST or QSART, which I think have their own problems. I think it still, in conjunction with these others, gives us support.
DR. FREEMAN: Do we have enough? Jen, who's chatting over there, do we have enough to word this appropriately? Does anybody leaving want to add anything to this, including Rayaz?
DR. LAURIA: I'm leaving, so make it nice [inaudible - off mic].
(Laughter.)
DR. FREEMAN: Can we word this appropriately

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to -- yeah?
DR. SMITH: I'm questioning, and someone made this point yesterday, and I can't remember who it was. We have a set of tier 2 tests that I bet the majority in the room, an overlapping Venn diagram is uncomfortable with each one individually in some way or another.
Does a combination of two of these tests that we're just not very excited about actually add additional validity or is it just making us comfortable with it?
DR. FREEMAN: Are you multiplying the discomfort? I think that's the challenge.
DR. SMITH: Or are we hiding the discomfort?
DR. FREEMAN: Yes.
DR. SMITH: Someone made this point yesterday, and I can't remember who, the data to drive our --
DR. FELDMAN: I just don't think we have enough data to include CCM.
DR. FREEMAN: Are we talking CCM or --
DR. FELDMAN: I've been trying to be

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convinced otherwise for many, many years, but I really do think it's still -- it's simply not there yet. This is an opinion, but it's not an opinion just based on emotion. I mean, it really is an opinion based on data, in fact, and Rayaz knows that. That's the reason he commented.
DR. FREEMAN: And I think none of us are hiding this from Rayaz.
David Herrmann?
DR. HERRMANN: QSART's localizing; QST isn't. But at least those are being assessed somewhat in the distribution of -- the stimulus is being applied in the distribution of where patients are experiencing maximal symptoms, for what that's worth.
DR. FREEMAN: I have growing comfort with it as a surrogate measure, growing comfort. I'm not entirely comfortable, but I share that view, and I don't know as much about the data.
So I think we're not going to resolve this here. Let us word this in a way that perhaps satisfies everybody. I think as we've allowed

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people to ventilate a little bit, it's become clear that there's not as much comfort with the technique as all that.

Anybody want to add anything to the discomfort -- to the discussion?

(Laughter.)

DR. FELDMAN: Are we saying -- [inaudible - off mic]?

DR. FREEMAN: Well, we are saying that there are this group of tests, and we will word it appropriately to say that there are issues with all of these tests, and they are different issues, and that there are challenges with including these, what we are calling tier 2 tests, in a clinical trial for X, Y, and Zed reasons. I think I can work with this.

DR. FELDMAN: Are you going to say 2 of the 3 equate a tier 1? I thought David made a really good point -- I guess he left -- but the idea that if someone is really interested more in function and really doesn't care about the INFD, they would want that as their inclusion criteria. I hadn't

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thought of it that way, but it was a very nice point.

DR. FREEMAN: And I think it's a very reasonable point.

So certainly, there are the two, quantitative sensory testing and autonomic testing. Again, very few centers can do these with sophistication.

DR. FELDMAN: I agree.

DR. FREEMAN: To some extent, in a clinical trial -- which is really why we're here -- I think this is not as big an issue as all that. And I think we can deal with this I think quite reasonably. And I'm not sure that we should have the two of the three, and perhaps word it in the way that David suggested rather than move two or three of them, move up.

DR. FELDMAN: So include all three of them with a measured discussion.

DR. FREEMAN: Exactly.

DR. FELDMAN: I think that's a fair approach.

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DR. FREEMAN: Okay. So one or two more areas of discussion. Thanks so much for staying. I want to define the idiopathic. And idiopathic means that we've excluded all causes of neuropathy, and clearly there would be very few arguments about including these three: plasma glucose, B12, and perhaps a little argument about with and within without metabolites, and using serum protein, immunofixation, electrophoresis. I think no arguments about that.

Let me just get a show of hands from the neurologists in the room for Biogen doing the trial for Kromasil doing the trial for Aptinex. Should they do B12 metabolites? What's the decision tree? Chris?

DR. GIBBONS: Yes.

DR. FELDMAN: I don't know the data. Are there data there to support that?

DR. GIBBONS: For methylmalonic acid?

DR. FELDMAN: I mean, rather than --

DR. FREEMAN: High methylmalonic acid, where the cutoff should be excluded, is what Chris is

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saying.

Brian's view is what?

DR. FELDMAN: B12.

DR. FREEMAN: B12 alone. Gordon?

DR. SMITH: The way we handle this is B12, and then for borderline B12, follow up with metabolites. And then I guess the question is -- we've sort of slipped through the prediabetic state.

DR. FREEMAN: Oh, no. We haven't slipped.

DR. SMITH: Okay. You're going to come back to that?

DR. FREEMAN: We have not.

DR. SMITH: I agree with Eva.

DR. FREEMAN: What are you agreeing with? What are you saying?

DR. SMITH: B12.

DR. FREEMAN: B12 only. In a borderline --

DR. SMITH: Then metabolites.

DR. FREEMAN: Metabolites. And how do you deal with metabolites?

DR. SMITH: I've hoped well.

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(Laughter.)
DR. FREEMAN: Let's see how you do it. So an elevated methylmalonic acid.
DR. SMITH: Yes, someone with a borderline B12 with an elevated MMA is out.
DR. HOKE: Where is the data to say that those are actually B12 responsive small fiber neuropathy patients? A lot of these, I treated them, and they don't improve.
DR. SMITH: As I mentioned yesterday, the way we're handling this in one trial is that patient, we supplement. They come back I think three months later, and if there's no change -- maybe 3 or 6 months. If there's no change in their phenotype, we assume that this was an irrelevant or non-related abnormality, and then we enroll them. And then for the other trial, we're a little more restrictive.
DR. FREEMAN: Bear in mind that you want to err on the side of specificity in a clinical trial and this is different to clinical practice.
DR. SMITH: And the one where we're allowing

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it, these are diabetic patients, so they were hiding under the cover of diabetes.
DR. FREEMAN: All right. And I think with the autonomic, we say that we want to exclude a specific cause, and the only obvious cause is the acetylcholine receptor antibody.
Anne Louise?
DR. OAKLANDER: These are the AAN guidelines for [inaudible - off mic].
DR. FREEMAN: Okay.
DR. OAKLANDER: [inaudible - off mic].
REPORTER: I'm not getting you --
MALE VOICE: You have to turn the mic on.
DR. OAKLANDER: I don't know why it turns off.
These are the AAN guidelines for evaluation of sensory polyneuropathy, not for small fiber neuropathy. And while there's a robust literature linking M proteins to demyelinating polyneuropathies, I'm not aware of a literature linking it to small fiber polyneuropathy.
DR. FREEMAN: Well, yes and no. I mean

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there is at least an association with M spikes and autonomic neuropathy. And I would say that you don't want in any kind of peripheral neuropathy trial to have patients who have a paraproteinemia. It would be, to me, intuitively obvious.
Let's move on to the others that perhaps are to a larger extent associated with small fiber neuropathy, and I've left out HIV. What should we do?
Gordon, perhaps you can weigh in on this. This was your topic. What should Biogen do in their clinical trial? How many of these should they do? What should they not? Just go through, you said B6 should be done to look at toxicity.
DR. SMITH: No. I said no, no, no, no, no, no, no, no, no, no, no, no, no and no.
(Laughter.)
DR. FREEMAN: So I just want to be clear on that. You would say that a clinical trial can be done without doing a metabolic screen, without checking renal function, without checking liver function, without TFTs?

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DR. SMITH: Yeah. No. Joking aside, I think doing basic metabolic and CBC is a prudent thing to do. But in terms of checking ANA, and sed rate, ACE and so forth, I would say no.
DR. FREEMAN: Okay. Even given the large Netherlands predisposition, a prevalence of sarcoid in their series, you think that is --
DR. OAKLANDER: We looked at ACE. In our 2016 paper, we looked specifically at ACE because it was so often abnormal. And those patients were tested -- the ACE-positive patients were tested for sarcoid. None of them had it. ACE is positive. We checked at MGH. There's like a 30 percent rate of ACE positivity among all the ACE tests run at MGH.
DR. FREEMAN: Okay, we get it. Anybody who would think that any of these, including HIV, should be done as an assessment?
DR. RUSSELL: Roy, can't you just leave it open that specific causes of neuropathy should be excluded and leave it up to the judgment of the investigators?

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DR. FREEMAN: We can certainly --
DR. RUSSELL: Because otherwise, you're going to drive yourself crazy. I mean, you've got to exclude celiac disease. You've got to exclude this and --
DR. FREEMAN: I'm totally fine with that.
(Crosstalk.)
DR. RUSSELL: You've got to exclude this and [indiscernible.]
DR. FREEMAN: I think that that's absolutely acceptable.
Chris?
DR. FELDMAN: I agree, James.
DR. GIBBONS: There is a bundled question with this, and you're implying that part of the clinical trial, I think you're going to be required to hit multiple ones, LFTS, CBCs --
DR. FREEMAN: And they will. They will certainly do that.
(Crosstalk.)
DR. GIBBONS: That will be part of the trial --

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DR. FREEMAN: They don't want to give their drug to patients who have renal failure, liver failure, all of those things.
DR. FREEMAN: Right. But the question ultimately, is that going to be the exclusion criteria for small fiber neuropathy? And it seems like no.
DR. FREEMAN: Okay. I think we're all on the same page with this. The elephant in the room is this one, and I'm going to just float something up in the interest of time, and that is to say we don't know the relationship between small fiber neuropathy
in its various forms and the prediabetic state. We don't know whether it's causative, we don't know whether it's associated, we don't know whether it's the fact that it is present in one-third of the U.S. population, and you are bound to see some patients with it.
I know there are arguments on both sides of the equation. The epidemiology, as Gordon mentioned, are not perfect -- as Rob mentioned, the

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epidemiology is not perfect. My floating balloon would be to say that this is pure small fiber neuropathy. This is a mixed small fiber neuropathy. This is small fiber sensory predominant neuropathy in a patient with impaired glucose tolerance. That would be my suggestion, and there's yet another discussion, which will be as to whether we can just look to fasting plasma glucose and hemoglobin A1C, or whether we need to use the 2-hour postprandial glucose.
So the balloon is that we will say this is what the patient has, more neuropathy in one, two, or three flavors, or without impaired glucose tolerance.
How does that sit?
DR. LEVINE: I think that's a great idea, And I would try to word it even a little more strongly because if we've got three pharma companies here and more pharma companies getting into this field, it would be a huge waste of potential data not to capture this. So I think we capture it, but we don't necessarily have to

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exclude somebody on the basis of IGT because we don't know that that's necessarily causative. so I agree.
DR. FREEMAN: Okay.
DR. SMITH: I don't think you need to do a glucose tolerance test. It would be great to have data. And if our pharma colleagues would like to do it, we'd be very excited to have it. But I think the real question is not prediabetes, and from my perspective, I don't think you need to do a 2-hour glucose tolerance test to determine if someone in whom you don't have clinical suspicion of diabetes has diabetes.
So I think that's sort of the second; can you get by with a fasting plasma glucose for an A1C, and I would say yes to those/
DR. FREEMAN: I think most of us would agree with that.
DR. OAKLANDER: Our 2016 paper supported that.
DR. FREEMAN: Anybody disagree? Anybody says it's obligatory to do a glucose tolerance

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test?
DR. FELDMAN: Well, the ADA no longer says it's obligatory. So I think the ADA now new guidelines is not obligatory. So you can just --
DR. FREEMAN: This is newer than 2016?
DR. FELDMAN: Yes. No, they just came out with an addendum in 2017. I believe I have it on this computer, where I think you can just use F -- actually, I think it was just A1C.
DR. FREEMAN: Oh, really?
DR. OAKLANDER: We should follow the ADA guidelines.
DR. FREEMAN: Yes, I think that will make everybody happy.
DR. FELDMAN: I'll get that from Rodica and sent it to you.
DR. FREEMAN: That would be great.
So all that remains really is the special criteria for an immune-mediated small fiber neuropathy and then additional discussion.
Todd, you want to take us there?
DR. LEVINE: Yeah. I don't have an answer.

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I think the difficulty is, if you start doing enough tests, you will find some things that are abnormal, like ACE levels and ANAs and SSAs in a significant percentage of these people, and it doesn't necessarily mean that they have that disorder. So it's a question of how you define it. In someone with known sarcoid who develops a small fiber neuropathy --
DR. SMITH: Let's go with -- we're in the idiopathic world. My take on it --
DR. LEVINE: Is any testing needed to exclude --
DR. FREEMAN: What I'm asking -- and it's a very simple question. And the reason why I don't have a slide, despite you sending me those slides, is I don't have an onset because I'm not sure that we are there yet, and I want to be sure that you are --
DR. LEVINE: I think you can just say -- I would exclude patients with known autoimmune disease.
DR. FREEMAN: Okay. So in the patient with

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known autoimmune disease, you are designing a clinical trial with an immunomodulatory agent. Is there anything special that you would do? Karin Faber made the point yesterday -- and she's gone now -- saying that in her clinical trial with IVG she's doing at the moment, it's the same old stuff. She's not doing anything special to increase the probability of a response.
Are you in concurrence with that?
DR. LEVINE: No. So again, the one that Chris and I are working on, although we can argue about whether Pestronk's antibodies mean anything, we're specifically choosing patients that have one of those two auto antibodies.
DR. FREEMAN: Of the antibodies, yeah.
DR. LEVINE: Now again, it may or may not work; that may not mean anything. But I think if you're trying to design a trial for an autoimmune disease, or with immunomodulatory therapy and presumed autoimmune disease, you need some evidence, and your paper as well.
DR. OAKLANDER: Yeah.

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DR. FREEMAN: What do you think, Anne Louise?
DR. OAKLANDER: Well, I don't think you should be giving immunomodulatory therapies to people unless you think they have -- unless they have an immune cause.
DR. FREEMAN: Are you telling us that no patient with a small fiber neuropathy, without a known autoimmune disease, should get IVIG? Is that what you're saying, I a clinical trial?
DR. LEVINE: Or some evidence of an autoimmune disease.
DR. FREEMAN: Some evidence.
DR. OAKLANDER: So here are things that I think. And it's very imperfect, so I'm not saying anything cast in stone. But what everybody uses as evidence is, number one, presence of a systemic --
DR. FREEMAN: I just want to be clear. We are excluding. We are dealing in the idiopathic world, so there's no --
DR. OAKLANDER: How about doing an SSA/SSB? I mean, Sjogren's is so common.

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DR. FREEMAN: No, because those are not idiopathic. Those are small fiber neuropathy due to Sjogren's.
DR. OAKLANDER: Right, but that's what I meant. Should we include SSA? I thought we were voting on what blood tests.
DR. FREEMAN: You voted, and we said -- I want to be clear with the question.
(Crosstalk.)
DR. OAKLANDER: I don't understand the question.
DR. LEVINE: Are you asking should patients with idiopathic small fiber neuropathies be enrolled in autoimmune or immunomodulatory therapies/
DR. FREEMAN: It's not even that. It actually is you decide that there may be an immunological cause of an idiopathic small fiber neuropathy. You want to set up a clinical trial. You're an IVIG company, and you want to do a clinical trial. And you can do one of two things. You can take the current fiber approach and say we

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just don't know at this point; we are going to treat every idiopathic peripheral neuropathy patient in a clinical trial. Or you can say, okay, I want to increase the likelihood of a response, so I want to have these entry criteria: rapid onset, severe symptoms; some immunological marker, which is not a disease, but may or may not be an API phenomenon; something, want to do a skin biopsy and see inflammatory markers.
I'm throwing up what could be possible ways to increase the probability of response time, giving you the potential to enrich your clinical trial. That's what I'm really saying. What is your enrichment strategy or are we not there yet?
DR. LEVINE: Well, we don't have any data for it, but I think something close to the table that I tried to present yesterday with all the variables that you just mentioned gets us close.
DR. OAKLANDER: And I would add prior response to immunotherapy to the list. If a patient comes in and said, "Doc gave me a Medrol dose pack for something else, and Oh my God, my

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neuropathy was really improved."
DR. FREEMAN: Okay. Eva and James.
DR. RUSSELL: Roy, can I just actually read the 2018 ADA criteria so everyone's clear about this?
DR. FREEMAN: Two thousand and what?
DR. FELDMAN: Eighteen.
DR. RUSSELL: 2018. "Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose or the 2-hour plasma glucose value during 75-gram oral glucose tolerance test or A1C c criteria, which you've got up there. Generally, fasting plasma glucose, 2-hour plasma glucose during the 75-gram oral glucose tolerance test and the A1C are equally appropriate for diagnostic testing."
DR. FELDMAN: Right. So those are the new criteria. So that's why I'm saying we can just use A1C.
DR. FREEMAN: So that's pretty much this, isn't it?
(Crosstalk.)

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DR. RUSSELL: You can use any of those.
DR. FREEMAN: I don't think it's actually changed.
DR. RUSSELL: It hasn't.
DR. FREEMAN: So it's any one of these three.
DR. FELDMAN: So we can just use that.
DR. FREEMAN: Go back to the question that we were discussing. Is there -- and this is I think pretty much my last point -- is there any way that we should suggest that an immunomodulatory trial could be enriched or are we not there yet?
DR. HAROUTOUNIAN: I think it's very trial specific, so I don't think it should be in our core criteria, but we can certainly suggest researchers who are doing trials in disease-modifying -- those kinds of agents, that they can consider reaching their trials by those parameters.
DR. GIBBONS: Certainly one of the challenges you're asking and we're sort of facing is that many of the presumed problems may not yet have been identified. So as new antibodies come on

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board that we think are pathogenic, that would make sense, and that would be part of the trial question. But I think if there is a presumption of associated immunomodulatory mechanism, then yes.

DR. FREEMAN: So I'm hearing or at least -- and part of this is my sentiment that we're not there yet and that we can suggest, to tease that, are in the wings and an approach. But there is nothing definitive yet about an immunomodulatory trial.

DR. LEVINE: I know you keep saying this, so I know you're going to yell at me. But I think in this section, in talking about trial design, we have to talk about objective outcome measures. So autonomic testing biopsies --

FEMALE VOICE: Agreed.

DR. LEVINE: -- we've got to make that --

DR. FELDMAN: But that's not what we're doing at this meeting.

DR. LEVINE: No, I know.

DR. FREEMAN: There's no doubt, of course. Todd, I'm going to yell at you.

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DR. LEVINE: See? Told you.

(Laughter.)

DR. LEVINE: At least I was prepared.

DR. FREEMAN: And on that note, unless anybody has anything else to add, I think --

DR. FELDMAN: I want to thank you because you have actually herded cats. And we actually have I think a fairly good consensus, which I wasn't sure we were going to be able to reach. So thank you, Roy. I mean that, very much.

(Applause.)

DR. FREEMAN: This has been really interesting. I've learned an enormous amount. My dog just bit his dog walker yesterday, but other than that, I would say --

(Laughter.)

Adjournment

DR. FREEMAN: -- it hasn't been herding cats; it's been herding dogs.

(Whereupon, at 3:01 p.m., the meeting was adjourned.)

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