

*ACTION - CONCEPT MEETING ON
SMALL FIBER NEUROPATHY*

April 6, 2018

*A Matter of Record
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<p>L*4343*L* Page 1</p> <p>1 ACTTION</p> <p>2</p> <p>3</p> <p>4</p> <p>5 CONCEPT MEETING ON</p> <p>6 SMALL FIBER NEUROPATHY</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12 Friday, April 6, 2018</p> <p>13 8:02 a.m. to 3:01 p.m.</p> <p>14</p> <p>15</p> <p>16</p> <p>17 Westin Georgetown</p> <p>18 Washington, DC</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p>Page 3</p> <p>1 PROCEEDINGS</p> <p>2 (8:02 a.m.)</p> <p>3 DR. FREEMAN: Good morning, all. Welcome to</p> <p>4 day 2. I do not wish to equate being hanged with</p> <p>5 developing a consensus with the group of you, but</p> <p>6 there is a parallel. So what I want to do in this</p> <p>7 introduction is to concentrate the mind a little</p> <p>8 and get everybody right on target because come</p> <p>9 1:00, we will be working to develop a consensus</p> <p>10 statement. And our assignment, I initially had</p> <p>11 written charge, but I thought it was a little bit</p> <p>12 too close to being hanged, is to develop a case</p> <p>13 definition, which is to say inclusion and exclusion</p> <p>14 criteria.</p> <p>15 So we're not looking at outcomes. We're not</p> <p>16 looking at what is used in clinical practice. This</p> <p>17 is a case definition for a randomized control</p> <p>18 trial, which is to stay inclusion and exclusion</p> <p>19 criteria. And it's getting to be an enormous</p> <p>20 amount of work to do this, and I want to try and</p> <p>21 keep our eye on the ball so to speak.</p> <p>22 Now we could use this in observational</p>
<p>Page 2</p> <p>1 C O N T E N T S</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Sensitivity and Specificity of QST 8</p> <p>4 Nurcan Uceyler, MD</p> <p>5 Sensitivity and Specificity of Skin Biopsy 35</p> <p>6 Giuseppe Lauria, MD</p> <p>7 Corneal Confocal Microscopy Included in</p> <p>8 Diagnostic Criteria 57</p> <p>9 Rayaz Malik, MBChB, FRCP, PhD</p> <p>10 Autonomic Testing Included in</p> <p>11 Diagnostic Criteria 82</p> <p>12 David Herrmann, MBBCh</p> <p>13 Q & A and Panel Discussion</p> <p>14 Moderator - 125</p> <p>15 - Eva Feldman, MD, PhD</p> <p>16 Consensus Building 153</p> <p>17 Adjournment 338</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p>Page 4</p> <p>1 studies, in case control studies, could be used in</p> <p>2 cohort studies, but the aim is to develop something</p> <p>3 that can be used, will be used, in randomized</p> <p>4 control trials, ideally phase 1/phase 2</p> <p>5 trials -- sorry. I should have said phase 2/phase</p> <p>6 3 trials, phase 2/ phase 3 trials. And if it</p> <p>7 spills over into clinical practice, so much the</p> <p>8 better, but that's not the focus.</p> <p>9 Now, what I want to do again to get</p> <p>10 everybody focused is to present approaches that</p> <p>11 have been used to this. I have a view on this, but</p> <p>12 I'm not going to be too prescriptive at this point,</p> <p>13 but later on. But I want people to begin to think</p> <p>14 over the course of the morning in these terms. And</p> <p>15 there really are I think sets of approaches to</p> <p>16 this, one of which comes from the neuropathic pain</p> <p>17 grading system, which was redeveloped following the</p> <p>18 redefinition of what neuropathic pain in the</p> <p>19 current era is, which is a very neurologically</p> <p>20 based approach, pain being a lesion or disease</p> <p>21 affecting somatic sensory nervous system, so, a lot</p> <p>22 less tight than the previous definition, which was</p>

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

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

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

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

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1 It is, if you wish, the quantified version
2 of the neurological examination that we do,
3 actually nothing else, quantified version. We do
4 get a thermal and mechanical perception and pain
5 thresholds as functions of the small nerve fibers,
6 A delta and C, plus large fiber functions and
7 muscle nociceptor functions.
8 Standardization is a very big issue here.
9 That's for the work of the German research network,
10 neuropathic pain. DFNS is so valuable, I would
11 say, putting together single test 13 in a very
12 standardized manner so that we can all do our
13 assessments in a way that we can also compare the
14 results from different groups. Very important
15 other points, individual comparison with normative
16 value. So when we do the test, what is the normal?
17 With what should we compare our results? And I
18 will show you examples also from our group, how
19 much the results can differ depending on with what
20 you compare all this.
21 I'm not sure who of all of you has undergone
22 QST, him or herself. It's very, very valuable to

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1 do this, to also understand how difficult all this
2 is and how subjective -- and that is not a
3 keyword -- the answers that we get from the
4 patients are and how we should then put them in
5 order and evaluate also. So I would like to very
6 quickly go through the major items that are tested
7 with QST, and I will show you how the DFNS protocol
8 is working.
9 The DFNS protocol is very often cited, but
10 what is behind it is actually that we give the
11 patients always the same instructions. That's the
12 major point. Everybody everywhere in each lab does
13 give the same instruction, and how do we now get to
14 the thresholds? The first five tests are actually
15 for the small nerve fibers, and when we look here,
16 for instance, for the cold detection thresholds,
17 what do we tell the patient? This is not the
18 validated English version. This is just the
19 translation I made now for this presentation from
20 the German version.
21 So please press the button immediately when
22 you first feel a change. The patient should push

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1 the button when he or she feels the change in
2 temperature to cold or cooler, cold or cooler. Then
3 you press the button and have value. For warm,
4 it's just the same. Press the button when you feel
5 warm or warmer, and then you get one detection
6 threshold after having repeated this three times.
7 And the third test, which is thermal sensory limen,
8 ask the patient to immediately press the button
9 when feeling a change to cold or warm, and tell us,
10 do you feel this as cold or do you feel this as
11 warm? And this is also repeated 6 times, one after
12 the other, and the patient has to tell you so you
13 get several results, which is an average
14 afterwards.
15 This is, I can say already, one of the tests
16 which is most unreliable, I would say, where you
17 get most diverse results. It is very, very
18 difficult, even for a normal person, to really find
19 out is this now getting colder, is it now getting
20 warmer? This is very, very difficult to say, and
21 that's why the TSL actually is the one that we in
22 general do not rely so very much on. So cold and

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1 warm detection thresholds are much more robust,
2 still having otherwise a range of possibilities to
3 answer.
4 Paradoxical heat sensation, maybe I should
5 also say a word on that. This is a number 4. This
6 is not really a test. This is what the patient is
7 telling us. When we cool down to thermode, some of
8 these patients tell us, "Oh, it's getting hot."
9 We're cooling down to thermode, and all of a sudden
10 they say it's warm or even hot, painful thought.
11 This is paradoxically heat sensation when cooling
12 down, also as a sign of an impairment of these
13 little fibers, PHS.
14 Cold pain thresholds, of course, please
15 press the button immediately. When you feel cold,
16 you get a second sensation, which is then pain.
17 And for the heat pain threshold, the same thing,
18 the other way around. So your skin will be now
19 warmed up. At some time, there will be a second
20 perception in addition to warm. Please press the
21 button immediately when you perceive such a painful
22 feeling, and this is also repeated 3 times in the

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

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

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

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

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1 can turn this argument around and say, 13 tests,
2 test one hour. Who has one hour to do all these
3 tests? They are much too long.
4 Very important, don't forget, we cannot
5 localize the pathology with this method. When we
6 do this, we look at all this. We look at the
7 stimulated side up to the brain until the patient
8 tells us something. So we do not know where the
9 pathology really when we get a pathological result
10 out of this.
11 Well, this is not very well reasonable, but
12 that doesn't matter. I have tried to make it in a
13 standardized way, so I have always this blue box on
14 the side with some items I thought would be
15 important information to get out of the papers that
16 I found for quantitative sensory testing of a
17 thermal threshold testing in papers that are
18 dealing with idiopathic small fiber neuropathy.
19 I will start here with one paper by Periquet
20 and colleagues, 1999. His colleagues investigated
21 44 patients with small fiber neuropathy, and the
22 SFN criteria were simply clinically suspected. So

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1 these are patients with burning feet, toes, and
2 dysesthesias. They used CASE IV, which I am not
3 familiar with. Some of you will be familiar with
4 this. I'm not. This case 4 seems to have
5 normative values of the company. I also do not know
6 what is in. I didn't find any data on that. And
7 there is some thresholds determination, which is
8 different from what I've shown here. Again, it
9 seems to be a protocol. I'm not familiar with
10 this.
11 This group did not calculate some
12 sensitivity or specificity, but what they did is
13 they somehow compared skin biopsy and QST and come
14 to the conclusion that QST is less sensitive than
15 skin biopsy making the diagnosis of these small
16 fiber patients. And the main result, when you look
17 at the results of this QST measurement, is 23 out
18 of 32 patients that were investigated had somehow a
19 pathological threshold for this thermal perception.
20 I would say here is a caveat. As far as I
21 understood, the QST results do not only cover
22 thermal perception, but there is also some

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1 vibration, a detection put into it. So I think
2 this is a mixed result. One should be careful
3 maybe with this, so one study.
4 The next one is 1999, Tobin and colleagues,
5 looking at 15 patients with idiopathic small fiber
6 neuropathy we would call it. No control group,
7 again using the normative values of CASE IV
8 clinically suspected, so no really criteria. They
9 didn't do the assessment themselves. They looked
10 into the medical records of these patients. And
11 again, no sensitivity specificity calculation, but
12 the conclusion that QSART in this case was most
13 sensitive to really find all these patients. And
14 when you look at the cohorts, 10 out of 15 with
15 pathological thresholds. No standardized
16 assessments, very small patient group. I think
17 these are some of the caveats that need to be
18 considered.
19 Next, Magda 2002 presents data of 14
20 patients; again, no control group; again, the
21 normative values of the company, again CASE IV,
22 clinically suspected cases. This is impressive

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1 when you look here, 14 out of 14 patients with a
2 pathological threshold for thermal perception,
3 which is quite impressive I would say. None of the
4 other studies that I will show you will reach this
5 high number, and very similar caveats, again, here,
6 particularly also in a very small group, not to
7 forget.
8 The next one is Scott 2003, looking at 20
9 patients clinically suspected. Now, they use the
10 Medoc thermode, following the manufacturer's
11 recommendation, and I think also using the
12 manufacturer's control values, which is now not
13 comparable with what we have seen up to now. They
14 did a calculation for sensitivity and specificity,
15 and say 78 percent of sensitivity, 46 percent of
16 specificity for small nerve fiber impairment.
17 Twelve out of 20 patients were pathological.
18 Here comes a very important study, Devigili
19 and colleagues, 2008. This has been cited a lot,
20 lot, lot; 42 patients having been investigated in a
21 very standardized manner. As far as I've
22 understood 24 additional control subjects have been

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1 investigated as well, and there was another
2 database of age and gender-matched normative values
3 that these values have been compared with.
4 The criteria actually came from the study,
5 the current criteria that we are using, Devigili
6 2008. These are, however, based also on prior
7 criteria from Stewart and Lacomis, looking at
8 clinical presentation, thermal perception, and skin
9 biopsy and using here the Medoc system, threshold
10 determination, again, a little bit different of
11 what we have seen; sensitivity 57 percent, 37
12 percent of specificity, and 38 out of 67 patients
13 with pathological findings.
14 Scherens and colleagues 2009, this is not
15 one of the DFNS centers I can say. This is the
16 group of Christoph Maier in Bochum who investigated
17 now with the DFNS protocols, so very correctly, 42
18 patients who had burning feet and toe, clinically
19 suspected. They are using the Medoc system, and
20 they are using the DFNS protocol: sensitivity,
21 38 percent, 80 percent of specificity, 5 out of 16
22 patients, 31 percent, pathological thresholds. So

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1 again, very different numbers.
2 Here are two studies that I only have as
3 abstracts. Many information are missing here, but
4 just to give you an idea, Shukla and colleagues,
5 2005, 25 patients clinically suspected small fiber
6 neuropathy, 18 out of 25 with pathological thermal
7 perception thresholds, and on the other side,
8 Lefaucheur and colleagues, 2015, 35 patients, no
9 control group, clinically suspected, warm detection
10 threshold, 55 percent pathological; cold detection
11 threshold, 32 percent.
12 DR. FELDMAN: And there is no indication of
13 which devices?
14 DR. UCEYLER: This is, unfortunately, just
15 the abstract that I got.
16 DR. FELDMAN: Oh, okay.
17 DR. UCEYLER: Unfortunately, I couldn't get
18 the full paper, unfortunately.
19 This paper, we talked about that yesterday.
20 This is a very large group from the Dutch cohort,
21 deGreef and colleagues of this year, more than 900
22 patients, really a big, big group. Devigili, 2008

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1 criteria were used. QST is not so much the focus.
2 Please correct me, Karin, when I say this. So
3 there is not much information in the paper really
4 in detail, but as far as I understood yesterday
5 also from our personal communication, this is,
6 again, a different protocol. This is Bakkers and
7 colleagues, 2015, I think from the same group, also
8 a modified and optimized not really QST. That's
9 why in the paper also it says TTT, which is
10 temperature threshold testing. And here, quite a
11 high number, 614 out of 921, so 67 percent of
12 patients with pathological thresholds.
13 So maybe I confused you a little bit, but
14 that's good because this is the situation. So we
15 have very diverse numbers because we have very
16 diverse methods and devices and everything. What I
17 would like to show you now are the results of three
18 studies that we have performed. And where I have
19 learned quite a lot, I think about QST and how to
20 deal with these results, and this I would like to
21 share with you.
22 This was the first study, which is published

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1 2010, where we were really at the beginning, and we
2 had only 24 patients. But it is now for all these
3 three studies the same lab, actually also the same
4 technician who is doing this. This is the same
5 DFNS protocol, et cetera. This is the homogeneity,
6 and now look at the results.
7 We had 24 patients, and how we go ahead is
8 that we always recruit an additional control cohort
9 with our subjects for the group analysis to get
10 this kind of plot. And at the same time when
11 you're a clinician or when you're doing a study,
12 you have to compare, of course, your results with
13 normative values for the individual patient to find
14 out is this now pathological, yes or no.
15 At that time, we had from the DFNS cohort
16 the Rolke 2006 paper with the first normative
17 values that we were able to compare our data. So
18 what did we find out? We saw with the Devigili
19 2008 criteria the Somedic thermal tester using the
20 DFNS protocol and now comparing our patients with a
21 Rolke normative database, 20 out of 22 with
22 pathological thermal perception thresholds, which

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

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1 protocol; and in this group, 58 patients with
2 isolated small fiber neuropathy, so idiopathic
3 small fiber neuropathy that we have. And in the
4 meantime, we had collected -- though this is now
5 work of 10 years -- 273 healthy controls in our
6 groups. So all of this has been done in the same
7 lab where you saw the results before.
8 What do we see here? Again, we have this
9 control group, which is now much bigger, and now we
10 have also new 2010 normative values, Magerl et al.,
11 for the DFNS cohort. Rolke 2006, four years later,
12 Magerl at 2010. Devigili criteria Samedic tester,
13 DFNS protocol, what do we see? 28 out of our 58
14 patients when comparing with the current normative
15 database of Magerl et al. have pathological thermal
16 perception thresholds, which is less than
17 91 percent, which I showed you before.
18 DR. FREEMAN: Cold pain and heat pain, is
19 that behind one of the --
20 DR. UCEYLER: Cold pain threshold, heat pain
21 threshold, not much really happens. It doesn't
22 show much.

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

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1 not tell us, we cannot find out in the clinical
2 examination and nowhere else. It's interesting.
3 DR. FREEMAN: And these were not
4 fibromyalgia patients, these were --
5 DR. UCEYLER: Oh, no, definitely. Burning
6 feet and toes, this is not fibromyalgia. This is
7 idiopathic small fiber neuropathy for sure, second
8 study, so this is not yet published.
9 Now comes a third one, which we're currently
10 working on the manuscript. This is another cohort,
11 56 patients with idiopathic small fiber neuropathy.
12 Now I have stratified for gender, female and male.
13 We have the large control group and still the
14 Magerl cohorts to be compared individually.
15 Everything else is the same in Rolke's work;
16 nothing has changed now 14 out of 56 with
17 pathological thresholds. So only 25 percent.
18 So what is with the other 75 percent of all
19 patients who do have small fiber neuropathy? They
20 do have this, but they have normal thresholds here.
21 When we go ahead with this -- I'm not saying that
22 this is all the truth.

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1 DR. FELDMAN: They do have it based on skin
2 biopsy?
3 DR. UCEYLER: They did have a skin biopsy,
4 all of them.
5 DR. FELDMAN: So this is based. So you're
6 saying when they do have it, you're saying they do
7 have it base on skin biopsy?
8 DR. UCEYLER: Be careful. For the skin
9 biopsy, this is also not the gold standard. So
10 Giuseppe will present the data. I don't know what
11 he will be saying about this. There is no gold
12 standard.
13 DR. FELDMAN: So when you say they
14 definitely have disease, what is the gold standard
15 for you to say that?
16 DR. UCEYLER: This is now a study. What is
17 the gold standard? The story of the patient, I
18 have burning feet and toes. This is the first
19 thing.
20 DR. FELDMAN: So it's pain.
21 DR. UCEYLER: Pain, tingling, dysesthesia.
22 Some of them will have pathological thresholds.

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

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

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

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1 how big this 5 to 95 confidence interval is. Until
2 you get pathological, you really need a very, very
3 severe impairment of your small nerve fibers until
4 you drop out of these normative values. And of
5 course here, this is a very, very large group also
6 with older controls. I think that explains a lot.
7 A little excursion before I come to the end.
8 Of course, 13 tests, as I said, you don't need all
9 of this. What about bedside tests? There have
10 been some attempts. This is just one example from
11 the group of Rausch Perrone and Kia [ph] in
12 Germany, where they tried to get some bedside
13 testing for Fabry-associated small fiber
14 neuropathy.
15 In addition to some questions in the
16 questionnaire that they put together, they say
17 apply Tip Therm in random digit order to find out
18 cold and warm detection thresholds. This is a
19 bedside test, of course, not the standardized
20 protocol. If you want to look for hypoesthesia,
21 use one von-Frey filament and ask the patient, and
22 of course the tuning fork, which is standard for

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1 every neurologist.
2 So summing up, I was surprised actually
3 when, again, screening that they're not so many
4 studies actually investigating idiopathic small
5 fiber neuropathy using quantitative sensory
6 testing. It has its advantages, no question.
7 There are some drawbacks that we have to keep in
8 mind. The numbers for sensitivity and specificity
9 are very diverse. This has its reasons I already
10 said.
11 So logical QST does not exclude other
12 differential diagnosis, and the crucial aspect
13 aspects, in my opinion, the standardization of
14 course, we have to have something that is really
15 standardized with DFNS protocols since more than
16 10, 12 years now, I think is doing quite a good job
17 here. Training the devices, lab certification are
18 the major keywords here and the size and
19 composition of the control group that we are
20 comparing with is something to be kept in mind.
21 I think that's it already. Thank you for
22 your attention.

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1 (Applause.)
2 DR. FELDMAN: I think to stay on time, we'll
3 take the questions during the panel. So next up is
4 Giuseppe.
5 Presentation - Giuseppe Lauria
6 DR. LAURIA: So thank you very much also for
7 the kind invitation. I will try sharing with you
8 some conceptual point with a critical spirit on a
9 monster that I guess I've contributed to create,
10 which is a skin biopsy. So it will be a little
11 journey over the years.
12 So starting from this, this is where we were
13 20 years ago. Everything has started here in
14 Sweden at the Karolinksa Institute, and then there
15 were two labs, one in Minneapolis, Canada, and the
16 other one at Hopkins with Justin and Jack Griffin.
17 And from then to the time with younger guys, so
18 myself and Maria Nolano went back to Milan.
19 This is where we are now. So the
20 big covered countries I guess for USA -- you missed
21 just one in Alaska. And there are some others. I
22 know there is one which will be set up in Israel

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1 soon and one in Australia. So it is quite
2 impressive how the biopsy spread out through the
3 countries.
4 So the career that this little thing, this
5 little piece of skin has done, over the year has
6 been really great because it allowed actually the
7 investigator to overcome the need of the sural
8 nerve biopsy to investigate the myleinated nerve
9 fibers, which actually, even through the biopsy,
10 can be assessed with the electron microscope, as
11 you see here, in the dermis and even in the
12 epidermis. It's quite difficult to find them, but
13 they are there.
14 The history, very briefly, you know first
15 identified by Langerhans. He used to be a medical
16 student at that time, and then 50 years later,
17 there were great scientists who even provided the
18 first quantification and found first it proximates
19 to this gradient in the body. And going through
20 these historical notes, I will put my point, which
21 I believe are quite interesting for the discussion
22 today. So the first availability of the antibody

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1 that we use against the epitope that is relevant,
2 than the normative, the guidelines, and then the
3 transvalues for the two methods that are used, as
4 you know.
5 You know that these fibers are quite
6 interesting because they are naked. Actually, they
7 lose the Schwann cell ensheathment while they cross
8 the dermis, the junction. It's quite interesting
9 because this is what happens also for the large
10 myelinated [ph] fibers while they approach the
11 inner core of the mechanical receptors, so they are
12 in close contact with cells, which role is not only
13 structural, but might have some role also in the
14 transmission of sensation. But you also know that
15 these fibers undergo a strict segregation during
16 the development. In particular it is interesting
17 how they target the different levels, the different
18 part of the skin based on the expression of a
19 number of growth factors,
20 transition [indiscernible] factors, so mainly NGS,
21 they're running Schwann.
22 This is to show you the reason why for many

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1 years it was impossible to identify these fibers in
2 the epidermis because the only available antibodies
3 were against the, uh, a game dabchick epitopes.
4 So, but the number of a peptidergic epitopes. The
5 number of peptidergic fibers in the epidermis is
6 low.
7 So what has changed has been the
8 availability of antibodies against this protein
9 gene product 9.5 that stains pretty well all the
10 fibers in the superficial layers of the skin that
11 you see here. And what is this? This is
12 antibodies against the cytosolic enzyme that
13 removes the ubiquitin and is transported with the
14 slow component of the axonal transport. So it is
15 actually an unspecific, cytoplasmic protein, and
16 this is what we target. Since it is very abundant
17 in nerves, it is used as a marker for the
18 peripheral nerves as in our case.
19 The other interesting thing is that
20 although, as you know, not all these small size
21 neurons in the DRG are nociceptors, so they express
22 the TRPV1 receptor, capsaicin receptor. All the

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1 fibers in the epidermis do, so it means that there
2 should be a kind of segregation also for the
3 expression of this. And this is a quite clear
4 overlap with a marker stain in the cytoskeleton.
5 So the first point is that the fibers with
6 the clinic that we use commonly in the labs are
7 staying using a marker which is not specific for
8 the fiber function. The second thing is that the
9 fibers and epidermis are nociceptors. I think they
10 can be defined in this way.
11 The second point is that -- well, actually
12 the biopsy [indiscernible] has boosted the story of
13 the small fiber neuropathy, clearly, because before
14 the first studies in the mid-90's of the last
15 century, the diagnosis was more blurred. At that
16 time, the first studies first demonstrated that
17 some patients with symptoms could be attributed to
18 damage or impairment of the small nerve fibers
19 despite a normal function of the large fibers at
20 the nerve conduction studies, and even at the
21 pathological level have an impairment, damage, a
22 loss of these fibers looking at the skin, so a very

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1 distal neuropathy.
2 This has been assessed in different times.
3 There's a nice paper that David published and sent
4 me years ago showing the agreement between the skin
5 biopsy and the sural biopsy. And there is about
6 one-quarter of those patients who had the normal
7 morphometry in the sural and impaired, and the loss
8 of fibers in the skin. So that's a figure that we
9 record.
10 But the other important thing is that at
11 Hopkins, Justin, Jack, and all the people working
12 at that time provided the first normative reference
13 range that actually were adjusted by age decade;
14 not by sex but by age decade, but with the
15 80th percentile interval that you see here; and
16 providing also some diagnostic performance of the
17 technique compared to the two different
18 percentiles, so 10th and 5th. And looking at the
19 5th, you see this with this specificity and this
20 low sensitivity, providing also positive predictive
21 value and negative predictive value, which we will
22 spend some words later.

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1 But the other important thing is that they
2 didn't find any difference in terms of age decades
3 since there wasn't any age related decline. So
4 what happens is this mean plus the standard
5 deviation of this percentile cutoff and was capped
6 and used. And what has happened is that for more
7 than 10 years, our lab, but older labs actually,
8 made reports based on a mean value that was applied
9 to both sex and any age. So the point is that more
10 false positive or false negative all this time.
11 Going to the following point, in 2005 with
12 the groups who have published or started working
13 earlier on the biopsy, we did these guidelines that
14 were related essentially to the standardization of
15 the protocol for assessing the density of the
16 intraepidermal fibers using the two techniques,
17 which is the bright field and the
18 immunofluorescence, and finding an agreement on the
19 counting rules, so how do we count these fibers,
20 otherwise.
21 This is what has remained since then. What
22 has remained essentially, just to make it simpler,

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1 we count this fiber. We measure the length of the
2 epidermis and we obtain this density per linear
3 length of the epidermis. This is what is done in
4 both the -- so the method that's been analyzed by a
5 number of panels, of tasks, this is the AAN in
6 2009. Then in 2010, we revised with the former FNS
7 and the PNS, publishing this guideline that was
8 kind of a revision of what we had said five years
9 before.
10 But the other important thing, which is a
11 little bit far from the clinical studies, in the
12 meanwhile, it became quite clear that the same
13 method could be applied, those and animal models.
14 This is just an example of a paper we published 15
15 years ago on the effect of EPO on diabetic
16 neuropathy in a streptozotocin model to control the
17 diabetes and the regeneration of the fibers that
18 will work very well. But also it became quite
19 clear that we can use the biopsy to analyze with
20 different techniques of the nerves. This is just
21 comparable with the sciatic nerve analysis. This
22 has been used mainly in CMT models, but this is

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1 fine. You see here, that's a model of a CMT4 with
2 the outfolding myelins.
3 Let me go on to the point. In 2005 and '10,
4 there had been the standardization of the procedure
5 and the country rules for both the technique with
6 the agreement that distal leg biopsy was enough and
7 was fine for diagnostic purposes in small fiber
8 neuropathy, and that the preclinical model of
9 peripheral neuropathy could be -- I mean, the
10 biopsy was fine also for assessing them. But the
11 other important thing is that interlab
12 standardization on the procedure and the counting
13 is a very relevant issue. It remains a very
14 relevant issue.
15 Moving on, in 2010, we with a group of 9, 10
16 labs worldwide, we provided this normative
17 reference arranged for clinical use in this quite
18 large group of healthy controls divided by sex and
19 age decade providing this 5th percent cutoff, which
20 you see is not the same over the different age
21 groups. And indeed, what we found is that there is
22 a the decrease by more or less, less than one fiber

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1 per millimeter for the [indiscernible - mic
2 fades] -- without any major influence of height,
3 weight, and BMI.
4 More recently, we made an assessment to see
5 whether it was reliable making the biopsy on the
6 right -- or on the left side, because actually
7 these are mainly patients targeting this
8 examination on the patients with symmetrical
9 polyneuropathy, that by definition it's
10 symmetrical. And we found there was great
11 agreement between the sites, but also, and I think
12 it is quite important, there wasn't any variation
13 within 3 weeks. And 3 weeks is the turnover time
14 of the keratinocytes.
15 So these fibers, which enter this ecosystem,
16 which is the epidermis crossing a very tight
17 barrier, their density does not change while the
18 keratinocytes make their own turnover up to the
19 stratum corneum, which strengthens, I think, the
20 use of the biopsy in clinical practice but also in
21 private [indiscernible].
22 Then more recently also the

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1 immunofluorescence group provided the normative
2 references divided again by sex and age decade, and
3 quite interesting, they found that there wasn't any
4 influence of the BMI and that there was a decrease
5 of more or less a 0.5 fibers per millimeter per
6 each decade, quite interesting because when we
7 compare the two techniques, we found that actually
8 there was this ratio, which is known. We find you
9 can count many more fibers when you use the
10 immunofluorescent technique, and the ratio was 1 to
11 2, so it is the same looking from another
12 perspective with a very good diagnostic agreement
13 if less than one fiber under 5th cutoff was
14 tolerated.

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

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1 the inter-rater variation on the same section.
2 So it brings to the consideration that the
3 values, which are very close to the cutoff, just
4 normal, must be considered with caution before
5 providing a diagnostic judgment. And the other
6 important thing is that this group in Germany tried
7 to see what happened when three observers assessed
8 the density -- I mean, they were pretty bad,
9 although they were in the same center. And it was
10 a disaster, but it was really great that they
11 published it.

12 (Laughter.)

13 DR. LAURIA: It was really great because
14 they said, well, we have trained all together.
15 They are doing exactly the same, but why?
16 Well, that brings me to point number four,
17 what we have learned and what we've got so far,
18 that we have age and sex adjusted, the normative
19 value for both the techniques, that we have an
20 excellent agreement between the right and left side
21 inpatient with symmetric neuropathy, that there's
22 no variation at 3-week follow-up, and there is an

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

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

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

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

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

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

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

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

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

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

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

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

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1 1998, so since the first one. Well, let's focus on
2 the DL, on the distal leg. But if you look on the
3 sensitivity
4 rate of true positive, it is ranging, in a way,
5 very wide spectrum, and actually it remains unclear
6 because it goes from a 0.35 to 0.90.

7 Again, following our experience -- Yes?

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

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

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

20 DR. LAURIA: Yes, because at that time, we
21 were using the cutoff, which was a set since the
22 1998 paper that was 13 plus, with a 6 point

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

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

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

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

13 DR. FREEMAN: You set it. Okay.

14 DR. LAURIA: Yes.

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

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

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

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

22 So this is just to remember that they used

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1 to be a pre-digital [ph] area. These fibers
2 reappear, so can regenerate why the clinical
3 picture recovered. So this is an example. This is
4 another example in the patient treated with
5 steroids. So this is another example showing that
6 the underlying disease goes better, and the pain
7 goes away, and the regeneration of the fibers is
8 pretty clear here. And this is the other example
9 on the changes related to the prediabetic
10 neuropathy patients.
11 So what we know essentially is that these
12 fibers goes away. There is a relationship with the
13 clinical picture in terms of the sensory symptoms
14 and pain, and that the patient with painful
15 neuropathy can still have a complete innervation of
16 skin. Where the pain comes from here is not that
17 clear, but keep in mind that also patient with
18 complete insensitivity to pain can have a complete
19 innervation of the skin.
20 This is clear. This is from a case with an
21 hereditary sensory autonomic prototype 4. And this
22 brings us to something that has been commanded

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1 a fixed clear specificity, which is 95 percent,
2 which is the number of true negative. But to me it
3 is impossible intrinsically to test the
4 sensitivity, so the number of true positives are
5 the method because again, it is a self-reporting
6 thing. We don't have the gold standard, so we have
7 to decide what is the gold standard.
8 Again, it is impossible to define what is
9 the positive predictive value and the negative
10 predictive value, so the percentage of those below
11 the cutoff will truly have a neuropathy or do not,
12 which actually vary also with the prevalence of
13 disease in the population. I have to tell you that
14 we know little about that. This is what happens in
15 terms of a change for the positive and the
16 negative. So the high prevalence increases the
17 positive predictive value and decreases the
18 negative.
19 A few things regarding the epidemiology of
20 the disease. To my knowledge, this is the only
21 focused paper, my friends in Maastricht, and things
22 they've done, which is essentially one-tenth of

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1 yesterday. So what happens in patient with
2 conditions in which essentially there is no pain?
3 Again, some disease, yes, there might be some in
4 ALS. We have revised our [indiscernible - off mic]
5 with about 60 patients, and 75 per cent of these
6 patients without pain have a complete innervation
7 of epidermis. And there isn't any correlation with
8 genotype; this is facial and so on [indiscernible].
9 But underlying this, we have used a couple of
10 animal models, of ALS animal models, to demonstrate
11 that also in the animal models, very early, there
12 is a complete innervation of the skin that you see
13 here, and that in this model, it will be attributed
14 to a specific neurotoxic effect of a splice variant
15 of peripherin targeting exactly the small size
16 neurons and causing a change in the assembly of the
17 neurofilament.
18 So going to the point 6, biopsy results
19 blind to the clinical phenotypic is really little
20 informative. That's an important thing. The other
21 point is that the availability of the cutoff value
22 based on the 5th percentile made a skin biopsy with

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1 stroke, 11 [indiscernible] per 100,000, more or
2 less.
3 So what is the conclusion, my conclusion?
4 The strength. We have sex and adjusted normative
5 value, which is tailored to patient. It's a good
6 agreement within the two methods. We can use
7 either, and that's fine. It's a very good method,
8 which is reliable also from the animal models. In
9 humans, there is a high reliability between sites
10 and 3 weeks. Also, there isn't any influence, any
11 biological influence for the [indiscernible - off
12 mic], and there's a high specificity.
13 So it is a reliable, confirmatory tool in
14 candidate patients. This is what we want in a
15 randomized clinical trial, I think. We want to
16 know the number of true negative. The limitation,
17 there is a poor interlab agreement without the
18 quality program, so it is mandatory for a
19 multicenter because we don't know the sensitivity.
20 We don't know what is the positive and the negative
21 predictive value, so it is useless as a screening
22 tool, simply.

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1 Finally to me, it should not be used as a
2 unique tool to determine the patient, the
3 subgroups, and it opens a number of issues related
4 to a number of other pain syndromes. So there is
5 another number of other issues, but I don't have
6 time. One is the morphology of the fibers; another
7 one, what I think would be interesting, the
8 measurement of the dermal nerve fiber length, this
9 was an unbiased assessment that we did in which we
10 found a very nice correlation with the dermal nerve
11 fiber density, but maybe we can discuss it later.
12 Thank you.
13 DR. FELDMAN: Perfect.
14 (Applause.)
15 DR. FELDMAN: I think again with the idea of
16 staying on time because we have such a long time
17 for discussion also, we'll just keep moving
18 forward. So next is Rayaz and CCM.
19 Presentation - Rayaz Malik
20 DR. MALIK: Thank you, Roy.
21 The question is, to the audience, is corneal
22 confocal microscopy ready for prime time? And I'm

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1 sure you're all saying no. So here's my next 20
2 minutes or 25 minutes to try and convince you
3 otherwise.
4 This is the technique, corneal confocal
5 microscopy. It's relatively rapid in expert hands,
6 non-invasive, it's repetitive, and it images
7 corneal nerves. These are nerves and cells that we
8 can image in the cornea patients, whether it's in
9 the clinic or whether for cohort studies, or for
10 clinical trials.
11 Corneal nerves, while they are derived from
12 the ophthalmic division of the trigeminal nerve in
13 the skin, we know there are 200 nociceptors per
14 millimeter squared, but the cornea is actually
15 claimed to be the most density innovative tissue in
16 the body. Dominantly it is sensory nerves,
17 probably in humans, actually. In animal models,
18 there is debate as to the proportion of sensory
19 sympathetic, parasympathetic, but in humans, it is
20 predominantly sensory nerves with the cell body in
21 the trigeminal ganglion, and they express
22 substance, BCGRP, so neuropeptides. And there is a

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1 small proportion which are sympathetic, which again
2 expressed the usual propeptides.
3 Corneal nerves, what are they? Well, you
4 can scan through the different layers of the cornea
5 and capture the layer that you need to capture,
6 which is the subbasal nerve plexus. This is what
7 we're interested in or we can image readily. We
8 can't actually image these nerves very well, and
9 these are I guess equivalent to the intraepidermal
10 nerve fibers. So what we're really looking at is
11 the dermal or the subbasal plexus. And if you look
12 at electron microscopy, what you see is very
13 similar to the skin, these are the bundles of nerve
14 fibers. And in cross-section, you can see these
15 are the unmyelinated axons.
16 So what we have done -- actually, I can't
17 remember, Giuseppe, when INF started or really hit
18 prime time; probably a long time before. But the
19 first study, actually, that was done for CCM is
20 2000, and it was a lady called Maria Rosenberg
21 who's an ophthalmologist in Finland, who described
22 the potential for looking at the corneal nerves and

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1 relating it to MNSI.
2 Around about that time, we actually started
3 a study, which is funded by the JDRF, and we set up
4 a protocol, which allows you to capture 6 images
5 per patient. This is a typical or very good
6 example of corneal nerves, you can see. And
7 essentially what we've done is set up a protocol
8 which allows you to quantify this in an objective
9 way. So one of the key parameters is corneal nerve
10 fiber density, which is the large nerve fibers that
11 run at least 75 percent of the image, and we
12 calculate, really 1, 2, 3, 4, five, no, 5 nerve
13 fibers, and then you calculate the density.
14 The other additional parameter, which I
15 think is important, is corneal nerve fiber length,
16 which is the total length of nerve fibers present
17 in a given image, and then corneal nerve branch
18 density, which is the number of branches. And more
19 recently actually, we've looked at the area of
20 these nerves as well and we believe that that is
21 probably the best way of looking at nerve repair.
22 So essentially, these are the parameters that we

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1 measure.

2 To take away the subjectivity that is always
3 present when you take one person who thinks there's
4 an INF there or There's a corneal nerves there,
5 We've actually got an automated system that we
6 developed with image analysis engineers, whereby
7 you can take an image and instead of measuring it
8 and taking 30 minutes and not really being sure
9 whether this is a nerve fiber or isn't, automated
10 image analysis takes about 25 seconds, and you can
11 see that there's a very good correlation between
12 automated and manual assessment. So that's
13 actually freely available to anybody who wants to
14 use it.

15 So what we've set about doing is to convince
16 people in the audience or other people whether or
17 not this is worthy of becoming an FDA endpoint.
18 And really, if you go to the FDA website, they say
19 to you that you need to fulfill certain criteria.
20 So is it a biomarker? Is it a physical sign or
21 laboratory measurement that occurs in association
22 with a pathological process, and does it most

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1 importantly have diagnostic or prognostic utility?

2 In terms of diagnostic, this is the first
3 study we did from actually an innovative grant from
4 the JDRF for \$53,000, and what we showed in that
5 particular study using the old corneal confocal
6 microscope, which is this is actually from the new
7 HRT III, but this was from the old one, which
8 weren't as good, the images, that compared to
9 healthy controls subjects, you could see diabetic
10 patients with mild moderate and severe neuropathy,
11 there was a progressive reduction in corneal nerve
12 fiber length.

13 Subsequently -- and actually meta-analysis
14 was done in 2016, but there are many more studies
15 now. There've been other centers, including our
16 own, which were included in this meta-analysis
17 where there were over 1600 patients that compared
18 550 with diabetic neuropathy, 590 without diabetic
19 neuropathy, and 500 healthy controls. And you can
20 see that they actually more or less show that
21 corneal nerve fiber density, branch density, and
22 length differentiates controls from those with

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1 neuropathy, and also actually detects an early
2 deficit even in those considered to have no
3 diabetic neuropathy because the diagnostic criteria
4 that were used were symptoms and signs in
5 neurophysiology. So this is showing you that
6 corneal confocal microscopy is detecting early
7 small fiber neuropathy with good p-values in terms
8 of significance.

9 Also have a normative data set. This
10 particular one we published is 343, but we now have
11 in excess of 700 healthy subjects. But what you
12 see here is this is very similar to the INFD.
13 There is progressive reduction with age, not as
14 marked actually as the INFD. You can see the IFND
15 starting around 10 and it gets down to 1 by the
16 time you get above 70. But there is nevertheless a
17 progressive fall in the different parameters that
18 you see, and this is age related. Again, similar
19 to INFD, actually there is no effect of weight,
20 BMI, and sex.

21 The other measure that we think may be a
22 better measure is corneal nerve fiber size, which

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1 actually is not looking at individual nerve fibers,
2 but looking at the area of these corneal nerves.
3 And what you see here is this is corneal nerve
4 fiber density. You see progressive fallout for the
5 increasing severity of neuropathy, and this is
6 nerve fiber; again, progressive fallout with
7 increasing severity of diabetic neuropathy.

8 In addition, if you look at the area itself,
9 if you look at the size frequency distribution, you
10 can see these are healthy controls and these are
11 diabetic patients with increasing severity of
12 neuropathy. And you can see again. So this is
13 showing you that there's a difference between
14 diabetic patients with progressively increasing
15 neuropathy severity and healthy control subjects.

16 In addition, if you look at the sensitivity
17 and specificity, or the AUC, the area under the
18 curve, for these different measures, nerve fiber
19 density, nerve [indiscernible], nerve fiber length,
20 nerve fiber area, what you see is that even in
21 people with relatively early or minimal diabetic
22 neuropathy, there is actually an AUC which is

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1 approximately 0.8, and this gets much better the
2 more severe your neuropathy, which is what you
3 would expect in terms of a diagnostic measure.
4 There is now, hopefully impressed, because
5 he's just gone back with the second review, pooled
6 multinational consortium study, which was done with
7 998 participants from five different centers, which
8 included 516 people with type 1, 484 with type
9 diabetes. And in this particular study, despite
10 the fact that we had different diagnostic tests
11 that were used to define neuropathy, despite the
12 fact that we had different protocols that were used
13 to actually undertake the CCM from using 1 image to
14 8 images, we still get an AUC which is comparable
15 between the automated and the manual system for
16 corneal nerve fiber length, which is around 0.71,
17 and the sensitivity and specificity was around 68
18 and 66 percent, which, again, fares reasonably well
19 compared to QST.
20 A big question always that I'm asked is,
21 CCM, how does it compare to intraepidermal nerve
22 fiber density, which is the gold standard. And to

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1 address this, we did a study of about 80 patients
2 and healthy controls subjects, and essentially what
3 we did is we compared skin biopsy in the dorsum of
4 the foot with corneal confocal microscopy. And we
5 looked and essentially asked how good was each test
6 for identifying diabetic patients with neuropathy
7 based on symptoms, signs, neurophysiology. What
8 you see actually is that the sensitivity for
9 corneal nerve fiber density was better than
10 intraepidermal nerve fiber density, and the
11 specificity was comparable.
12 In a further study we've just published, we
13 again recapitulate that with a larger cohort where
14 we've compared skin biopsy with corneal confocal
15 microscopy. So this is the ROC curve for corneal
16 nerve fiber density, length density actually, and
17 this is intraepidermal nerve fiber density. And
18 you see here using the optimal cutoff, so CNFD,
19 INFD, that the AUC actually for corneal confocal
20 microscopy is 0.81 compared to 0.73, and the
21 sensitivity 0.77 for CNFD compared to 0.61 for
22 INFD, 0.79 and 0.8.

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1 The other question that is always asked is,
2 well, you know, corneal nerves, they're short
3 nerves, they're up there. They don't really have
4 this dying back process. So in order to address
5 this, actually, what we've done is looked at the
6 cornea itself and looked at more proximal central
7 parts of the nerve compared to the more distal
8 inferior wall. So we've compared changes in the
9 same patients proximally and distally.
10 This is a map of a cornea. You can see here,
11 this is the central bit and then you have the
12 inferior wall down here. And what you see actually
13 is if you look at the length of nerves in the
14 inferior wall compared to the central more proximal
15 bit, there's actually greater damage in the more
16 distal inferior wall compared to the central part.
17 So you can see here, this is diabetic patients with
18 diabetic neuropathy. Without diabetic neuropathy,
19 the gradient is much greater than the central
20 corneal nerves.
21 Prognostic utility, there are actually three
22 independent studies, but this is two independent

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1 studies published 156 patients recruited with
2 type 1 diabetes. At recruitment, 101 had no
3 neuropathy. They underwent assessment to exclude
4 neuropathy or include neuropathy based on nerve
5 conduction symptoms and signs, and they underwent
6 baseline examination for neuropathy measures and
7 ophthalmic measures.
8 Ninety patients were reexamined after
9 47 months and 18 percent then developed neuropathy
10 according to this criteria. We then went back and
11 looked at what measures, in terms of demographics,
12 lifestyle, neuropathy measures, ophthalmic
13 measures, were different in this group who
14 developed neuropathy compared to those who didn't
15 develop neuropathy. And what we show is that the
16 retinopathy stages according to ETRS criteria was
17 different. So if you developed diabetic
18 neuropathy, then you had a higher neuropathy score,
19 but corneal nerve fiber length you can see was
20 significantly lower in those who develop diabetic
21 neuropathy compared to those who didn't develop
22 diabetic neuropathy.

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1 Another study from Canada from Bruce Perkins
2 group, 65 type 1 diabetic patients followed over
3 three years. You can see very similar incidence of
4 diabetic neuropathy based again on the same
5 criteria; 17 percent developed diabetic neuropathy.
6 They actually exhaustedly looked at risk factors
7 for developing diabetic neuropathy, and in addition
8 undertook very detailed neurophysiological
9 examination, quantitative sensory testing, LDI
10 flare, and corneal confocal microscopy.
11 When you compared those with new onset
12 diabetic neuropathy with those who didn't get
13 diabetic neuropathy, you see that there is no
14 difference for TCNS, neurophysiology, abrasion [ph]
15 perception, and autonomic function or LDI flare.
16 But you can see corneal nerve fiber length
17 significantly reduced in those who develop
18 neuropathy compared to those who didn't.
19 Is it clinically meaningful as a measure of
20 how the patient feels, functions or survives?
21 Well, for IFSN, we did a study now almost eight
22 years ago where we showed that in patients with

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1 idiopathic small fiber, 25 patients referred by the
2 neurologists exhaustively excluded all of the
3 causes. ISFN, we showed that in fact there is a
4 reduction in corneal nerve fiber density, nerve
5 fiber length, and nerve branch density in patients
6 with ISFH. Furthermore, these parameters correlate
7 with the neuropathy symptom profile, neuropathy
8 deficit score, and even the sural nerve conduction
9 velocity.
10 Autonomic neuropathy is something that we
11 believe is -- although the corneal nerves are
12 predominantly sensory, we do find that in this
13 particular cohort of patients -- so these are
14 patients who had antidiabetic gastroparesis and
15 severe diabetic autonomic neuropathy. You could
16 see they had a significant reduction in corneal
17 nerve fiber length, compared to healthy controls,
18 compared to diabetic patients without
19 gastroparesis. And you can see the AUC is actually
20 spectacular in terms of nerve fiber density, nerve
21 fiber length, nerve branch density, and very high
22 sensitivities and specificities for these

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1 parameters for patients with autonomic neuropathy.
2 In a smaller cohort of people with
3 idiopathic small fiber neuropathy, only 15. We've
4 now looked and showed that 6 actually of these had
5 autonomic symptoms. And what we now show is that
6 corneal nerve fiber length was actually more
7 significantly reduced in those with painful ISFN
8 and also autonomic symptoms compared to painful
9 symptoms alone, whereas skin biopsy didn't really
10 differentiate the two. Although it was reduced in
11 both groups, it wasn't different. Here you can see
12 that it was reduced in both groups, but more so in
13 those with autonomic symptoms. We've also got data
14 on diabetic patients, painful and painless
15 neuropathy, and we show actually that there is a
16 reduction in those with painful neuropathy compared
17 to those with painless neuropathy.
18 Other neuropathies, chemotherapy induced
19 peripheral neuropathy is something that we've
20 looked at in a small cohort of patients with
21 esophageal and gastric carcinoma. And what you see
22 is that, actually, even before they got

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1 chemotherapy, there's already a reduction in
2 corneal nerve fiber length. And in fact what
3 happens here is not that there is further reduction
4 in corneal nerves, but in fact there is an increase
5 in the number of nerves, which is consistent with
6 on the third cycle, there is actually new sprouts
7 or n regeneration going on. But this is actually
8 related to pain, so much like Giuseppe has said,
9 looking at actual nerve fiber numbers maybe is not
10 that meaningful. You need to take the patient as a
11 whole and you need to look at what's going on in
12 terms of nerve fiber, not only damage but repair,
13 in relation to pain.
14 Other conditions where we've looked at this
15 CIDP. This is wit Mark Stettner from Germany and
16 other inflammatory neuropathies. So you can see
17 typically people would say, well this should be a
18 large fiber neuropathy, but you can see corneal
19 nerve fiber density, nerve branch density, nerve
20 fiber length consistently reduced in all three
21 conditions. And in addition, there are actually
22 some cells, that you can see the Langerhans cells

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1 in here, which we've looked at, and you can see
2 there is increased expression of these immune cells
3 in this inflammatory neuropathy.
4 We also looked at people with HIV, so this
5 is in collaboration with people in Imperial,
6 Prof Rice [ph], where we've taken healthy control
7 subjects, patients with HIV without sensory
8 neuropathy according to the sensory score that they
9 use in HIV, and patients with HIV sensory
10 neuropathy. And you see here that there is a
11 progressive fallout of nerve fibers more so in
12 those with sensory neuropathy compared to those
13 without.
14 In New York with a group in genetics, we've
15 actually looked at patients with Friedreich's
16 ataxia where we have again shown that patients with
17 Friedreich's ataxia were significantly low
18 accordingly on nerve fiber density, branch
19 intensity, and length compared to healthy control
20 subjects. In addition, we've also shown that the
21 DAA triplet repeats, which are characteristic of
22 Friedreich's ataxia, in terms of the frataxin gene,

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1 correlates highly significantly with the CCM
2 values.
3 So in terms of CCM and other peripheral
4 neuropathies, you can see that there's a whole host
5 of conditions, peripheral neuropathies actually,
6 that have been shown to have involvement of corneal
7 nerves, including Fabry's disease, ISFN, hereditary
8 neuropathies, CIDP, Wilson's disease, Graves'
9 disease, amyloid neuropathy, and HIV neuropathy.
10 Is it a surrogate endpoint? Does it change
11 in a clinical trial? The proof of principle study
12 that we did many years ago -- the first one was
13 2007, subsequently in 2013, was diabetic patients
14 undergoing pancreas and kidney transplantation.
15 And we simply measured neurological exam, nerve
16 conduction, skin biopsy and corneal confocal
17 microscopy. And what we showed actually over 12
18 months is that nothing happened in terms of
19 symptoms and signs, nothing happened in terms of
20 neurophysiology, and although there was a trend for
21 INF to increase, this wasn't significant.
22 What did improve at 6 months and at 12

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

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1 epidermis itself, so the mean dendrite length.
2 Here you see a significant increase at 12
3 months but also 36 months suggesting that perhaps
4 intraepidermal nerve fiber density is good as a
5 diagnostic, but perhaps not so good in a
6 therapeutic trial.
7 ARA 290 is exploratory. I suppose it's a
8 drug which has been suggested to have a particular
9 impact on inflammation and tissue injury and tissue
10 repair. So we've done, in conjunction with RM [ph]
11 several studies now, ARA 290 in patients with
12 type 2 diabetes, where we showed that nerve fiber
13 density actually didn't -- it says 28 days dosing
14 by the way -- didn't really improve much, but in
15 nerve fiber length, you could see significantly did
16 increase. In particular, nerve fiber area was
17 increased as was nerve branch density.
18 Sarcoid neuropathy, we have shown similar
19 changes, 28 days dosing increases in nerve fiber
20 area at the lower dose and the higher dose. But in
21 particular we also show in skin biopsies, there is
22 a relationship between the improvement in corneal

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1 nerve fiber area and the expression of GAP-43,
2 which is supposed to represent regenerating no
3 fibers. And clinically relevant is the 6-minute
4 walk test in sarcoidosis. We see a correlation
5 with improvement in the 6-minute walk test and
6 improvement in the corneal nerve fiber area.
7 An independent study by Vera Brill's group
8 looked at omega-3 supplementation in neuropathy in
9 type 1 diabetes published in Neurology this year,
10 where they looked at changes over 12 months in
11 terms of neurophysiology, quantitative sensory
12 testing, and autonomic function. What they found
13 actually, over 12 months, there was no significant
14 improvement apart from a borderline improvement in
15 peroneal F wave and I think vibration, with heart
16 rate variability going down actually at 12 months.
17 Corneal confocal microscopy, you can see here that
18 there was actually a significant improvement in
19 corneal nerve fiber length. Baseline 8.1 increased
20 to 12 months to 10.1. There was also significant
21 increase in corneal nerve branch density.
22 We have also got data in patients undergoing

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1 bariatric surgery. This is a cohort of about 40
2 patients with type 2 diabetes, and you see here
3 over 12 months that there is actually an
4 improvement in corneal nerve fiber density, corneal
5 nerve branch density, and corneal nerve fiber
6 length.
7 There are now 8 interventional studies.
8 This is the SBK data, which is the longest, which
9 is 36 months, but you can see this is the omega-3.
10 This is cibinetide ARA in type 2 diabetes, in
11 sarcoidosis, bariatric surgery, and you could see
12 all consistently show that corneal confocal
13 microscopy actually is able to show a change within
14 12 months and then progresses out to 36 months.
15 So we believe that we've kind of ticked most
16 of the boxes. We need to do bigger studies and
17 these are currently ongoing, particularly in terms
18 of cohort studies for diagnosis; and started as
19 kind of almost a single man operation in
20 Manchester, then my collaborator moved to Brisbane
21 in Australia and has now grown with many more
22 centers that are doing corneal confocal microscopy

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1 across Europe, predominantly North America, South
2 America, Middle East, China.
3 In fact, I'll read this out to you, but
4 there are now 582 HRT III across the world of which
5 there's about 18 in the US. But in the last two
6 years, they've sold 160 to China. So you can
7 expect some big studies that are going to come out
8 of China very soon.
9 There are 562 HRT IIIs across the world, and
10 there are actually 2100 HRT III machines which can
11 be modified to become like the corneal confocal
12 microscopes that we use. Thank you.
13 (Applause.)
14 DR. FELDMAN: We do have time for a couple
15 of questions. I'd like to just make one comment,
16 and that is you showed the Perkins study where 65
17 type 1 diabetics at nerve conduction studies were
18 not a good marker of developing neuropathy. If you
19 look at the DCCTE, [indiscernible], Jim Albers,
20 published a paper of what was a 1,500 type 1
21 diabetics and showed that nerve conduction studies,
22 particularly the sural amplitude and the peroneal

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1 motor conduction velocity was a very robust marker
2 of developing neuropathy in that particular cohort
3 over a five-year period.
4 How about questions? We have time for a
5 few. Yes?
6 DR. STEINER: This morning, the discussions
7 were great. The discussions today and yesterday
8 were fabulous, so thank you. I'm coming at this
9 from the industry perspective and looking at
10 this -- for example, if your target is painful
11 small fiber neuropathy, which is what we're
12 interested in, how do you approach this with some
13 type of an algorithm? Which is how Roy started out
14 this morning, because if pain doesn't correlate
15 typically well with IENFD counts, and the positive
16 and negative predictive values aren't that good,
17 and also if the IENFD counts are not as reliable,
18 and mixed sensory neuropathies, QST with lower
19 specificity would concern me to enroll those
20 patients in a trial, and with low sensitivity we're
21 not going to be able to enroll patients --
22 So basically, how do you screen for the

<p style="text-align: right;">Page 81</p> <p>1 target population that you want? And I'm also 2 wondering in the context of how important the 3 clinical judgment is, should we be considering 4 something such as independent review boards, which 5 we use in MS trials to confirm definite relapsed. 6 So that's all. 7 DR. FELDMAN: So that's a fairly broad 8 question for the two minutes he has, so why don't I 9 ask you, Rayaz, just maybe to comment on your 10 opinion on using CCM, where she has said -- she 11 discussed skin biopsy, QST. Maybe you could just 12 comment on CCM, and then that fairly broad question 13 we can address during the discussion. 14 DR. MALIK: I don't think if you've got a 15 trial where you believe that it's going to affect 16 pain, you need -- it's not CCM or INFD, or even 17 QST. I think they are to look at disease 18 modification. That's where you've got to -- in 19 terms of using these particular tests, whether it's 20 INFD, CCM, or QST as entry criteria, I think we 21 need to wait for the definition as to what we are 22 going to propose as an inclusion for somebody who's</p>	<p style="text-align: right;">Page 83</p> <p>1 syndromes that we can recognize. They may have 2 different etiologies, they may be idiopathic, but 3 we can recognize different clinical syndromes 4 within this broad umbrella of small fiber 5 neuropathy. 6 The one I'm going to be focusing on 7 exclusively today in a laser-like fashion will be 8 the distal small fiber neuropathy syndrome. I 9 won't be talking about autonomic subtypes of small 10 fiber neuropathy because the use of autonomic 11 testing modalities in a syndrome that presents with 12 dysautonomia is intuitive. I'll be looking at the 13 data in distal small fiber neuropathies. I will 14 not be looking at the data in non-length-dependent 15 small fiber sensory neuropathy or neuropathies 16 because there's relatively little systematic data 17 of diagnostic testing and autonomic testing in 18 those syndromes. So that's what I'm going to be 19 focusing on. 20 With that in mind, I want to go back again 21 to working definitions of distal small fiber 22 neuropathy, and what you'll notice across most</p>
<p style="text-align: right;">Page 82</p> <p>1 got small fiber neuropathy. 2 DR. FELDMAN: Yeah, that's very reasonable. 3 I think, again, to stay on time, then, we'll go to 4 our final talk of the morning, and that's from 5 David. 6 Presentation - David Herrmann 7 DR. HERRMANN: Just a couple of disclaimers 8 before I start. I have no disclosures relevant to 9 this talk. I'm not an expert in autonomic function 10 testing. I have an interest in small fiber 11 neuropathy and have been involved more on the 12 sensory side of things. But because one of my 13 former fellows got interested in autonomic testing, 14 I'm speaking here today. So most of the work I'll 15 review, people in the audience have contributed to. 16 I want to go back to this question -- as we 17 think about autonomic testing in the context of 18 small fiber neuropathy, I want to go back to what 19 we're thinking about clinically because I find the 20 term "small fiber neuropathy" to be too broad and 21 not very useful for our purposes. They're clearly 22 well-defined clinical subtypes or clinical</p>	<p style="text-align: right;">Page 84</p> <p>1 studies that have been discussed yesterday and 2 across the studies I'll review, there are some 3 cardinal features that allow you to enter a study 4 or a coupled study. These include distal 5 paresthesias or neuropathic pain, usually pain, but 6 some are paresthesias. You need to have normal 7 strength clinically. You have to have an absence 8 of upper motor neuron signs. And in a qualified 9 sense, you have to have an absence of significant 10 large fiber sensory dysfunction. You also have to 11 have normal nerve conduction studies. 12 Two qualifications, there's discussion about 13 what absence of large fiber signs means. This can 14 be a complete absence of large fiber science, which 15 may be necessary to identify enriched cohorts that 16 may have a sodium channelopathy, for example, but 17 in most of the studies, trivial or mild distal 18 large fiber sensory dysfunction has been included 19 in this working clinical definition of what is 20 distal small fiber neuropathy. There's also been 21 varying rigor in what are normal nerve conduction 22 studies. That's not my task today to discuss that,</p>

<p style="text-align: right;">Page 85</p> <p>1 but there have been a range of different sets of 2 nerve conduction studies applied. 3 Now you ask, why am I talking about these? 4 Because nowhere on this slide is any mention of 5 autonomic symptomatology, or autonomic testing, or 6 autonomic characteristics. So the question is, in 7 the distal small fiber neuropathy syndrome that we 8 as clinicians recognize, dysautonomia doesn't 9 appear as entry criterion in any of these studies. 10 And this is for the borne out. There have been 11 many cohorts looking at this clinically defined 12 distal small fiber neuropathy. These are older 13 ones. I'm aging myself. My name is on here. 14 These are almost 16 years ago, early turn of the 15 century. 16 But again, if you look at the clinical exam 17 components of this, it's really examination of 18 distal somatic neurologic impairment. There is no 19 component of any autonomic testing clinically, and 20 you'll see across different studies, some have 21 included trivial distal large fiber sensory 22 dysfunction.</p>	<p style="text-align: right;">Page 87</p> <p>1 far higher across a range of symptoms than in 2 control groups, suggesting that autonomic symptoms, 3 if you inquired carefully, are relatively prevalent 4 in the clinical syndrome of painful feet or distal 5 small fiber neuropathy. 6 Now with that in mind, the question is, has 7 autonomic testing being looked at given the 8 relative prevalence of autonomic symptomatology 9 across multiple cohorts? And the answer is yes. 10 And I'll talk about a little bit of the data of 11 some of the modalities and what modalities have 12 been used. And again, I'm not going to cover every 13 autonomic modality. I'm just going to pick on a 14 couple. 15 Sudomotor function has been extensively 16 interrogated, and most systematic studies in large 17 cohorts -- and I'm going to focus on larger 18 studies, not studies with 8, 10, 12 patients in 19 primarily -- have involved evaluation of the sort 20 of performance characteristics of QSART, 21 quantitative sudomotor axon reflex testing. I will 22 talk briefly also a about electric chemical skin</p>
<p style="text-align: right;">Page 86</p> <p>1 Others have been more restrictive. 2 So the question is why, again, think about 3 autonomic testing? And the reason is across 4 multiple studies -- and forgive me if I've included 5 some cohorts of members of the audience who've done 6 work in this area. But across time, across 7 multiple studies, autonomic symptoms turn out to 8 be relatively common in patients who present with 9 clinically sensory dominant syndrome that I've 10 outlined across various of these studies, and I'll 11 highlight one study to make the point, that of Vera 12 Novak. 13 So Vera looked at 92 patients who presented 14 with painful feet felt to be neuropathic. 15 Importantly, with respect to a question of 16 dysautonomia, diabetic neuropathy was screened out 17 of the cohort. She applied a systematic autonomic 18 questionnaire to both the patients and to controls. 19 And across the range of autonomic symptoms, some of 20 the parasympathetic dysfunction, some of adrenergic 21 dysfunction, the frequency of autonomic 22 symptomatology on a standardized questionnaire was</p>	<p style="text-align: right;">Page 88</p> <p>1 conductance or SUDOSCAN, not because I believe the 2 data is there in small fiber neuropathy, but we're 3 going to be tossed with some recommendations at the 4 end of this, and it's an evolving literature, and 5 its use has also been expanding. So in the 6 interest of being complete, I'll touch on that. 7 Thermoregulatory sweat testing has been 8 another modality that's been evaluated. It's very 9 sensitive, but unlike QSART it's not localizing. 10 And I think this is important. If we want 11 confirmatory tests or supportive tests of a distal 12 neuropathy syndrome, we want those tests to be 13 localizing to the peripheral nervous system. QSART 14 is because it interrogates the postganglionic as 15 sudomotor sympathetic fibers. Thermoregulatory 16 sweat testing is abnormal in a high percentage of 17 patients with distal small fiber neuropathies, but 18 it's only available at a couple of centers, it's 19 very tedious, and it's not applicable to 20 multicenter studies, so I'll focus mainly on QSART. 21 Cardiovagal testing is widely available, and 22 it's been looked at quite extensively in patients</p>

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1 with distal small fiber neuropathy, particularly
2 heart rate variability with deep breathing.
3 There's been somewhat less study of adrenergic
4 modalities, but they have also been studied in
5 distal small fiber neuropathy, and these
6 modalities, sudomotor testing, cardiovagal testing,
7 and testing of adrenergic responses can be combined
8 and have been combined in some of these cohorts in
9 the autonomic reflex screen with calculation of a
10 COMPASS autonomic severity scale or CAST scale.
11 And I'll discuss this to some degree combining
12 these modalities of testing.
13 Now, when autonomic function studies have
14 been done in clinically defined distal small fiber
15 neuropathy, the syndrome I described, it turns out
16 they're frequently abnormal across a number of
17 cohorts, and a pattern emerges. And the classical
18 early study was that of Stewart, et al., who looked
19 at 40 patients back in 1992; found they had a
20 distal small fiber neuropathy syndrome. They were
21 permissive of mild distal large fiber sensory
22 dysfunction, and some 80 percent of 40 patients had

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1 an abnormal QSART response mostly in the distal
2 lower extremities.
3 Cardiovagal testing by contrast was abnormal
4 in only a small percentage of patients, 28 percent
5 of patients. So Stewart, et al. back in 1992
6 concluded that sympathetic sudomotor fibers are
7 frequently affected in the syndrome, and they
8 suggested that evaluating of sweating is a useful
9 diagnostic test. But autonomic nerve fibers
10 controlling heart rate are less affected.
11 Moving forward in time to the study of Vera
12 Novak, again, out of Ohio State, looking at 92
13 patients with painful feet, QSART abnormalities
14 were again seen in 73 percent of patients. Very
15 similar to the Stewart et al. study, the
16 abnormalities tended to be length dependent
17 mirroring the clinical symptomatology.
18 Cardiovagal tasting in their hands was also
19 reduced in a fairly high percentage of patients,
20 somewhat higher than the Stewart et al. paper. But
21 in their hands, head-up tilt [indiscernible]
22 testing, and measures of adrenergic function, they

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1 had no patients who had significant orthostatic
2 hypotension or syncope in that particular cohort.
3 Phil Low's group from the Mayo Clinic in
4 2006 did a larger study, and they looked at 125
5 patients who again had that clinical syndrome of
6 distal small fiber sensory neuropathy with a
7 similar inclusion criteria to Stewart et al. in the
8 features I outlined. And in 125 patients,
9 basically, they changed this a little bit. They
10 allowed patients to have trivial distal nerve
11 conduction study abnormalities. They allowed
12 inclusion of such patients.
13 So of the 125 patients, 78 had normal nerve
14 conduction studies mirroring the typical distal
15 small fiber neuropathy cohorts we've discussed; 47
16 had abnormal nerve conduction studies. And they
17 arrived at the same result, 77 percent of patients
18 had a distal QSART abnormality. And whether you
19 had normal or abnormal nerve conduction studies,
20 that percentage didn't change. Cardiovagal
21 abnormalities and adrenergic abnormalities were
22 also present in a significant percentage of

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1 patients, but again in a significantly lower
2 percentage of patients than sudomotor
3 abnormalities.
4 So I've gone through a range of studies here
5 across time that suggest a high frequency of
6 abnormality of QSART in the syndrome, less so of
7 cardiovagal testing.
8 DR. RUSSELL: David, in that paper, how did
9 they really define small fiber neuropathy?
10 DR. HERRMANN: So each of these -- and I'm
11 getting to Giuseppe's work now because this was the
12 first real attempt to define it. All of these --
13 DR. RUSSELL: In that paper they didn't do
14 intraepidermal nerve fiber.
15 DR. HERRMANN: No. So all of these, whether
16 it be Stewart in 1992 before skin biopsy, this is a
17 clinical case definition, some with no large fiber
18 signs, some with mild large fiber signs. But it
19 was a clinical symptom and sign definition.
20 Now I come to the seminal paper of Devigili
21 et al. and Giuseppe Lauria's group that
22 really transformed the field from thinking about

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1 sort of clinically suspected or a clinical syndrome
2 of distal small fiber neuropathy to say can we
3 integrate these tests, these adjunctive measures,
4 supportive measures, objective measures, or
5 standardized measures into some set of actual
6 diagnostic criteria that we could use going
7 forward. And we've heard a lot about this.
8 I'm going to speak a little bit more on this
9 topic, but I want to make one point. In
10 Dr. Lauria's cohort, almost 50 percent of patients
11 had sudomotor or vasomotor symptoms that were not
12 included in the diagnostic or inclusion criteria,
13 and a high percentage had the abnormality of laser
14 Doppler flowmetry. So again, autonomic dysfunction
15 was fairly prevalent in this cohort.
16 So in reading this, one of my former fellows
17 who's now the head of neuromuscular at University
18 of Nebraska, Parawat Thaisetthawatkul, who I think
19 was a fellow at Rochester in 2001, he went on to do
20 a peripheral nerve fellowship with the Jim Dyck and
21 then an autonomic fellowship with Low. So he
22 basically felt well qualified to maybe look at this

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1 question. He said, "David, with all this data on
2 QSART, can we add autonomic testing to the criteria
3 of Devigili et al?"
4 So he looked at patients who had sensory
5 symptoms, most head pain without muscle weakness or
6 upper motor neuron dysfunction. And they had very
7 strictly normal nerve conduction studies, including
8 either a medial plantar being normal or peroneus
9 tertius, or EHL, in addition to standard distal
10 nerve conduction studies. They underwent QSART
11 sought with a Q-Sweat device; turns out to be
12 relevant. QST skin biopsy, which was read in a
13 moss [ph] fashion in our laboratory to look for
14 evidence to support small fiber neuropathy.
15 In his clinic, about 1200 patients had been
16 referred during the accrual time; 535 patients had
17 clinically defined peripheral neuropathy or
18 suspected peripheral neuropathy. Over 400 had
19 large fiber features and were excluded because they
20 didn't meet these inclusion criteria, but 101 had
21 clinically suspected small fiber neuropathy, sort
22 of fitting prior cohorts. The characteristics of

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1 these patients I won't go through, but we heard
2 yesterday talks from Gordon and Rob Singleton and
3 others relating to risk factors and testing across
4 this disorder.
5 Diabetes was somewhat underrepresented in
6 the cohort, and alcoholism had high representation.
7 I wonder about alcohol, whether it depends on how
8 systematically you ask about it. But leaving that
9 aside, what he did was he took those 101 patients
10 and he said how would Devigili criteria perform in
11 this sort of validation cohort if you'd like in
12 identifying or supporting small fiber neuropathy in
13 a clinically suspected cohort.
14 Just to go over the Devigili criteria, you
15 needed symptoms of sensory neuropathy, normal nerve
16 conduction studies, which perfectly mirrored
17 Parawat's inclusion criteria, but then you need
18 abnormalities on 2 or more among small fiber
19 examination, QST, which was just elevated thermal
20 thresholds, and IEFND distally. And in this
21 cohort, about 38 percent of patients met the
22 Devigili criteria of patients who had a clinically

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1 suspected small fiber neuropathy syndrome.
2 Then Parawat said can we integrate autonomic
3 testing and how does that modify the diagnostic
4 yield, if you will? So what he said as a
5 hypothetical criteria, he said in these patients
6 let's set as a criterion that patients need to have
7 two or more abnormalities of QST. There was one
8 difference which may be relevant, is he added in
9 heat-pain threshold testing, and this was all done
10 on a CASE IV device, and QSART, INFD.
11 If you did that, you had a diagnostic yield
12 of 56 percent, but you needed abnormalities on two
13 or more of these three modalities. But we realize
14 in practice that not every center test has INFD,
15 QSART, and a CASE IV QST machine, but that may be
16 feasible in a trial, but clinically not. So he
17 said can we have a more relaxed set of criteria,
18 and he did that with what Gordon Smith talked about
19 yesterday in mind.
20 Because we know in the clinic, our pretest
21 probability of neuropathy is not universal, so
22 recognizing that not every center may have

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1 this -- and from prior data, we know that if you
2 have an abnormal pin exam, so you don't just have
3 symptoms of small fiber neuropathy, but you have
4 signs that are supportive, your pretest probability
5 of a definable neuropathy on some confirmed
6 interest such as intraepidermal nerve fiber
7 density, is higher.
8 So he said if you have an abnormal clinical
9 exam, can we relax those criteria by just requiring
10 one or more abnormalities of either QSART, INFD, or
11 both? We didn't include QST as a confirmatory test
12 for the following reason. There was a 2003 AAN
13 guideline, including Peter Dyck as one of the
14 co-authors that said that because QST is
15 non-localizing to the peripheral nervous system, a
16 psychophysical test, it shouldn't be used as a sole
17 diagnostic criteria and confirmed presence of
18 neuropathy. And so using that, they've had a
19 normal pin exam where the pretest probability of
20 neuropathy was lower because all you had was
21 symptoms, and he still required the stringent
22 criteria of 2 or more abnormalities among these

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1 three. And it really didn't change by relaxing the
2 criteria. It really didn't change the diagnostic
3 yield much.
4 I won't go into the individual sensitivity
5 and specificity if you use these as the gold
6 standard of QSART, QST, and skin biopsy. But just
7 to make the point, in this cohort, QST was quite
8 sensitive, but it had quite poor specificity if you
9 used these criteria as a gold standard.
10 Yes?
11 DR. HAROUTOUNIAN: Just a quick question
12 maybe. Are those the same patients, the 56 versus
13 57 percent, or as a Venn diagram, there are some
14 patients who fell out of those --
15 DR. HERRMANN: Same patients, just different
16 set of -- you're changing the criteria slightly.
17 But when we looked at whether you could just use
18 QSART alone using this is the gold standard, or the
19 reference standard, or QST alone, or skin biopsy
20 alone, these were fairly sensitive QSART and skin
21 biopsy performed relatively well and had reasonable
22 specificity and positive predictive value. But QST

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1 was quite sensitive but had poor specificity.
2 So really what Parawat concluded was that
3 assessment of both somatic and peripheral autonomic
4 fibers does enhance diagnostic criteria for small
5 fiber neuropathy, and then he wanted to know why.
6 And just very briefly, in a follow on study with
7 patients with similar clinical features, what he
8 did was he did more comprehensive autonomic testing
9 with autonomic reflex screening test and computer,
10 the CAST. So this included cardiovagal testing and
11 adrenergic testing as well to QST again and skin
12 biopsy.
13 Just by way of brief conclusions, there was
14 no association between ankle INFD, any QST measure,
15 and the CAST QSAR subscore, the CAST
16 vagal [indiscernible] score, the CAST adrenergic
17 score, or total CAST. So his conclusion was that,
18 really, in this population of patients, the
19 involvement of different populations of small
20 fibers can be relatively variable, and therefore
21 the autonomic evaluation does give an independent
22 look, really. It's not duplicative of somatic

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1 evaluation.
2 DR. SMITH: Sorry to interrupt, David. My
3 curiosity got the better of me. Was there a
4 phenotypic difference between the 56 or 57 percent
5 who met his updated criteria versus those who did
6 not? Did they look the same or did they look
7 different, from just a clinical perspective?
8 DR. HERRMANN: So I don't have a perfect
9 answer because we didn't look at those patients at
10 that granular level. I think we should go back and
11 look at that. In terms of the broad inclusion
12 features, distal sensory symptoms and pain, normal
13 nerve conduction studies, normal strength, et
14 cetera, they were the same. But I think going back
15 and looking again in more granular detail at those
16 who met or did not meet the criteria I think is a
17 good question, and can't answer that now.
18 So there was no correlation between these
19 measures, and that's why he concluded that looking
20 at both autonomic function and somatic function may
21 potentially be synergistic. But there's a
22 cautionary note in all of this, and that comes from

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

9 If you go back and look, if you look at Phil
10 Low's work, he said QSART's highly reproducible.
11 But if you go back -- first of all, it's a
12 different set of equipment, and if you go back and
13 look at the statistical methods used in those early
14 1980's papers, it's, it's hard to know what
15 statistics were used, whether it was an intra
16 cross-correlation coefficient or a PCN correlation
17 coefficient, it was not well defined.

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

22 Amanda?

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1 DR. PELTIER: Can I make one point?
2 DR. HERRMANN: Yes.
3 DR. PELTIER: So we are in the process of
4 publishing -- we did a repeat reliability study,
5 and one of the things that we found was that
6 temperature, skin temperature was a very important
7 factor. So if you made sure that their limbs were
8 warm and that they were warmed to at least 31
9 degrees Celsius, that that significantly improved
10 their reliability.

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

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

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

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

13 Very briefly --
14 DR. RUSSELL: David, sorry. Can I just make
15 a point here?
16 DR. HERRMANN: Yes.
17 DR. RUSSELL: When you're looking at
18 reproducibility, if you measure the sweat volume,
19 that's the problem, so the actual volume. If you
20 say to yourself, I'm going to define this by normal
21 versus abnormal, or I'm going to define it by a
22 percentile, then reproducibility may be much

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1 better.
2 DR. HERRMANN: Okay. So briefly, SUDOSCAN,
3 and then I'll have two slides where I just
4 summarize my thoughts.
5 DR. FELDMAN: You're fine on time.
6 DR. HERRMANN: Okay. So SUDOSCAN, there's
7 been a proliferation of use of this. Many in this
8 room now, or several, have done studies of it. And
9 I think what's been attractive is that it's simple,
10 and it doesn't have some of the administration
11 issues that Amanda and James and others have
12 pointed to with QSART.

13 So most of the studies of this have been in
14 diabetic peripheral neuropathy, and that's
15 important here. But it's been marketed -- I say
16 marketed -- as a biomarker of sweat gland or
17 sudomotor function. And it's very simple. You
18 apply your hands and feet to stainless steel
19 platforms shown here. And by the way, there are
20 many, many studies that are literature.
21 I focused on ones of experienced
22 investigators that we know. This is a study from

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

14 In Solomon Tesfaye's diabetic neuropathy
15 study, he showed a marked difference between those
16 with DPN and no DPN when using a cutoff of 77
17 microsiemens at the foot with lower conductance in
18 those with diabetic neuropathy. But this was
19 severe diabetic neuropathy. These surals were
20 absent on average. The peroneal velocity was 32
21 meters per second. The peroneal EDB amplitude was
22 0.3 millivolts.

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

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

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

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

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

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

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

7 DR. HERRMANN: You did?

8 DR. FELDMAN: Yes.

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

22 So I think there are some interest here, but

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1 there's a lack of data in larger, well-defined
2 small fiber neuropathy cohorts, so we're not at a
3 point where this can really be recommended, in my
4 view, as part of diagnostic criteria.
5 So just to summarize, I have two slides
6 left. One is what guidelines are there on how we
7 should be using autonomic testing in distal small
8 fiber neuropathy at this point, and they come from
9 the 2010 AAN and AANEM guidelines. Many of us were
10 authors on these but did not write the autonomic
11 section of these. That was sort of led by Phil
12 Low.
13 Really, I'd say that autonomic testing
14 should be considered in the evaluation of patients
15 with suspected autonomic neuropathies. We know
16 that, but the evidence rating and the
17 recommendation was weak in distal small fiber
18 sensory neuropathy. They felt that it would be
19 better if you used a combination of sudomotor
20 testing, cardiovagal testing, and adrenergic
21 testing to get a higher degree of accuracy, but I
22 think it's not practical across multiple centers,

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1 multiple sites, multiple time points to do a full
2 cast or even a modified cast.
3 So I think while doing one autonomic test
4 such as QSART with the standardization that Amanda
5 and James and others have report to may be feasible
6 and well trained investigators, just like you need
7 training for QST or skin biopsy, you need this for
8 QSART. But I think a full cast while may be
9 dealing with some of the issues with single
10 strategy testing is probably not feasible in a
11 clinical trial setting, at least multicenter trial
12 setting.
13 So to summarize, symptoms of dysautonomia
14 and sudomotor dysfunction are common as far as we
15 know from the published literature across multiple
16 codes, including cohorts that have a high number of
17 idiopathic patients. Sudomotor testing, I do feel,
18 as diagnostic sensitivity and distal SFN, based on
19 the work of Parawat, afferent and efferent C fibers
20 are variably involved.
21 Another cautionary note there's going to be
22 another big series that hopefully will be developed

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1 through Peter Dyck senior who's looked at this
2 independently. So I think there's some question
3 about the older normative data of Q-Sweat and maybe
4 some new and normative data. And I think that the
5 conclusions will be similar, that autonomic testing
6 and somatic testing test independent aspects of the
7 syndrome and are likely additive. But I think the
8 rates of autonomic function abnormalities in fact
9 are likely to be lower in that cohort.
10 QSART is most studied, but uncertain
11 reliability or suitability for multicenter use.
12 But I think Amanda answered some of those
13 questions. Then there's this question of which
14 device, and if everyone's using the Q-Sweat, we
15 have to make sure that normative data is
16 standardized to the use of that.
17 But I will make this point to this question
18 of pretest probability of disease and some of the
19 comments Gordon made, is I think if we're going for
20 specificity and we want to make sure people truly
21 have the disorder at entry, we should think about
22 having to confirmatory or supportive measures,

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1 especially if we're going to allow patients in who
2 only have symptoms but no clinical signs because I
3 think that's a patient with lower pretest
4 probability.
5 I think it's something for us to discuss.
6 Do we allow patients into trials who have symptoms
7 because this is a symptom dominant disorder, or do
8 we require that they have abnormal pin exam? And I
9 think that can be a point of discussion, but if
10 you're going to just have symptoms alone, I think
11 you need two supportive tests. And one of those
12 could be QST and a localizing study such as a QSART
13 or skin biopsy.
14 Then finally, SUDOSCAN not ready for prime
15 time in my view just yet, but assessing both
16 somatic and autonomic small fibers may also be
17 relevant to measure differential treatment effects
18 on populations of small fibers. So to the points
19 of Professor Malik and others, some of these
20 measures may be more amenable to change and fiber,
21 and have a different sort of dynamic turnover, and
22 may respond to treatment in different time frames.

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1 So there is an added value of having a
2 multidimensional assessment of the patient, and
3 I'll stop there.
4 (Applause.)
5 DR. FELDMAN: We have time for a few
6 comments or questions.
7 DR. HERRMANN: Chris?
8 DR. GIBBONS: I think you did an excellent
9 job considering you're not a self-proclaimed
10 autonomic neurologist, but I think I just want to
11 echo your points on the SUDOSCAN, and I know we've
12 talked about this before.
13 I think this is sort of a unique situation
14 actually in science where there's been sort of a
15 systemic pervasive publication bias with
16 significant modification of data by the company
17 that seems to have been across the publications.
18 Certainly there are many lower-tier publications
19 that came first, that really escalated the quality
20 suggestion of this device, and I think we just have
21 to be exceedingly cautious about that.
22 DR. HERRMANN: Gordon?

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1 DR. FELDMAN: Gordon?
2 DR. SMITH: Yes. I agree with that. Our
3 study was in just free-range patients with I'd say
4 probable neuropathy, so they had to have signs and
5 symptoms, and I think that explains why skin biopsy
6 didn't perform very well. And SUDOSCAN didn't
7 perform very well either, yet the company hijacked
8 what I think was a precautionary publication and
9 turned it into a marketing ploy. And we've been
10 looking at this in CIPN, and it looks completely
11 useless.
12 DR. FREEMAN: What Chris didn't say is we
13 have data, which I think does not support the use
14 of this device.
15 DR. HERRMANN: My own clinical use of it, we
16 did not enter into any studies. But early on, we
17 tested it clinically and stopped testing it
18 clinically. So I'll just leave it at that.
19 DR. FELDMAN: So I guess I'll echo in.
20 Brian and I just published a paper where we
21 actually looked at 4,000 Chinese patients. And
22 what we did is over a three year period, we did a

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1 study in Pinggu, which is a suburb north of
2 Beijing. We just published this paper last week,
3 where we hired a group of people -- it's very
4 interesting what you can do there that we could
5 actually not do here. And every third door, they
6 would knock on the door and ask if the patient
7 would like to come and be completely phenotyped
8 metabolically, all demographics, and then a careful
9 phenotype for neuropathy.
10 So the results were actually extremely
11 interesting and to be expected in terms of how many
12 people had IGT, prediabetes with neuropathy, frank
13 diabetes with neuropathy previously undiagnosed.
14 We did SUDOSCAN on all of those patients, and it
15 was not particularly useful, less useful than we
16 found in the obesity population where it wasn't
17 that useful.
18 DR. HERRMANN: Anne Louise?
19 DR. FELDMAN: Anne Louise.
20 DR. OAKLANDER: I just want to add that
21 we've been looking at SUDOSCAN in children because
22 we have a particular interest in seeing if there

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1 are surrogate tests that could avoid skin biopsy in
2 children as well. And while it's actually feasible
3 to do SUDOSCAN down to as young as age 2, data from
4 both normal children and children with neuropathy
5 are really not impressive.
6 I think it's kind of hard to submit your
7 papers for publication when you don't have -- it's
8 hard to -- you know what I'm trying to say. But I
9 guess what this goes to highlight is that we should
10 try and get our studies out even if they do not
11 show good diagnostic performance.
12 DR. FELDMAN: So we will continue this
13 discussion, I think. Roy is going to make a few
14 comments, and then what we'll do is we'll adjourn
15 for a break, which will be around 10:30, and then
16 we'll reconvene at 11:00 on the nose. And if I
17 could ask all panel members to be sitting at the
18 panel by 11:00.
19 Roy?
20 DR. FREEMAN: I want to do two things. One
21 is if we could show the -- we do have the
22 housekeeping slide, so now the checkout time, I

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1 would suggest you do it now rather than at 12 noon.
2 You see the usual kind of stuff, lunch in the usual
3 place, internet access as it was.
4 The other point I want to make now is that
5 the Europeans are going to need to take an early
6 flight. So what we thought, just because the
7 essence of this meeting really is the consensus
8 building, that we would take a working lunch. So
9 we'll make the announcement after the panel, but
10 grab your lunch and just bring it back, and we can
11 get going on that.
12 We do have a panel now. We've given it an
13 hour and a half or so. I want to eat into that
14 just a little bit, again, continuing the theme of
15 focusing the mind on the consensus building. So if
16 you could maybe bring the next slide.
17 What I want to do in the next couple of
18 minutes is give you a taste, a smattering of
19 diagnostic criteria, case definitions that have
20 been used in the literature. Some of these are
21 courtesy of Simon and also I think -- I just want
22 to say I thought David did a remarkable job of

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1 synthesizing many of the issues. But I want to use
2 what I'm going to say in the next five minutes to
3 synthesize where I think we should be going in the
4 consensus building.
5 Now these are the Milan, Italian, Devigili
6 et al. criteria, and as you see, there's a menu, at
7 least two of the following. Now, one of the
8 points -- and it may have been -- this was a
9 single-center study. It may have been explicit in
10 the study, but missing from the criteria are
11 actually symptoms, and I think that's going to be
12 an area to discuss.
13 Giuseppe, you may want to weigh in on this
14 at some point, but I would prefer not now. But as
15 we heard even in David's talk, we have been a
16 little vague on the symptoms, and the symptoms may
17 be neuropathic pain symptoms. They may be non-pain
18 symptoms. They may be autonomic symptoms. They
19 may be some combination of both. But that's
20 something we are going to need to address, and
21 we're also going to need to address what
22 combination of symptoms, what's the menu, 2 of 5, 2

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1 of 6, 3 of 2.
2 Clinical signs of small fiber impairment,
3 and this has been discussed as well. But he had
4 pinprick, thermosensory loss, allodynia,
5 hyperalgesia with distribution consistent with
6 peripheral neuropathy, and in his criteria
7 length-dependent or non-length dependent. This
8 also will be a focus of discussion.
9 Then finally, we have symptoms, we have
10 signs, the clinical examination. He did not
11 specify how that clinical examination needs to be
12 done. Was this structured? What kind of
13 instrument? Where exactly was the testing done?
14 It will be something to think about.
15 Then finally, the special
16 investigations -- and this will be the focus of the
17 discussion -- he had a QST and intraepidermal nerve
18 fiber density as part of his criteria. You heard
19 Nurcan give her talk. He only used warm and
20 cooling threshold, not heat pain and not cold pain,
21 and this too will be a focus of discussion.
22 The background to this, before I forget,

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1 should be that you should bear in mind what I think
2 we heard Deb Steiner of Biogen say, and I'm sure
3 the other members of industry are thinking this as
4 well, which falls under the heading of what is a
5 poor drug company to do when they have a hundred
6 sites that they need to recruit for a small fiber
7 neuropathy study and maybe five of them have QSARTs
8 and three of them are able to do it with suitable
9 interrater reliability.
10 So this is an inherent problem, that we will
11 need in some way to come up with a working solution
12 to. Now, David used the term "varying degrees of
13 permissivity." With respect to the exclusions, we
14 will need to think about that. Any sign of large
15 fiber impairments, Giuseppe, as I said, was
16 hard-nosed. He was rigid. He was totally
17 non-permissive, nothing in the large fiber
18 domain --
19 (Laughter.)
20 DR. FREEMAN: -- no major impairment and no
21 abnormality on sensory nerve conductions. We will
22 need to come up with a stance on how permissive we

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1 are going to be. And my mind does harken back to
2 the immunomodulating talk on pornography.
3 (Laughter.)
4 DR. FREEMAN: All right. Then we have
5 Karin's approach, which in some way really I think
6 is a variation on Giuseppe's theme. However, she
7 includes the hard-nosed approach presence. Here
8 we have a menu, two of the following, a little more
9 specific as far as the symptoms are concerned:
10 burning feet, allodynia, diminished pain,
11 temperature sensation, and how she begins to
12 introduce the autonomic aspects. And we are
13 going to need to work on how we are going to
14 incorporate autonomic features in this.
15 Are we going to use some of these structured
16 questionnaires? Are we going to be vague about
17 this? When I use vague in the best sense of the
18 word, are we going to leave it in the hands of the
19 investigator or are we going to have specific
20 structured questions? And she has an array of
21 autonomic symptoms, and one of the possibilities,
22 which I will float this afternoon, is that we need

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1 to think of this disorder as having really three
2 components: pure sensory, pure autonomic, and
3 mixed sensory autonomic, and come up with a way to
4 deal with this.
5 So here we have a variety of autonomic plus
6 sensory symptoms, and here we have some fairly
7 rigid exclusions as well, very similar to Giuseppe,
8 and also the illnesses, history, alcoholism, and a
9 variety of disorders, which require laboratory
10 testing. So again, giving some structure to this,
11 begin to think along these lines.
12 A number of us were at the Toronto neurodiab
13 meeting, and I think several in the audience over
14 here. And we at that meeting developed small fiber
15 neuropathy criteria within DPN, but often used
16 outside. And we then put together what we call
17 possible, probable and definite. I've never liked
18 the word "definite." I have much prefer
19 "clinically confirmed," but we can call it as we
20 will if we go there.
21 And here, length-dependent symptoms, length
22 dependent, not ganglionopathy, not proximal as a

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1 Giuseppe allowed, with clinical signs where were
2 possible, so a combination of symptoms and signs.
3 And bear in mind the point that David made so well
4 in his talk about in the absence of signs, what we
5 need, probable normal nerve conduction studies,
6 symptoms, signs, and normal nerve conduction
7 studies. And then definite, big spiel, normal plus
8 altered intraepidermal fiber density and abnormal
9 quantitative sensory testing thermal thresholds,
10 thresholds not paying, at the foot; so another
11 approach to this, not dissimilar, but taking a
12 slightly different stance, looking at it in terms
13 of possible, probable, and definite.
14 Of note is at that same meeting -- and I've
15 never quite understood how this happened, and
16 perhaps Rayaz will be able to explain, but Rayaz
17 wrote a -- there were a number of different papers
18 that came out of this, the autonomic paper, and
19 Rayaz wrote a paper, which was also a consequence
20 of that meeting, but took a fairly permissive
21 stance with respect to nerve conduction studies.
22 So even at the same meeting, there was clearly some

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1 divergence of views on how hard-nosed to be about
2 large fiber function.
3 Then finally, one of the older
4 papers -- again, thanks, Simon, for pulling this
5 out -- from Lacomis, and his was a modification of
6 John Stewart's, which David mentioned in his talk,
7 small fiber neuropathy, sensory neuropathy manifest
8 by paresthesias that are typically painful, so
9 defining no menu, but just one specific approach.
10 And this was in the age of the burning feet,
11 tingling toes, age, with abnormal findings of small
12 fiber function on at least one neurological
13 examination, specialized electronic diagnostic
14 testing, or pathological studies; so a kind of a
15 menu but a little looser than developed in the
16 ensuing years, and then for research, he got more
17 specific, and then have the usual array of
18 exclusions.
19 Okay. That's all I have to say. With that,
20 do check out to come back -- come back at 11:00, I
21 think. And remember, we are on a really tight
22 schedule.

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1 DR. FELDMAN: Roy, should I ask, should we
2 do the regular panel at 11:00 or do you just want
3 to start the consensus building? What do you want
4 to do?
5 DR. FREEMAN: I think we should do -- my
6 preference would be to do a brief regular panel
7 just because I think there's some areas to flush
8 out, but maybe let's -- I think that's a great
9 idea.
10 DR. FELDMAN: So maybe 30 minutes of a
11 panel.
12 (Crosstalk.)
13 DR. FREEMAN: Exactly. I think that would
14 be great. Thanks.
15 (Whereupon, at 10:33 a.m., a recess was
16 taken.)
17 Q & A and Panel Discussion
18 DR. FELDMAN: Giuseppe? Let us go ahead and
19 begin without him. I'm going to try to go up some
20 tree branch like Bob did yesterday and actually be
21 fairly definitive, and ask the following question
22 of the panel.

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1 So let's assume, which may or may not
2 happen. But let's assume that a couple of hours
3 from now we've said that possible neuropathy are
4 positive symptoms; probable neuropathy are positive
5 symptoms and positive clinical signs; and
6 clinically definite neuropathy requires a
7 confirmatory test.
8 Among the tests that you have each discussed
9 today, what I'd like to hear from each of you
10 really are the pros and cons for the individual.
11 So yes, why, for example, we should use QST, or no,
12 why it should not be one of the confirmatory tests;
13 and if you believe it should be the only
14 confirmatory tests or if you believe it should come
15 from a menu of confirmatory tests.
16 So it'd be really nice at the end of 30
17 minutes for all of us to have a clear understanding
18 of your opinions. And why don't I start with you,
19 Rayaz?
20 DR. MALIK: So should CCM be used as a
21 confirmatory test, I would say the data, if we
22 compare to the INFD, is sufficient for me to now

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1 say that we should be using it. Now, I'm happy to
2 hear from the audience whether there are
3 deficiencies which need to be addressed, but I
4 think equally they ought to address if the same
5 deficiencies apply to any of the other endpoints
6 and what needs to be addressed for those. But for
7 CCM, I believe that we have enough data now to use
8 it.
9 DR. FELDMAN: So let me throw that piece
10 open to the audience. Any comments? As the
11 moderator, I'm not going to take an opinion, yay or
12 nay, on any of these particular tests. So I'd like
13 to throw it up to the audience.
14 Rob?
15 DR. SINGLETON: So we have been collecting
16 data from very well phenotyped patients with
17 diabetes either with or without neuropathy. And
18 like Dr. Malik's group, ours has been under the
19 auspices of a DP3 three grant through NIH. And our
20 focus has been on looking at the correlation of CCM
21 and other confirmatory measures of neuropathy with
22 clinical features and then progression over time.

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1 And I have to say our data is quite different from
2 the Malik group in that we find in these phenotype
3 patients that other confirmatory measures -- skin
4 biopsy, sural amplitude for instance -- correspond
5 very -- they correlate very well with the severity
6 of neuropathy that patients with diabetes have, but
7 we've not found that same correlation with confocal
8 corneal microscopy, and not with really any of the
9 different types of measures of confocal corneal
10 microscopy, and that's left us unsure about whether
11 this is really a measure that can be used as a
12 confirmatory test.
13 I think that a lot of the data for CCM looks
14 at -- Rayaz, I haven't seen that you've looked at
15 the severity of neuropathy in the patients that
16 you've diagnosed, and I worry that this is not
17 looking at subtle neuropathy, but looking at very
18 severe neuropathy. And I think it would be useful
19 to see from your data if there is more about that
20 severity spectrum about how this works as a
21 diagnostic test.
22 DR. FELDMAN: Rayaz, do you want to comment?

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1 And then we're going to move on to each of the
2 other --
3 DR. MALIK: Sure. I think in the most
4 recent paper where we've looked at the different
5 parameters, in the severe groups, it's very clear
6 that it's very good, but in the less severe groups,
7 the early neuropathy groups, it doesn't perform as
8 well. It still has a reasonable AUC, reasonable
9 sensitivity/specificity, but it's not as well.
10 That I think actually highlights a common
11 problem, whether it's INFD, whether it's QST,
12 whether it's CCM, whether it's any test you want,
13 it's the operative definition that you use to
14 diagnose a condition, which will define, determine,
15 what your sensitivity/specificity is going to be,
16 and that often we forget. If you hear Nurcan's
17 work, you look at that and you think, well,
18 25 percent or 50 percent sensitivity is terrible,
19 but it's what's the operative definition; how
20 stringent you've been to define that condition that
21 will determine.
22 Often as investigators, actually we do play

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1 games, and we move the curve up and down to make it
2 the most optimal sensitivity and specificity. So
3 I'm happy to see your data, but data is data.
4 DR. FELDMAN: Yes?
5 DR. HAROUTOUNIAN: Can I make a brief
6 comment just based on the systematic review? As I
7 showed you yesterday, the data on the CCM, all the
8 studies that we looked at showed CCM actually
9 differentiates well between patients with
10 idiopathic small fiber neuropathy versus controls.
11 But I think one concern, our thought is that there
12 were five CCM studies in the whole cohort compared
13 to, for example, 58 QST studies. So I think
14 although the data, at least just by looking at the
15 literature, looked quite promising in terms of the
16 number of studies published on the area, they are
17 somewhat low compared to the other parameters, for
18 instance.
19 DR. FELDMAN: And maybe last comment on CCM,
20 and then we'll move to the next
21 Yeah, Gordon?
22 DR. SMITH: Yes. I just want to expand a

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1 little bit on our data and then kind of go over and
2 talk a little bit about skin biopsy. The
3 diagnostic performance is actually pretty similar
4 to skin biopsy and the diabetic cohort, but to
5 emphasize Rob's point, there are much more robust
6 correlations between INFD and actually sensory
7 electrophysiology and pain and functional outcomes,
8 so timed up and go and measures of balance.
9 But the areas under the curve are a 0.6, 0.7
10 type level. What really performs well are clinical
11 measures, UENS or NTSS-6. We've actually looked
12 at, not for CCM but for nerve conduction studies
13 and INFD across a very large group, I think
14 probably upwards of 400 patients with diabetes, and
15 looked at diagnostic performance. And it turns
16 out -- and we've modeled this in a Bayesian way; we
17 presented this data a couple of years ago -- that
18 the positive predictive value of both nerve
19 conduction studies and in particular skin biopsy is
20 terrible because of the frequency with which in
21 diabetes, patients have completely asymptomatic
22 reductions. And then when you start to model what

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1 would happen in a higher prevalent condition, the
2 predictable sorts of things happen.
3 So I guess the point is it's really
4 important to consider the populations in which
5 we're examining these tests and really think in
6 terms of predictive values because when you
7 translate it into the positive and negative
8 predictive values, it's not very good at ruling
9 things in. It's actually quite good at ruling
10 neuropathy out.
11 DR. FELDMAN: Well, that's actually helpful.
12 One quick point, and then we're going to
13 turn -- I've got to let Giuseppe know, what we're
14 doing is just talking about each of these
15 individual modalities and asking the opinion of the
16 panel of whether or not they could be used as a
17 confirmatory clinical test.
18 So go ahead, Chris.
19 DR. GIBBONS: So just one quick question.
20 I'm not familiar with the data on this. Is there
21 information on non-length-dependent small fiber
22 neuropathies in CCM?

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

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

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

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

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1 again.

2 DR. LAURIA: This is something that we have

3 thought about also some years ago because of many

4 things. When you refer to a healthy population,

5 like in genetics, you know something, but you can

6 go even deeper. If you change from a monoclonal to

7 a polyclonal, you might have different. So, yes.

8 DR. FELDMAN: So the answer's yes.

9 David, I saw you shaking your head also.

10 DR. HERRMANN: We've got an identical trend

11 that in our lab -- well, I want to just bifurcate

12 this a little bit. I think there are problems with

13 many, many, many false positive skin biopsies. In

14 our laboratory, all the time we have patients who

15 diagnosed based on a skin biopsy with uncertain

16 clinical history. When we repeat it in our lab,

17 it's normal; and it's not just borderline; it's

18 normal.

19 So that's one aspect of the spectrum. And I

20 think what's driving that is as much as we try to

21 standardize the technique and send it to a central

22 lab, I think it can be problems in the harvesting,

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1 in the fixation, in the crowd protection, and in

2 the staining. And sometimes those are obvious by

3 way of seeing obvious crush. There are other times

4 when you look at the biopsy and they may be

5 mischief, but it's not that easy to tell that

6 there's been mischief except for the fact that

7 there's understanding of fibers [indiscernible].

8 So just like we see a lot of absent surals

9 out in the community, you can get a lot of low ENF

10 densities. So that remains a problem, but it can

11 be dealt with if you really standardize

12 interlaboratory quality assurance. But then we've

13 had the flip side of the problem where in our

14 laboratory we're getting fewer and fewer abnormal

15 studies. And I think what it is, is over time

16 we've become more and more fastidious about trying

17 to detect problems, improve quality assurance,

18 changes in antibodies.

19 So I think the normative data that we now

20 use, the work that you and multiple labs did, is

21 probably meaning that many people who fall in the

22 low normal range, if we re-did the normative data

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1 with the new antibodies and sort of rigorous

2 testing, I think we might find that the cutoffs are

3 a bit higher. That's just my experience.

4 DR. FELDMAN: I actually think that's a very

5 important point.

6 Anne Louise? Into the microphone, please.

7 DR. OAKLANDER: [Inaudible - off mic].

8 DR. FELDMAN: And turn it on, please.

9 DR. OAKLANDER: We grew these labs ourselves

10 in different places. Many of us had trained with

11 Jack of course. But I think this has become so

12 much more mature a technique that maybe the time is

13 right in a different setting for some kind of a

14 consensus statement or meeting about the various

15 technical parameters and quality control to

16 improve --

17 DR. LAURIA: Maybe we can re-emphasize this,

18 that this is what we are saying for more than 10

19 years. And listen, we have this experience, which

20 is a daily one because we are working with our

21 Dutch colleagues, with Michael, and we've got other

22 experience with other labs. And listen, there must

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1 be an agreement which you should not consider a

2 priori as fine.

3 DR. FELDMAN: So it's an agreement it sounds

4 like.

5 We're going to move on to the next.

6 DR. LAURIA: It is in place --

7 DR. FELDMAN: -- okay. Two seconds, Chris.

8 DR. GIBBONS: Okay. Just a quick comment.

9 One thing, we looked into why the counts might have

10 been going up.

11 DR. FELDMAN: Can you turn on your

12 microphone?

13 DR. GIBBONS: Sorry. We looked into why

14 counts might also be going up, and we did find

15 there was a change in physician perspective, and

16 the referrals were now coming in to rule out some

17 small fiber neuropathy in nebulous cases, which is

18 probably one of the reasons why we were seeing a

19 higher count, but at least in our own referrals.

20 DR. FELDMAN: So let us move now, just

21 because we want to keep moving forward, to QST.

22 And I'm going to ask Amanda, as the panelist who

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1 did not speak on any of the four, to give her
2 opinion on, if she had to say choose two of the
3 four, which she would choose. But first, let's
4 hear QST, yay or nay.
5 DR. UCEYLER: Well, the QST, I presented the
6 pros and the cons. It is a tool that is used now
7 for such a long time. There's lots of experience
8 with it. We have some items that obviously do
9 reflect small fiber function better than the
10 others. So if I would have to choose, I would say
11 the perception threshold is cold and warm, and
12 pinprick I'd say cold and pain. Heat pain
13 thresholds seem not to be that helpful.
14 It has its problems, no question. If you use
15 it, you should be very careful with the controls
16 that you are comparing with, but if I would have to
17 answer should it be included, yes or no, it would
18 be a yes.
19 DR. FELDMAN: I would ask Amanda to comment
20 now, and then I'm actually -- is James here?
21 DR. RUSSELL: Yes.
22 DR. FELDMAN: I'm going to actually ask

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1 James to comment on QST and the different
2 modalities in QST also because he's done some work
3 on it that I think is very informative and
4 interesting.
5 Amanda?
6 DR. PELTIER: So I guess I would say that
7 there should be first tier and second tier tests,
8 and I'm still divided as to whether QST should be
9 in the first tier simply because it is very
10 subjective, and the problem with it is that if you
11 have somebody who really thinks they have fiber
12 loss, as Roy showed, you can fool the test. So
13 using that as a sole diagnostic criteria would not
14 be ideal, but I think using as a confirmatory test
15 I think would be very reasonable.
16 The same thing I would do with QSART because
17 I think QSART can be very helpful, but I would
18 never rely on QSART as a sole diagnostic tests
19 simply because it's very hard to make sure that
20 everybody's doing it correctly, to make sure
21 they're off all their medications, and to make sure
22 that they're warm, et cetera. So I would say I'd

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1 have kind of a first tier and second tier test.
2 Rayaz, I don't see confocal well enough to
3 know at this point to have an opinion on whether it
4 should be in the first tier or the second tier. So
5 that would be my comment.
6 DR. FELDMAN: James, would you like to
7 just -- couple comments on QST.
8 DR. PELTIER: And I would not include
9 cardiac autonomic testing at all.
10 DR. FELDMAN: Yeah, I'm going to talk about
11 autonomic testing separately I think because I
12 thought Roy made the great point of pure autonomic,
13 pure small fiber, and then mixed.
14 So James.
15 DR. RUSSELL: For QST, the most widely used
16 devices are those devised by Somedic, which dates
17 from about 35 years ago initially and has been
18 developed since that time; the Medoc and the CASE
19 IV. And each of them has potential issues not only
20 with the intrinsic device but also the
21 interpretation. I would say in terms of bulk of
22 data, the bulk of data really is with the Medoc and

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1 the QST.
2 The problem with these devices -- and it's
3 less a problem with the CASE IV than it is with the
4 MEDOC -- is that many of them use methods of
5 limits. And the problems with the methods of
6 limits are that they can be highly inaccurate in
7 determining the actual threshold, the perception
8 threshold at the time the person perceives that
9 stimulus.
10 So I don't want to spend a lot of time going
11 into all the technical details, but I would say
12 that you have to be aware that the person using the
13 device really needs to understand the limitations.
14 Now the CASE IV has been shown to be very
15 reproducible provided that the technicians are
16 highly trained at a central center and follow the
17 instructions exactly. You also do have to warm the
18 limb, so the limb has to be warmed to 31.5 I think
19 were the original instructions or higher. So you
20 have to bear all those things in mind.
21 I would say, bearing in mind that the
22 overwhelming amount of data, whether you're using

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1 the Medoc or the CASE IV or the Somedic, shows
2 relatively low levels of sensitivity and, depending
3 on your normative data and your methodology,
4 somewhat better measures of specificity. I would
5 say overall, this is probably not a very good
6 measure if you want a rigorous definition for small
7 fiber neuropathy.
8 DR. FELDMAN: Roy, did you have a comment?
9 DR. FREEMAN: Yes, just a very quick
10 comment. First of all, I'm not sure if we want to
11 do the positive, possible possible/probable,
12 definite or clinically confirmed, but I want to
13 raise a question about confirmed, and we use these
14 tests not just in small fiber neuropathy, but in a
15 number of other classifications along similar
16 lines.
17 We say that these tests confirm the
18 diagnosis as if they were the objective tests, that
19 the symptoms are subjective, the exam is pretty
20 useless, and then we come in with the heavy guns,
21 the confirmatory tests, the MRI scan.
22 First of all, I want to commend all of the

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1 speakers for a remarkable degree of I think
2 forthrightness and honesty in portraying the
3 strengths and weaknesses of their tests, which most
4 times -- and I sit in a number of these kinds of
5 meetings -- does not often happen.
6 But having said all of that, how do we want
7 to think of this group of tests, the panelists?
8 Are these confirmatory, are these the true
9 objective tests, or are these along the lines of
10 the clinical exam?
11 David?
12 DR. HERRMANN: I was actually thinking
13 something similar. I wouldn't use the word
14 "confirmatory." I would use the word "supportive."
15 DR. FELDMAN: Right. That is actually where
16 the discussion needs to go is, the robustness of
17 these tests. I like clinically supportive, maybe
18 then confirmatory, but what is the robustness of
19 these more objective measures? Not that the
20 clinical exam isn't objective. I think we all
21 agree symptoms aren't not necessarily objective, so
22 what is the robustness?

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1 Anne Louise, and then David, I'd like you to
2 really comment, again, summarize in just a brief
3 minute your thoughts on autonomic function.
4 Yes?
5 DR. OAKLANDER: I think it goes to be what's
6 the word we're confirming. I mean, if the word is
7 small fiber neuropathy, then, yes, a pathology test
8 is indeed confirmatory. If what you're trying to
9 confirm is does the patient have neuropathic pain
10 or are there complaints, objective versus
11 depression, then I don't think it's confirmatory.
12 So what is it we're trying to confirm before
13 we consider whether -- I do think that nerve and
14 skin biopsy are confirmatory for the question of
15 whether there is pathy of the nerves.
16 DR. FELDMAN: I think we're trying to
17 confirm the presence or absence of small fiber
18 neuropathy. That's at least what I'm up here on the
19 stage trying to do.
20 DR. OAKLANDER: And I think it's
21 confirmatory given the limitations of course
22 inherent in anyone test.

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1 DR. FELDMAN: David?
2 DR. HERRMANN: So as I said, autonomic
3 testing is not what I focus on or do specifically,
4 but I would say with regard to QSART, I think it
5 can be one of the options to support that definite
6 diagnosis, as definite as we can make of distal
7 small fiber neuropathy with the following caveats.
8 One, if you're going to use it, and it would
9 have to be detailed, there has to be meticulous
10 attention to the technical details, the training,
11 the warming, and everything that James and Amanda
12 said in order to make it a useful test. Any
13 clinical trial that would use that would have to
14 fulfill those standards and have that quality
15 assurance.
16 Two, in my view, I really do think we have
17 to suggest that its use depends on the cohort
18 that's being enrolled. If you just enrolling
19 patients with symptoms and not requiring signs
20 because of the inherent limitations in these
21 studies, I would like two modalities, so QST and
22 QSART, QST and skin biopsy. If however you're

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1 enrolling people who clinically have a higher
2 likelihood of neuropathy because you're saying in
3 this cohort we're going to have symptoms and signs,
4 then I think to QSART alone done appropriately or
5 skin biopsy alone done appropriately, could be used
6 to get you that extra piece of independent,
7 non-subjective data.
8 So that's the way I would view this.
9 DR. FELDMAN: Are there any concluding
10 comments here before we --
11 DR. SMITH: There's one comment I would
12 really like to make, and this audience really needs
13 to bear this in mind. And that is when you come up
14 with criteria that you've got to have two out of
15 the following three, or two out of the falling
16 four, there's a problem with us because in that
17 list, there may be things that really are not very
18 strong markers of small fiber neuropathy.
19 So if we came up with a list here and said,
20 well, okay, you need to have two out of three, and
21 your three would be the QSART, the thermal
22 perception threshold, and the nerve fiber density,

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1 then someone's got to go along and say, oh, okay,
2 fine. The thermal threshold's is abnormal, the
3 QSART's abnormal, but the skin biopsy is normal,
4 but we're still going to call it small fiber
5 neuropathy. To me, I find that problematic.
6 DR. FELDMAN: So you find skin biopsy the
7 gold standard. I mean, that's the interpretation of
8 what you're saying.
9 DR. SMITH: Than the other two, yes.
10 DR. FREEMAN: Can you clarify, listening to
11 everything that you've heard this morning, why
12 actually you say that?
13 DR. SMITH: Well, because I think, overall,
14 the data, provided it's again done with the proper
15 rigor, shows a high level of sensitivity and a high
16 level of specificity. And that would be the main
17 problem I have. There's also a problem with
18 actually doing these things, so while it is
19 relatively straightforward to obtain a skin biopsy
20 in send it to a central lab to be processed,
21 actually carting a Medicor or CASE IV machine
22 around, or having them at several centers, or

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1 having the QSART and doing them as we've discussed,
2 in other words, having the rigor during
3 performance, is going to be problematic if you're
4 going to do a multicenter trial.
5 DR. FELDMAN: Okay. Chris?
6 DR. GIBBONS: So I like to take the approach
7 sometimes when getting these questions, get them in
8 detail, if I'm seeing the patient in front of me
9 and I have a history that I think is convinced me
10 that they have a small fiber neuropathy --
11 DR. FELDMAN: So you have the symptoms.
12 DR. GIBBONS: -- I have the symptoms, or on
13 my exam is a clear length-dependent pinprick loss,
14 something I'm convinced is real --
15 DR. FELDMAN: So you have the signs.
16 DR. GIBBONS: -- then say I have these
17 different tests, which of these will alter my
18 decision that there's a small fiber neuropathy
19 patient in front of me?
20 If QST is normal or abnormal, would it
21 change my decision? Would sudomotor function
22 change my decision, biopsy, CCM, what have you?

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1 Which of these would be powerful enough to change
2 my decision-making process?
3 DR. FELDMAN: Why don't you answer that
4 then?
5 DR. GIBBONS: And I would say amongst the
6 group -- this is my own bias -- I would say biopsy
7 would be the only thing that might switch my
8 decision. Everything else might be confirmatory,
9 but if I had an abnormal sudomotor function test
10 with a normal exam, I would never be convinced.
11 If there's a normal length-dependent loss,
12 say a proximal biopsy was normal, distal was
13 abnormal, pathologically, I'd be much more
14 convinced by that demonstration than any of the
15 other tests.
16 DR. FELDMAN: Gordon?
17 DR. SMITH: As always, I agree with Chris.
18 (Laughter.)
19 DR. SMITH: And I just want to push back
20 on -- I mean, the positive predictive value can be
21 low, but in this setting, the very high negative
22 predictive value of skin biopsy is really useful.

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1 I guess I disagree that abnormal skin means that
2 there's small fiber neuropathy. But in this
3 setting I would say normal skin basically calls
4 into question in a trial setting whether Chris'
5 judgment is actually sound clinically.
6 DR. FELDMAN: So why don't we on that fine
7 note take a brief adjournment? Am I right, Roy?
8 So everyone should -- so no adjournment, just
9 everyone should get lunch or everyone should just
10 continue? Okay. You're not eating yet. I'm
11 sorry.
12 The panel can leave the stage, and you may
13 have the microphone.
14 Consensus Building
15 DR. FREEMAN: So what I want to do is really
16 begin the consensus a little early because I think
17 it may not be quite as easy as it appears. Let's
18 have some order here.
19 The first thing I want to do is to structure
20 what we're going to be doing, and the way I think
21 of this disorder, this disease, is actually having
22 three possible components: small fiber sensory,

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1 small fiber autonomic, and mixed. And I think for
2 purposes of this discussion -- when I say this,
3 proceeding for the rest of the morning -- I want to
4 focus predominantly on small fiber sensory with
5 some overlap into mixed, and I'm going to leave
6 autonomic for another date, another time just
7 because I think that it has additional aspects to
8 it, and I'm not sure that -- even the fabulous
9 presentation done by David Herrmann was done with
10 the proviso that he is not an autonomic expert, and
11 I was not convinced by that. It was one of my
12 favorite talks.
13 I suggested one possibility, we would do the
14 possible, probable, clinically supported, and I
15 actually like that approach. I want you to think
16 in those terms, but we're not quite there yet. The
17 way I want to approach this now is the gateway.
18 How do patients come in to the clinical trial? And
19 the factors that will bring them in will of course
20 be the history. And the way we think the history
21 is they will have symptoms, and these will either
22 be length dependent or non-dependent, and they will

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1 have to be a duration.
2 Now I'm going to say that we should focus on
3 the length dependent, but I want to try and put the
4 low-hanging fruit away first and let's discuss very
5 briefly one or two comments/questions about how
6 when we are developing this consensus, when we are
7 saying these are the criteria, how do we deal with
8 the ganglionopathy patent, the long non-length
9 dependent patent?
10 Giuseppe, for example, said that was fine.
11 Patients could either have length dependent or
12 non-length dependent. It's a little tricky in a
13 clinical trial for these guys who have 100 sites
14 and it gets a little vague, and you've got
15 fibromyalgia patients coming into it. So my
16 thought was perhaps is to have a little codicil, a
17 proviso that it may be, but to focus on the length
18 dependent, but I want to be sure that we are on the
19 same page with this.
20 DR. FELDMAN: Yeah, I fully agree with you
21 because we really want to do small fiber
22 neuropathy, not necessarily neuronopathy. So I

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1 think for clarity, with a proviso possibly, but for
2 clarity, we really ought to stick to length
3 dependent.
4 DR. FREEMAN: Giuseppe, you're okay with
5 that?
6 DR. LAURIA: Yes, sure.
7 DR. FREEMAN: Good. I like that.
8 So anybody who has a dissenting view? Anne
9 Louise?
10 DR. OAKLANDER: No, I'm not dissenting. I
11 agree completely, but I just want to say there's
12 another group who had length-dependent origin but
13 who it's not so severe that it's over most of their
14 body or over much of their body.
15 DR. FREEMAN: We take that. I think we're
16 all aware that at some point in a peripheral
17 neuropathy, that proximal parts are involved.
18 DR. LEVINE: Roy, one comment. We're
19 actually preparing a paper now. Just to clarify it
20 as we think about it, I don't think there's a great
21 correlation between a patient's pathology and their
22 clinical symptoms. So I think you have to be

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1 careful how you define this. You put it under the
2 history category. I think we define length
3 dependent clinically, but you may have a patient,
4 for example, whose predominant symptoms or in their
5 feet. You do a cath and a thigh biopsy, and very
6 often --
7 DR. FREEMAN: We're all totally aware of
8 that. There's a difference between symptoms,
9 pathology, physiology, structure.
10 So the next point is -- and again, thinking
11 of entry criteria for a clinical trial, your trial,
12 Biogen's trial, Kromasil's [ph] trial, how long?
13 How long do the symptoms need to be present? The
14 standard is six months. Some say three months.
15 The concern of course is you make it too short, the
16 natural history is going to be such that during the
17 clinical trial, they improve, get better, placebo
18 response is as good as the intervention. I would
19 advocate six months.
20 Anybody wanted to dissent on that?
21 DR. SMITH: I agree.
22 (Laughter.)

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1 DR. FREEMAN: Gordon, now that you're chief
2 of neurology, you need to behave, you know?
3 (Laughter.)
4 DR. FELDMAN: Maybe it's not feasible to
5 capture them in a clinical trial, and maybe they're
6 so rare -- there are people who just develop these
7 roaring neuropathies and become very disabled in
8 under six months. Not all of them are these
9 gradually progressive. It takes years to develop.
10 DR. FREEMAN: Steven at the back?
11 DR. SAINATI: The point I wanted to make is
12 I agree with the 6-month minimum duration; I think
13 that's a fairly good to cutoff. But I think we
14 should also have a maximum duration as well to --
15 DR. FREEMAN: Okay, good point.
16 DR. SAINATI: -- to rule out the burned-out,
17 end-stage patients.
18 DR. FREEMAN: Good point. There's always a
19 discussion, and maybe we should have this, as to
20 whether symptoms that have been present for a long
21 period of time, 5 years, 10 years, 20 years, are
22 going to be refractory to the intervention.

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1 Now, I'm not sure that this is part of the
2 inclusion/exclusion criteria and maybe it should be
3 built into the clinical trial, but -- Chris, and
4 then Giuseppe, and then Karin.
5 DR. GIBBONS: I think that's exactly the
6 point, is I think that would be an
7 inclusion/exclusion for a trial, not for definition
8 though, if it's burned out.
9 DR. LAURIA: The other thing is that we just
10 don't know. We don't know what happens.
11 DR. FABER: That's what I wanted to say. We
12 don't know whether patients are refractory to
13 treatment if they had symptoms for over 10 years.
14 DR. LAURIA: And basically a clinical trial
15 is made to figure out whether he can respond to a
16 new drug.
17 DR. FREEMAN: David, last point on this.
18 I'm still considering this low-hanging fruit.
19 DR. HERRMANN: The six-month mark
20 [inaudible - off mic]. [Indiscernible] -- it could
21 be a recommendation rather than prescriptive so it
22 doesn't tie a particular group doing a study into

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1 using six months versus eight months because it may
2 be vagaries of the trial.
3 DR. FREEMAN: Yes, absolutely. Somebody may
4 want to do a Q -- I agree. And when we speak of
5 immunomodulating, I'm fine with that. I think
6 perhaps the duration could have provisos, could
7 have codicils.
8 DR. GEWANDTER: I feel like a couple of
9 people said things and we kind of glossed over
10 them. And as the person who is writing, I'd like a
11 little clarity.
12 DR. FREEMAN: Sorry. Can you speak a little
13 slower?
14 (Laughter.)
15 DR. GEWANDTER: Sorry. When Dr. Louise said
16 how do you define length dependent, you're like,
17 yes, yes, that's very important. So how do we
18 define length dependent? So is it going to be
19 symptoms and signs have to both be length
20 dependent? Is it going to be one or the other?
21 What do you want to say?
22 DR. FREEMAN: Okay.

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

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1 DR. SMITH: We think we know this, but when
2 you talk to people who aren't neurologists,
3 actually, they have a hard time wrapping their mind
4 around this.
5 DR. FREEMAN: Articulate what we mean. Are
6 we talking about -- what do we mean when we say --
7 DR. SMITH: Well, you're the one who
8 recognizes it when you see it.
9 (Laughter.)
10 DR. GEWANDTER: I like below the knee.
11 DR. FREEMAN: No, no, no.
12 DR. GEWANDTER: Oh, see?
13 DR. FREEMAN: I think that exemplifies the
14 problem.
15 DR. SMITH: Maybe distal, distal,
16 predominant, symmetric -- symmetric, distal,
17 predominant or something.
18 DR. LEVINE: And distal onset, too, because
19 I think that's Anne Louise's point.
20 DR. SMITH: Yeah.
21 DR. LEVINE: Sometimes it's the whole body
22 by the time we get to them, but they know it began

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

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

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

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

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

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

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1 patient with specific sensory loss, a patient with
2 a congenital insensitivity to pain, all the fibers
3 done is a patient with a small fiber and
4 non-painful is small fiber neuropathy. In terms of
5 definition of the patients for a clinical trial,
6 considering that we are talking about clinical
7 trials for testing the efficacy of painkillers, I
8 agree with Eva.
9 DR. FREEMAN: Ahmet, Chris, and then we move
10 on.
11 DR. HOKE: I just looked at the PNR data,
12 and about close to 15 percent of our patients that
13 are designated as small fiber that have normal
14 nerve conduction studies but abnormal exam or
15 abnormal skin biopsy have no pain, based on their
16 reports. So it's a small percentage, but it's
17 still a non-significant amount.
18 DR. OAKLANDER: And it chooses the others,
19 small fiber, mediated, no sense of sensation.
20 That's very distressing and disabling. It's a
21 small fiber sensation, NAV 1.7 mediated as much as
22 pain.

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1 We have a very strong dermatology group at
2 MGH. Eva, you don't see those people because people
3 with itch don't think of going to a neurologist
4 right away.
5 DR. FELDMAN: Thank, God.
6 DR. OAKLANDER: I'm just saying, itch is
7 very much --
8 DR. GIBBONS: I just want to echo Giuseppe's
9 point, particularly the hereditary case, which are
10 classic examples and have to be included. So can't
11 this be the migraine with and without aura example;
12 small fiber neuropathy with and without pain?
13 DR. FREEMAN: I was thinking along those
14 lines as well.
15 So let's maybe move on, and I think we need
16 to come up with a constellation of symptoms.
17 There's not a great evidence base of what
18 constitutes the symptoms of neuropathic pain. I
19 and a couple of other people were part of a
20 consensus meeting to define the symptoms of
21 neuropathic pain suitable for genetic studies; why
22 genetic studies, a whole other story. But I think

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1 the consequences of this meeting are worth just
2 showing.
3 What is of interest is on the panel, there
4 were the development of one of the neuropathic pain
5 questionnaires and PSI and DN4, the development of
6 the LANS, another one of the neuropathic pain
7 screening instruments; DD [indiscernible] are both
8 a both a screening and an outcome, and the pain
9 detect another screening, so people who have
10 expertise to form the basis of the way we think of
11 neuropathic pain.
12 Now I'm not going to get into the difference
13 between evidence based and consensus statements,
14 but I think this is a reasonable rate. It was
15 actually a fascinating process. It was a delphi
16 method. I'll take it through the slides quickly,
17 but basically there were 20 participants, all gave
18 features that they thought -- symptoms that they
19 thought were consistent with neuropathic pain.
20 These were the major ones, and I'll take you to the
21 slide, which I hope everybody can see even at the
22 back.

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1 Is it possible or not? Can you see it? Can
2 you read it? Okay. So round two and then round
3 three. So with the delphi procedure, which was
4 rather interesting, we came up and focused on round
5 three over here.
6 Number one, 14 out of 15 felt that hot
7 burning pain was the hallmark of neuropathic pain.
8 Next was pain in a plausible anatomical
9 distribution, which I'm thinking when I look at
10 this and where we are, I think that's kind of taken
11 for granted, and I don't think that need be. If we
12 are using this to be one of a menu, 3 out of 6, 2
13 out of 5, I don't think that that need be, but I'm
14 open to whatever you say.
15 Pain in area of numbness, and that got 10
16 out of 15. Then prickling, tingling, pins and
17 needles, no mention of pain with this, so
18 addressing Ahmet's point, addressing Anne Louise
19 and others' points. Electric shocks and shooting,
20 perhaps somewhat painful, got 8. And we're down to
21 now 1, 2, 3, 4, 5, pain in an area of altered
22 sensation, which I don't think is applicable for

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1 what we're doing specifically if we thinking about
2 length dependent. And then you see a bunch of
3 those, which I will read just in case you can't see
4 them: numbness, non-painful; spontaneous pain;
5 paroxysmal pain; evoked pain; painful, cold;
6 itching. And you see these were really -- the last
7 punch got very few votes. It wasn't termed in this
8 way, but the hallmark of neuropathic pain.
9 So I think for me anyway, this conveys a
10 reasonable constellation of features that we would
11 think are typical of neuropathic pain.
12 Anybody want to add anything and anybody
13 want to move anything up in the hierarchy? Simon?
14 DR. HAROUTOUNIAN: I just want to make a
15 comment about the hot burning pain. Just by
16 reviewing the literature on the typical symptom
17 presentation, the burning pain is by far the most
18 prevalent, the reported type of pain in SFN
19 studies. And roughly it's about 50 percent. We
20 can talk about sensitivity, but it's by far the
21 most prevalent symptom.
22 DR. FREEMAN: Okay. We have one.

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1 Giuseppe, then Ahmet?
2 DR. LAURIA: We don't have any -- check on
3 the quality of the question, whether it's used in
4 those studies. So we don't how many questions have
5 been done. But in general, I will support the idea
6 to include -- I want to define spontaneous and
7 evoked in general because it strictly depends on
8 the number of words or number of possible items you
9 can have.
10 DR. FREEMAN: So just to maybe address that
11 because we have I think one definite. Over here we
12 have a couple of things that cropped up, but pain
13 evoked by light touch, and then there was just
14 evoked pain. So the nonspecific evoked pain didn't
15 get many votes in this, and there's no reason to
16 say that the 15 people were correct, whereas pain
17 evoked by light touch, by contact, by bed sheets,
18 which was regarded as one of the hallmarks, do we
19 want to leave it to specifically pain evoked by
20 light touch or do we want to elaborate, pain evoked
21 by warm water?
22 Any thoughts on this?

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1 DR. FELDMAN: I like pain evoked by light
2 touch. That's what we see.
3 DR. FREEMAN: That's what we see. So
4 consensus.
5 DR. SINGLETON: It has a historical detail.
6 I think the bed sheets question, we think of as
7 prototypic. We're not talking about exam here;
8 we're talking about --
9 DR. FREEMAN: These are symptoms.
10 DR. SINGLETON: -- we're talking about
11 symptoms.
12 DR. FREEMAN: Absolutely. We are in symptom
13 realm. So this is a patient's daily life.
14 Yes?: Anne Louise?
15 DR. OAKLANDER: So we're talking about
16 expert consensus, which is an absolutely valid way
17 to do it, but we also have to look at it from the
18 patient's perspective. So what do they think?
19 DR. FREEMAN: Well, not having patients here
20 at the moment, I think we're stuck with this at the
21 moment, but we do take your point.
22 Karin?

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1 DR. FABER: We did ask the patients this
2 several years ago, and this was an important thing
3 to them. So light touch or the sheet intolerant or
4 whatever you call it, that was an important thing
5 that patients --
6 DR. FREEMAN: Anything else to addresses
7 Anne Louise's point? Anything else that they
8 thought was important?
9 DR. FABER: Hot burning pain and pain during
10 exercise.
11 DR. FREEMAN: And during exercise.
12 DR. FABER: Walking.
13 DR. FREEMAN: Pain during walking. That's
14 not on the list. That's interesting. And that's
15 also one of the things we actually --
16 DR. LAURIA: The feeling of constriction of
17 the legs and feet is very usual.
18 DR. OAKLANDER: Deep pain and aches was
19 slightly more prevalent than tingling or pins and
20 needles; third was skin that has lost sensation;
21 need to move legs. So deep pains and aches in this
22 study of over 100 patients with confirmed was the

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

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

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

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

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1 definitive.
2 DR. SMITH: I would use the NeuPSIG criteria
3 for neuropathic pain and then say, and give
4 examples. So I wouldn't require five or six and we
5 each have our favorite or least favorite, I
6 suppose, domain of neuropathic pain. But we have
7 an operational definition that seems to work well;
8 I would use that. And then we can give examples.
9 You say here are six of the more common descriptors
10 of neuropathic pain in this population.
11 DR. FREEMAN: So you would leave it for a
12 clinical trial at the discretion of the
13 investigator.
14 DR. SMITH: No. What I would say, I would
15 use the operational definition of neuropathic
16 pain --
17 DR. FREEMAN: This is in fact the current
18 operational --
19 DR. SMITH: -- and give examples because --
20 DR. FREEMAN: This is the current
21 operational definition.
22 DR. SMITH: Right. But let's say we use

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

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

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

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1 might want to consider -- it's not really
2 exclusionary types of pain, but things that -- as
3 much as we think things suggest neuropathy, what
4 you're saying is really -- you're saying there are
5 types of pain that don't suggest peripheral
6 neuropathy. And in Gordon's suggestion, we could
7 serve offer those as examples in the same way.
8 So we say if your pain is not in a plausible
9 distribution, if your pain is very focal and
10 related to bone or joint, then those things are
11 less likely to be neuropathic pain. And I think by
12 doing so, you help to guide the investigator, but
13 you still leave open the concept that -- I think it
14 is appropriate to let investigator use some of
15 their judgment in this aspect because I agree that
16 when you get to -- you're going to do -- this is
17 the top of the funnel still, and you're going to
18 get to more specific things as you go forward.
19 DR. FREEMAN: Okay. I think now is about the
20 right time to ask the people from industry what
21 they would think. You guys are doing the clinical
22 trials -- sorry. Nurcan?

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1 DR. UCEYLER: I'm very sorry. Just a short
2 comment on this. I think we cannot simply pick out
3 six items that anybody here thinks might be of
4 interest. My sixth will be other ones, and those
5 of the others. We have to base this on evidence,
6 and there are obviously studies that are looking,
7 and we have data that can tell us which are the top
8 six in literature. If we want to give, really,
9 single items, I think we have to base this on
10 evidence.
11 DR. FREEMAN: So direct us to the evidence
12 because the evidence is not that great.
13 DR. UCEYLER: But the question is -- have we
14 asked this question? So where is the evidence?
15 Maybe we can ask Simon. We can ask Karin, who has
16 performed a study that's --
17 DR. HAROUTOUNIAN: What am I going to
18 suggest is that maybe if we come up with a top
19 six -- and maybe I could look again through those
20 70 -- 123 --
21 (Crosstalk.)
22 DR. FREEMAN: It was not that good.

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1 Let's hold this thought for a sec. I do
2 want to hear from industry as to how they think
3 this would play out in the clinical trial. You've
4 got two choices, which I'm going to put at the
5 extreme spectrum, into the spectrum. The one is
6 patients who have pain, which the investigator
7 thinks is consistent with neuropathic pain, so in
8 the mind of the investigator; and the other, you
9 have pain which fulfills four of the following
10 seven, eight criteria.
11 DR. STEINER: From my standpoint, the more
12 prescriptive that you can be, the better off
13 because I keep talking about having multiple sites.
14 So when you leave things up to the discretion of
15 the investigator, which we do do, then you see a
16 lot of variability. And we all talk about the
17 importance of homogeneity and clinical trials. And
18 if we're starting off with patients and we're
19 targeting painful small fiber neuropathy, we know
20 the patients are going to be coming into some type
21 of pain, and it's working down the list to be sure
22 that we're targeting those patients who have the

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1 pain due to their small fiber neuropathy.
2 So I guess that's why I mentioned either it
3 has to be really prescriptive or you do need to
4 have some type of an independent review by experts
5 so that you say here is the entire case. Here's
6 the history, symptoms, clinical signs, and whatever
7 diagnostic modality is selected, because otherwise,
8 I'm really concerned about the heterogeneous
9 population.
10 DR. FREEMAN: So let me translate this. You
11 would prefer to exclude patients rather than have a
12 broader net that funnels down. Yes. Okay.
13 Steven?
14 DR. SAINATI: Particularly in a phase 2
15 trial where you're trying to get your first
16 evidence of efficacy and you want a very well
17 defined patient population, you want to rule out
18 all these other masquerading disorders like
19 intermittent claudication, plantar fasciitis,
20 metatarsalgia, that's all very important.
21 As you transition into phase 3, you can
22 afford to be maybe a little bit broader. But there

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1 again, if you don't find evidence of efficacy and
2 safety, particularly efficacy, you're not going to
3 get a product label, so then it just goes out the
4 window.
5 DR. FREEMAN: Heikki?
6 DR. MANSIKKA: Just one quick comment. It
7 seems like many of the items that have been brought
8 up here in terms of how to describe the population
9 in terms of the neuropathic pain symptoms, they are
10 already being captured in the available
11 instruments. So like the DN4 pretty much captures
12 all those symptoms that were kind of touched on as
13 a critical symptoms. So maybe there is no need to
14 reinvent the wheel here, extensively.
15 DR. FREEMAN: Yeah. And the inventor of the
16 DN4 was one of the -- unsurprising one of the
17 participants in this consensus. However, I think
18 it's reasonable for us to say use of one of the
19 screening instruments is either recommended or
20 suggested. But I think we do need to come up with
21 our stance on this.
22 Anybody else? Anybody else from industry

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1 that I've left out? Anybody else want to comment?
2 (No response.)
3 DR. FREEMAN: Okay. So I think there is
4 enough for us to work with. I think it's been very
5 clear that industry would prefer to be
6 prescriptive. I think it's very clear that for
7 single-center investigative studies, it's in the
8 hands of the investigator. We will express this.
9 Simon will come up with his literature review. We
10 have this one. Karin will send us the results of
11 her patients.
12 Did it sound to me like Anne Louise had
13 patients or you were quoting --
14 DR. OAKLANDER: No, we did. We have the
15 survey.
16 DR. FREEMAN: You do. So you will send us
17 that. Anne Louise will send us -- Roi will send us
18 whatever they have. We will come up with
19 something. It will be a menu. Let me just say,
20 give me a sense. And this is between you and
21 lunch, so be quick and agree with the person
22 sitting next to you.

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1 If we just say, for argument sake -- we cast
2 the net a little wide and say we have seven
3 symptoms that we suggest helping these guys on the
4 left-hand side of the room, skier's left, want us
5 to be prescriptive, let's say we have seven
6 symptoms. What do you think is reasonable? 2 out
7 of 7; 3 out of 7; 5 out of 7?
8 DR. LEVINE: Roy, you had envisioned this
9 being just yes/no, not a certain scale that they
10 have to meet of each one.
11 DR. FREEMAN: Yes.
12 DR. LEVINE: I think if you do this, it
13 should just be yes/no; otherwise, it gets very
14 complicated.
15 DR. FELDMAN: I think 1 out of 7, because
16 what if you just have hot burning pain?
17 DR. FREEMAN: One out of seven.
18 DR. FELDMAN: Period.
19 DR. FREEMAN: One of the following.
20 DR. FELDMAN: Because that's the most common
21 thing.
22 DR. FREEMAN: One of the following.

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1 DR. GIBBONS: I would just like to say yes,
2 but perhaps that has to fall into the anatomic
3 distribution.
4 DR. FREEMAN: Okay. Nice point. Gordon?
5 DR. SMITH: That was my point, and I'm very
6 ambivalent about counting symptoms for reasons I've
7 already summarized. But I think the distribution
8 is not a symptom; that's a core part of the
9 definition of neuropathic pain. And I think the
10 straw man you set up didn't really capture that.
11 This isn't the investigator just does whatever they
12 think. The other straw man is using the accepted
13 NeuPSIG definition of neuropathic, and then you
14 would have to have something that's said in an
15 anatomic pattern that fits with a polyneuropathy as
16 Giuseppe said.
17 I would agree with Eva. If we're going to
18 do this, I would say one.
19 DR. FREEMAN: Okay. Anybody else want to
20 comment?
21 (No response.)
22 DR. FREEMAN: Okay. So we have one out of

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1 the following --
2 DR. HAROUTOUNIAN: One or more.
3 DR. FREEMAN: Of course.
4 (Laughter.)
5 DR. FREEMAN: Thank you for clarification.
6 I think that -- operationalize, we have
7 that. After lunch, we will deal with autonomic,,
8 which should be a little quicker. It's now 10 past
9 12. Grab your lunch and let's keep going.
10 DR. FELDMAN: So we're bringing our lunch
11 back here.
12 DR. FREEMAN: You bring your lunch here.
13 DR. FELDMAN: Perfect.
14 (Whereupon, at 12:12 p.m., a lunch recess
15 was taken.)
16
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20
21
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1 and with the mixed you can have pain plus
2 autonomic.
3 Now, the pros and cons of both. So let's
4 kind of get a sense of what people think just to
5 let this flow a little bit, mixed versus -- what
6 does mixed mean and could you enter the pure
7 sensory with an autonomic symptom? Giuseppe?
8 DR. LAURIA: My suggestion is predominantly
9 somatic or predominant autonomic because you can
10 have pure autonomic neuropathy with evidence of
11 somatic -- damage of somatic nerves, which can
12 be --
13 DR. FREEMAN: So Giuseppe is saying we have
14 the pure, painful -- let's just call it sensory,
15 and then there is a mixed., and we can have
16 autonomic in that. I'm assuming the mix will be
17 what we define sensory as plus one of the
18 following, two of the following, three of the
19 following, and we can discuss how these questions
20 need to be asked because if you think sensory
21 symptoms are vague, you have not heard anything yet
22 because most of you sitting in the audience have a

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1 AFTERNOON SESSION
2 (12:27 p.m.)
3 DR. FREEMAN: I think our rapporteur has
4 enough for the sensory. Let's move on to the
5 autonomic. I'm going to propose that we structure
6 this. As I said, we have sensory, which I think
7 we've covered adequately in terms of the symptoms.
8 And then we mixed. We're not going to go into the
9 autonomic, but the question with respect to mixed
10 is the following. There are two possibilities.
11 The one is we can say we have one set of
12 criteria for company, the investigator, who is
13 interested in painful small fiber neuropathy, and
14 that is the pure sensory. And then we will have
15 another set of criteria which we can. As Karin
16 current has done in her criteria, you can have not
17 only symptoms of pain but also one of the following
18 autonomic symptoms. So we can either say that this
19 is so tightly integrated with the painful that it
20 is acceptable to actually get into the clinical
21 trial if you have no painful sensory symptoms, but
22 autonomic, or we can say, okay, we have the mixed,

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

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1 would have the pure sensory, and then we would have
2 a mixed, and the mixed would have whatever we
3 decide with pure sensory, one of the following
4 symptoms as we decided, and we now have to decide X
5 of Y autonomic symptoms; one, how many; and two,
6 how we will ask for the symptoms so as to be
7 relatively specific, which is always a challenge
8 with autonomic symptoms.
9 So Chris was going to weigh in.
10 DR. GIBBONS: Having gone through some of
11 the questionnaire data, I think that's probably a
12 more appropriate approach rather than asking a few
13 specific questions. I think for the pain, we could
14 have gotten away with maybe six or seven of our
15 top. Here I just don't think we can. I think we
16 will have to be broader and use a questionnaire
17 inclusion, whether it's a symptom of autonomic
18 survey COMPASS, the Boston autonomic questionnaire,
19 but a questionnaire. And probably I think we would
20 require a minimum of two domains, if not three,
21 within this list.
22 DR. FREEMAN: Just to counter what Chris is

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1 saying -- and I agree in broad general principles,
2 but we certainly see patients who we all convinced
3 have autonomic failure, who may just have
4 orthostatic intolerance without anything else. And
5 this is the inherent challenge, and maybe we want
6 to be specific and maybe have two, or maybe we need
7 to grade and say we give orthostatic intolerance 2
8 points and a score of 1 is insufficient, but
9 somebody who has the full-fledge syndrome --
10 DR. GIBBONS: I think the counterpoint to
11 that is are they complaining of symptoms or do they
12 have --
13 DR. FREEMAN: We're still in the symptom
14 realm.
15 DR. GIBBONS: On the questionnaire,
16 frequency of bowel movements or what qualifies as
17 constipation, maybe they don't complain of it, but
18 they have constipation. That could be sufficient
19 to be one of the domains like the pure autonomic
20 failure group. There may be ways to get at that I
21 think more clearly.
22 DR. FREEMAN: Chris says more than one

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1 domain in the autonomic realm involved, and Chris
2 saying use one of the established questionnaires of
3 which there are a couple.
4 James? I just want to make one point.
5 Michael came up to me during lunch and he
6 emphasized with a sensory that we should draw on
7 what exists, pain detect LANS and DN4. And Chris
8 is in some way echoing that.
9 James?
10 DR. RUSSELL: I would agree with that. But
11 I think that one of the problems that we've come
12 across is that you really have to make sure that
13 the symptomatology is due to a likely autonomic
14 disorder and not due to some other factor. And I'm
15 particularly saying about the urinary problems
16 because the trouble is that women who have had
17 multiple children or men who may have prostate
18 problems or whatever, clearly are going to report
19 that as being positive, but you have to exclude
20 those other factors. GI, there may be another
21 factor accounting for that other than an
22 abnormality of the autonomic nervous system.

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1 DR. FREEMAN: Absolutely. Men have prostate
2 disease. Every American has reflux.
3 Simon?
4 DR. HAROUTOUNIAN: Just to clarify, are you
5 discussing those as inclusion criteria for a study,
6 or we're thinking about characterizing patients by
7 their autonomic profile?
8 DR. FREEMAN: We are not characterizing. We
9 not looking at phenotype. These are all inclusion
10 criteria. This is the case definition, what
11 constitutes an inclusion criteria or an exclusion
12 criteria for a clinical a trials. Phenotyping is a
13 whole other meeting.
14 Roi?
15 DR. TREISTER: We validated the COMPASS
16 question in this population, and I don't remember
17 all the items. There is a list of about 20 items.
18 I would guess if we would like to be inclusive, at
19 least one symptom of those would suggest it.
20 DR. FREEMAN: So we have one; Chris says two
21 Jen, you've got enough to work on over here?
22 DR. GEWANDTER: Yes.

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1 DR. FREEMAN: Anybody else want to comment?
2 So the suggestion is use one of the established
3 questionnaires. There are a couple of them. I
4 think Chris is leaning towards --
5 DR. GIBBONS: Just to clarify, I think
6 important for a writing perspective, when we say
7 inclusionary, are we defining this as this now
8 includes them into the mixed category from the pure
9 sensory? They've already hit those criteria?
10 DR. FREEMAN: In order to be mixed, you need
11 to --
12 DR. GIBBONS: You meet the first.
13 DR. FREEMAN: -- exactly. Maybe this is
14 low-hanging fruit for the autonomic. Do we want to
15 comment on what constitutes a pure autonomic small
16 fiber neuropathy or should we leave that for
17 another meeting?
18 DR. FELDMAN: I would leave that.
19 DR. FREEMAN: Okay. Eva is the timekeeper.
20 I like that role. Everybody agree with Eva?
21 Everybody always agrees with Eva. So we are
22 operationalizing it. We've operationalized.

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1 So we now are on the examination, signs
2 essentially. This is part of that consensus
3 meeting. It's an interesting story, another day,
4 another time. One of the important point is -- and
5 I'm addressing something that was raised by Deb
6 yesterday. What do the experts think with respect
7 to it is feasible for the non-expert --
8 DR. FELDMAN: Talk into the mic, Roy.
9 DR. FREEMAN: It's hard to look at the
10 slides and talk into the mic. What do experts
11 think is feasible for the non-specialist to assess?
12 This is the group that you saw, Didier [ph], and
13 the LANS guys, and the German guys. What do they
14 think? So they thought experts could easily assess
15 symptoms. We decided that consensus was greater
16 than 70 percent. They did not think that the
17 experts were capable -- and think clinical trials
18 over here -- of assessing signs.
19 DR. HAROUTOUNIAN: Non-experts, right?
20 DR. FREEMAN: Non-experts, non-specialists
21 were capable. Sorry. Did I misspeak? So just
22 give that some perspective.

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1 This was to me one of the more fascinating
2 two-day meetings that I participated in. But with
3 that perspective, I want to introduce the possible
4 signs. What I want to have as part of the
5 discussion is how specific do we need to be with
6 the elicitation of these signs? And Jen and Chris
7 are putting a lot of thought into what exists out
8 there, but I will just touch on this.
9 Do you want to insist that they use the
10 Neurotip; insist that they use a safety pin; insist
11 that they use that \$2,000 instrument that the DNS
12 use? What about tuning forks? We all have a
13 number of different tuning forks that we use. And
14 then how structured is the assessment of all of
15 these things?
16 Gordon structures the sensory exam very
17 nicely. Some people use the tuning fork. I
18 actually have gone around the room with a group of
19 our residents and ask them how they do the sensory
20 exam, one by one by one, and it is fascinating.
21 Nobody does it the same way, absolutely nobody.
22 And obviously, you are not going to get the same

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1 results.
2 So I want to -- again, just to editorialize
3 just a little because this is going to crop up, and
4 it's part of the same conversation, one of the
5 strengths of QST -- and we know it's a
6 psychophysical test, and we know it is subjectivity
7 attached to a computer, but stimulus delivery, the
8 algorithm for the response is in every way rigidly
9 documented. Even taking James's point about it
10 being time reaction time dependent, that's the
11 strength of QST, I believe, is that everything is
12 rigidly algorithmic.
13 Having put that aside, these are the
14 possibilities, and the first question is how
15 structured do we want to be with the way we
16 describe these signs?
17 DR. FELDMAN: Can I ask a question? And
18 that is you only have small fiber signs. In this
19 structured exercise that we're doing, are we not
20 going to list large fiber signs? Do we not need to
21 examine the patient for large fiber and exclude
22 large fiber as part of this or are we just going to

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

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

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

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

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1 actually has been prescriptive, and it is
2 remarkably infrequently.
3 So I think we have two options. It seems to
4 me that -- I don't know. This is maybe apple pie.
5 Of course we need to be prescriptive about this.
6 We need to define how to do it. We need to define
7 where to do it. We need to define what instrument.
8 And we need to define what is abnormal because this
9 is one of the critical pieces. And I want all the
10 neurologists, next time you're in front of your
11 residents, ask them how they do the sensory exam.
12 It is eye opening.
13 So I think we've got to get beyond that. So
14 the question is -- and here's the question
15 following that preamble. Do we, as Todd suggests,
16 say this is how it's done? Do we refer to the
17 paper that will then have been published by Jen and
18 Chris, hopefully, saying that this is how some have
19 done it, and we suggest that you use these measures
20 that exist in the in the literature? And these are
21 the two possibilities.
22 So I think we can on the one hand say we

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1 recommend that the instrument that the site and
2 what is abnormal be prespecified and that
3 investigators be trained in this method. And as I
4 often say when I talk about this, there are many
5 right ways for doing this, but for the purposes of
6 this study, there is only one right way of doing
7 it. So that is an approach that we can use.
8 Variations on that theme say a lot more
9 diplomatically than I have said it versus Todd
10 saying that we recommend that you do it this way.
11 So go, Simon, and I'm going to --
12 DR. HAROUTOUNIAN: I just wanted to
13 completely agree with you in terms of being
14 prescriptive, that each study prespecifies what
15 they test. I think in terms of what we
16 can -- whether we should recommend specific tools
17 and specific ways to measure, giving the data on
18 really lack of agreement of specific changes, I
19 wouldn't do that.
20 Maybe we should go with new recommendations.
21 If you look at the 2016 paper, the science says say
22 negative or positive neurological science upon

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1 sensory examination. We could go with something
2 like that, but prescribing that in each study, the
3 investigators will determine how they do this
4 examination and by which tools.
5 DR. FREEMAN: Karin, you've got some points
6 back there?
7 DR. FABER: Well, what I'm wondering is why
8 don't we use the data that we already have. So we
9 know for the Rydel-Seiffer tuning fork, for
10 example, that there are perfectly normative values,
11 and that's very easy to use bedside. And I'm quite
12 sure that every neurologist can use that. And our
13 residents all use that, so no differences in tuning
14 forks because they know I will kill them.
15 (Laughter.)
16 DR. FREEMAN: Eva?
17 DR. FELDMAN: I'm not advocating for the
18 scale we developed because it's inappropriate, but
19 I do know that if you use -- we did a lot of
20 pretesting of the MNSI, and I think if we're going
21 to actually do this and have it be helpful, you
22 should pick a scale that's simple to do. You can

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1 train other individuals, even non-physicians to do
2 it. And it's been shown to be reproducible,
3 reliable, and correlate highly with the disorder.
4 So I would actually advocate for the Utah
5 scale and to be prescriptive. And if we want to
6 give a scale, that seems to be the scale that's
7 most appropriate for small fiber neuropathy.
8 DR. FREEMAN: I think the reviewers would
9 tend to agree with that, wouldn't you, Chris and
10 Jen?
11 DR. GEWANDTER: Me?
12 DR. FREEMAN: Yeah.
13 DR. GEWANDTER: Yeah. As far as the domains
14 that were covered and had the most weight --
15 DR. FREEMAN: That certainly covers it best.
16 DR. GEWANDTER: -- I would say --
17 (Crosstalk.)
18 DR. FREEMAN: Chris showed 60 percent
19 compared to everything else. How prescriptive is
20 that scale with respect to the assessment of
21 hyperalgesia and allodynia?
22 DR. GEWANDTER: Good. Well, allodynia is

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1 not --
2 DR. FREEMAN: I don't think it was that
3 good.
4 DR. GEWANDTER: The pinprick is good.
5 DR. FREEMAN: Pinprick is good. Pinprick is
6 very good.
7 Temperature?
8 DR. SINGLETON: Temperature is not included.
9 DR. FREEMAN: Not included.
10 DR. SINGLETON: And I think that's by design
11 because I feel temperature is a far inferior
12 measure to pin in terms of its reproducibility.
13 DR. FREEMAN: This is getting granular, and
14 I think that's fine.
15 Giuseppe, do you include temperature? I
16 know you're looking at email over there, which you
17 should not be doing during this critical period.
18 (Laughter.)
19 DR. LAURIA: From a clinical --
20 DR. FREEMAN: So the question was, Rob said
21 temperature is irreproducible.
22 DR. LAURIA: In a clinical setting.

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

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

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

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

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

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

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

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1 How would we do with that? It's a little
2 vague, but it's better than what exists in the Utah
3 at the time.
4 DR. FELDMAN: Well, the Utah is actually
5 more prescriptive than Rob was recalling, because I
6 just went and taught the Utah to a group of
7 physicians in another country, and they do say to
8 take a cotton swab, for what it's worth, in their
9 in their instructions for allodynia.
10 DR. FREEMAN: I think we can come up with
11 something. I think there's enough to work up with,
12 between the Utah, between what we do, which is in
13 the process of being validated. So I think we can
14 come up with some instructions with provisos, and I
15 want to say that ours is not -- we don't promote
16 this as an entrance criteria for a clinical trial.
17 We do promote it as an approach to phenotyping
18 neuropathic pain. So we can come up with something
19 that we will circulate, and I think flesh it out.
20 I suppose how specific, how structured we've
21 agreed on. Where are we at this point? One of 3
22 three. We could group hyperalgesia and allodynia

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1 together and say 1 of 2, or 2 o 2, 2 of two teams,
2 too stringent.
3 DR. LEVINE: I think you keep them separate
4 and do 1 of 3. That's my vote.
5 DR. FREEMAN: You would keep allodynia and
6 hyperalgesia. So you would say pin feels even more
7 painful; brush fields painful, 1 of 3?
8 (Affirmative nods.)
9 DR. SINGLETON: If we're talking about the
10 Utah as our kind of Schema for inclusion, I would
11 recommend we actually follow the numerical entry.
12 DR. FELDMAN: Yean, me, too.
13 DR. SINGLETON: We have a qualifying score
14 that we validated as consistent with diagnostic
15 finds the greatest area under the curve
16 diagnostically for the Utah Early Neuropathy Scale.
17 One thing I would say about it is -- and I hope
18 this is going to -- so one thing I would say about
19 it is that it's possible to get to that score with
20 only large fiber features.
21 DR. FREEMAN: That is my --
22 DR. SINGLETON: So I assume that your next

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1 slide is going to be about the inclusion of large
2 fiber features in neuropathy on exam.
3 DR. FREEMAN: Well, I'm going to be
4 talking -- at some point, and I don't know where
5 that lies -- about the exclusions. And that's my
6 concern about using the Utah, is that it is
7 60 percent but there's a 40 percent. So I'm
8 advocating something along these lines, but with,
9 again, lots of codicils, lots of provisos.
10 Chris?
11 DR. GIBBONS: Well, I think the exam
12 includes what you're looking to exclude. So as a
13 consequence, you could simply revise the output
14 from the Utah into your separated and inclusion.
15 So if you have absent reflexes, you're excluded.
16 If you have weakness of the EHL, you're excluded.
17 But that's in the exam --
18 DR. FREEMAN: So that's why I don't think
19 it's a good idea to use the Utah as an entry score.
20 I'm very happy with the Utah as far as the approach
21 to assessing pinprick, although we can argue about
22 what the cutoff should be in terms of distal to

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1 proximal. I am not -- and again, I've not looked
2 intensely at it, but I'm not happy about its
3 assessment of hyperalgesia and allodynia.
4 I think there's enough to work with, but I
5 would like you to talk to me about the Utah, guys,
6 to talk to me about what you think a cutoff for
7 pinpricks should be, what's abnormal. So we define
8 how pinprick is tested. We define where it's
9 tested. We even define the instrument. What's
10 normal? What's abnormal?
11 DR. SINGLETON: It's obviously -- it's age
12 dependent, but I think in patients less than 60
13 years old, that reduced pin sensation that affects
14 the toes and the distal dorsum of the foot is a
15 abnormal.
16 DR. FREEMAN: Okay, and reduced -- again, I
17 just want to -- and I don't mean to put you on the
18 spot.
19 What's reduced?
20 DR. SINGLETON: Reduced is -- so you give
21 them a normal stimulus. I usually choose the upper
22 part of the back of the leg as my spot unless they

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1 tell me they have no sensation at that level. And
2 I say this is what normal feels like, and then I go
3 to their toe and I say, "Is it as sharp here as it
4 is on your leg?" And if they say yes, then we're
5 done with the pin assessment. If they say no, then
6 we decide how much less. But I want to see that
7 they agree that that pin sensation is less than
8 they expect on their leg, and then I'll work up
9 their foot, from their toe towards the dorsum of
10 their foot to see where they find normal sensation.
11 So if there is decreased sensation at their
12 toe, I want to see that by the time they
13 get -- someplace up there leg, it becomes normal.
14 So that confirms this idea that there's a
15 length-dependent quality to their pain sensory
16 loss.
17 DR. FREEMAN: So Todd, you've looked at the
18 MS literature I think more so than anybody. Do
19 they look at pinprick?
20 DR. LEVINE: They do. Let me think about
21 it. I have to remember.
22 DR. FREEMAN: While you're thinking, Anne

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1 Louise? Anne Louise, you were going to say
2 something?
3 DR. OAKLANDER: I was just saying I do the
4 same as them, essentially, but I work down. I'm
5 not saying that's better. I'm just making the
6 comment that the devil is in the details.
7 DR. FREEMAN: Okay. This is --
8 DR. FELDMAN: Roy, can I make one comment?
9 If we go with your idea, which I'm not saying is
10 neither good nor bad -- of just using brush, et
11 cetera, we just have to not have lots of
12 gradations. It either has to be yes or no, right?
13 Because this isn't a validated scale. So if you're
14 going to go with a non-validated scale, you have to
15 I think be very black and white.
16 DR. FREEMAN: Sorry. Which is the
17 non-validated?
18 DR. FELDMAN: Well, I don't know. You're
19 saying that maybe for hyperalgesia, we use a brush
20 on the toe, and it's either got to be yes or no.
21 It can't be a little bit.
22 DR. FREEMAN: Absolutely.

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1 DR. FELDMAN: So if we're going to do that,
2 we just have to be very --
3 DR. FREEMAN: That's painful --
4 DR. FELDMAN: -- very yes or no.
5 DR. FREEMAN: A brush should not be painful.
6 DR. LEVINE: It came back to me. It took me
7 a second. So odd sensations, paresthesias,
8 dysesthesia, in the EDSS, it's all yes or no.
9 Tuning fork is by seconds.
10 DR. FREEMAN: Let's just do pin because
11 that's all we're using
12 DR. LEVINE: Pin is going to be tough for us
13 because the first cutoff is loss of discrimination
14 between sharp and dull. So that's the first
15 gradation point. So it is kind of a yes or no
16 question.
17 DR. FELDMAN: It just needs to be yes or no,
18 and then that would be very appropriate.
19 DR. FREEMAN: How does that sound to you
20 guys? Do you feel this is sharp as a pin or not?
21 You don't do that, do you?
22 DR. SINGLETON: I think it's very reasonable

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1 to get a valid result when you ask people whether
2 they have reduced pin sensation, not just absent
3 pin sensation. I think that you lose
4 discriminating value when you all you're trying to
5 do is see whether they have pin sensation or not.
6 DR. FREEMAN: Yeah. Okay.
7 DR. SINGLETON: So I would argue for the
8 idea that it's possible to say they have decreased
9 pin sensation and still get a valid result.
10 DR. FREEMAN: Yeah. And I agree that
11 hyperalgesia and allodynia are all or none.
12 Allodynia certainly is all or none. Hyperalgesia
13 is a little trickier, and we do have data on this.
14 Gordon?
15 DR. SMITH: I'll be uncharacteristically
16 definitive. I think in regards to pin sensation,
17 the way the UENS is scored, if one were to create a
18 threshold, I would keep the threshold the same as
19 the scale performs as a 4. And I think that also
20 conforms to -- I've done a million UENS'S by now,
21 and there are a fair number of people who have no
22 other evidence of neuropathy who have a mildly

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1 subjectively reduced sensation to pin in their
2 toes. It's somewhat less common to see that in
3 both feet, so I would say a 4.
4 The other point to Eva is the UENS
5 instructions actually are not prescriptive in how
6 allodynia is assessed. I just went through the
7 paper. It says that it's done as per a typical
8 neurologic examination.
9 DR. FREEMAN: So we can be a little more
10 prescriptive. As I say, validation presented at
11 the APS a month or two ago.
12 DR. HERRMANN: One question I had, obviously
13 if you're going to you a standardized scale
14 [inaudible - off mic] -- you don't want to deviate
15 from what's been validated in it. But if you are
16 going to deviate, why not standardize the -- I mean
17 obviously do the same approach instructions for
18 testing on pinprick, gradations, and so forth in
19 scoring, but why not use a more standardized
20 instrument such as Neurotip or the Neuropin?
21 We use it in the CMT world, and I think it
22 just gives you -- some parts of the world don't

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1 like to use a safety pin just from a hygiene
2 standpoint. And I think it's inexpensive, it's
3 easy, and it just gives you a little bit extra
4 standardization. [Inaudible - off mic].
5 DR. FREEMAN: Neurotip is fine. Do you guys
6 recommend Neurotip or are you specific?
7 DR. SINGLETON: This is real interesting
8 because when we first validated this, we had
9 questions about the exact size, which size of
10 safety pin. This was something that held up
11 provocation of our -- I think it was which size of
12 safety pin were we talking about. Was it going to
13 small, or large, or in the middle? And we ended up
14 saying a size 12 safety pin because we had to do
15 something to satisfy the reviewers.
16 DR. SMITH: We ordered those, too. We've
17 stuck to that.
18 DR. SINGLETON: Yes, we have.
19 DR. SMITH: It's Office Depot.
20 DR. SINGLETON: They're pretty consistent.
21 As far as we know, they are sterile.
22 (Laughter.)

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1 DR. SINGLETON: Not disease --
2 DR. FREEMAN: David makes a very reasonable
3 point. In Europe, I think the UK are not happy
4 about using safety pins in the clinical exam.
5 DR. SINGLETON: Not okay with it because
6 why?
7 DR. FREEMAN: I'm not entirely sure.
8 DR. SINGLETON: A cultural difference.
9 Safety pins have some sort of negative connotation
10 in Europe?
11 DR. SMITH: They're ironically unstable
12 [inaudible - off mic].
13 (Laughter.)
14 DR. LAURIA: [Inaudible - off mic].
15 (Crosstalk.)
16 DR. SINGLETON: That's a bizarre idea.
17 DR. TREISTER: I think the pins are more
18 shaper than here. You can find here dull pins.
19 DR. FREEMAN: This is fascinating.
20 DR. LEVINE: I like the standard tool,
21 though. I think that's a good idea.
22 DR. FREEMAN: What was the question? What

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1 was that, Todd?
2 DR. LEVINE: I said I think the idea of
3 standardizing a tool is a good idea because there
4 is variability.
5 DR. FREEMAN: Neurotips -- just to I think
6 the last comment on this, do people know the
7 sharpness of Neurotips? Is that batch to batch
8 consistent?
9 DR. GIBBONS: They're not particularly
10 expensive. I frankly hate them, but I use them.
11 But the thing I find is that in fact they often
12 don't work. You take the tips off and the other
13 end comes. It just falls apart, and I don't like
14 them.
15 DR. FREEMAN: All right. So let's move on.
16 We really are moving along rather nicely.
17 DR. GEWANDTER: Can I ask a question, a
18 clarifying question?
19 DR. FREEMAN: Do you have enough, Jen, to
20 conclude?
21 DR. GEWANDTER: I have a question. We said
22 before that it has to be distal, at least the

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1 history for the symptoms. Then I just heard
2 someone say the exam should distal, but that could
3 be someone had a distal history but not anymore.
4 So what do we want to do about that?
5 MALE VOICE: Distal.
6 DR. FREEMAN: Distal.
7 DR. GEWANDTER: For the exam. So it has to
8 be --
9 MALE VOICE: UENS is a distal exam.
10 DR. FREEMAN: It's all distal. Even if it
11 spreads proximally, we're still interested in
12 distal.
13 Anything else? Are you okay with the
14 examination? I think there's enough to work --
15 DR. FELDMAN: So what did we decide,
16 actually? I'm a little confused.
17 DR. FREEMAN: No, that's a very good
18 question, what did we decide.
19 (Laughter.)
20 DR. FELDMAN: Did we decide to decide later
21 among our choices?
22 DR. FREEMAN: No, no, no. We decided that

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1 we would use allodynia, hyperalgesia, and pinprick,
2 and that one of those three was sufficient, and we
3 would standardize as much as we possibly could with
4 respect to all of those.
5 DR. FELDMAN: And for the pinprick, did we
6 decide to use the UENS?
7 DR. FREEMAN: We decided that we would use
8 the UENS and that we would have Gordon and Rob
9 define exactly how we would do that, and that we
10 would not be looking at the distribution, but we
11 would have a dichotomous result, either positive or
12 negative, normal or abnormal.
13 Is that okay?
14 DR. SINGLETON: Are we going to talk about
15 large fiber exam features here or are we going to
16 just like ignore that question?
17 DR. FELDMAN: And that was a question I
18 asked earlier, too.
19 DR. FREEMAN: That's a question, so I guess
20 now that two -- I obviously did not answer Eva well
21 enough; I thought I did. So I think for the
22 inclusion, this is my take on this, and let's float

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1 balloon up and see where this goes.
2 For the inclusion criteria for a clinical
3 trial, I thought that we should be focusing on
4 small fiber sensory symptoms and small fiber
5 sensory signs and small fiber sensory
6 investigations.
7 DR. SINGLETON: So are you advocating for a
8 pure definition of small fiber neuropathy?
9 DR. FREEMAN: What we are going to do
10 afterwards is -- and we do have time is to discuss
11 whether we are getting to take the hard-nosed
12 Italian approach, which is no large fiber aspects
13 at all or whether we are going to take the David
14 Herrmann permissive approach where we are going to
15 let some patients with a little bit of large fiber
16 stuff in.
17 DR. SINGLETON: I think we should talk about
18 that now. This is where the rubber hits the road.
19 DR. FELDMAN: I do, too.
20 DR. RUSSELL: Roy, another thing that needs
21 to be addressed in signs is when you test pinprick,
22 are you going to test it simply on a great toe and

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1 determine is it painful or not painful, or are you
2 going to do a proximal distal comparison? And the
3 reason why I bring this up is because if you look
4 at the MDNS, it actually asks is this painful? And
5 whether it's because some people don't like to
6 complain about pain or because of the different
7 pins, people will sometimes say, normal people,
8 that they don't feel it as painful when you touch
9 the great toe. They are normal, so you've got to
10 be very careful about how you define that.
11 DR. FREEMAN: Do you want to maybe say how
12 should be done?
13 DR. SINGLETON: Well, I think I already did,
14 how the UENS UFC is done. Whether that's how it
15 should be done, I don't know.
16 (Crosstalk.)
17 DR. SINGLETON: But it seems like there's
18 consensus that that concept that we're going to do
19 something that figures out if this has a distal
20 predominance and find it's proximal extent, that's
21 what we're talking about, and the MDNS does not
22 actually do that.

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

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

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

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

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1 So I don't even know if we want to go talk about
2 nerve conduction studies here as an exclusion. I
3 mean, maybe we don't even want to talk about
4 electrophysiology, and just keep it to a clinical
5 exam, and just then decide about what degree of
6 large sensory fiber impairment we could have to be
7 small fiber predominant. But keep those three.
8 DR. FREEMAN: This approach.
9 DR. FELDMAN: Right. Keep that approach.
10 And you've defined pure SFN.
11 DR. FREEMAN: Pure is easy.
12 DR. FELDMAN: Right.
13 DR. FREEMAN: I think the decision that we
14 have to come to is the difference between small
15 fiber predominance and mixed, and one of the points
16 is no motor fiber impairment at all. And I think
17 just to make the point, and maybe it's worth
18 discussing very briefly, somebody's talk said that
19 they thought that the pure was 5 percent of the
20 small fiber population. Giuseppe would say
21 probably more. Karin would say probably more. And
22 I think this emphasizes perhaps national

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1 differences, but I think it's important to bear
2 this in mind.
3 So I think I'd like to focus the discussion
4 on how do we definitely -- we have one point and I
5 think universally agreed you cannot have any motor
6 fiber involvement.
7 Anne Louise?
8 DR. FELDMAN: And I also don't think you
9 should have any absent tendon reflexes. So if your
10 ankle reflexes are gone and you have motor fiber
11 impairment, you need to go into the mix axonal
12 neuropathy.
13 DR. FREEMAN: Is everybody in agreement with
14 the tendon reflexes?
15 DR. SINGLETON: Eva, if you're 70? How
16 about that? If you're 70 years old and your
17 reflexes are absent?
18 DR. LAURIA: I agree with Eva.
19 (Crosstalk.)
20 DR. FREEMAN: Eva, Rob says what about age?
21 DR. RUSSELL: Well, the other thing is what
22 if you've got an L5/S1 radiculopathy? So maybe

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1 absent tendon reflexes --
2 (Crosstalk.)
3 DR. OAKLANDER: Let's look at the easier one
4 first, which is weakness.
5 DR. FREEMAN: We've decided motor is out.
6 That's gone. You cannot have that.
7 DR. OAKLANDER: What if the patient has no
8 motor complaints and they're not weak, but when you
9 test them, you find --
10 DR. FREEMAN: We're out.
11 DR. FELDMAN: Well, then it's not pure small
12 fiber.
13 DR. FREEMAN: Karin?
14 DR. FABER: Well, I completely agree with
15 Eva, I think, to have these three components, and
16 the muscle weakness indeed is quite easy. I do
17 agree that you should have retained reflexes
18 because otherwise it's large fiber neuropathy. And
19 of course we can all think of a lot of exceptions,
20 but I think this is the general rule. I would very
21 much like to stick to that.
22 Indeed, if you ask us, we say that the pure

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1 small fiber neuropathy is the majority, but of
2 course it has to do with the fact that we are a
3 tertiary referral center, so there may be bias in
4 that.
5 DR. FREEMAN: Just to give Rob's
6 counter-argument, and I don't know what the cutoffs
7 are for the Kromasil study, for the Aptinex study,
8 and for the Biogen study, but Rob makes the point
9 that most -- and here we get into the discussion
10 that Gordon raised, what is normal elderly. But
11 many who we think of as being normal elderly may
12 have lost ankle reflexes.
13 Eva?
14 DR. FELDMAN: So that's because they have a
15 mixed axonal neuropathy of aging. The
16 Scandinavians did those beautiful studies early on
17 in the late '60's early '70's where they biopsied
18 the elderly, the impaired nerve conduction studies,
19 demyelinated fiber densities, and biopsied them
20 with ankle reflexes, et cetera.
21 So what you see when you lose your ankle
22 reflexes, you have a clear decrease in your

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1 myelinated fiber density. I mean, I really do
2 think that if we really want to have a small fiber
3 predominant neuropathy, you do need to have
4 retained reflexes because those absent reflexes
5 indicate you have a mixed axonal neuropathy due to
6 aging. And it may be normal aging, but it's aging,
7 so loss of myelinated fibers.
8 DR. FREEMAN: The question is -- so you are
9 saying small fiber predominant. If you have lost
10 your ankle reflexes, you are out. You are not --
11 DR. FELDMAN: The difference [inaudible -
12 off mic] -- because you can have reduced --
13 DR. FREEMAN: We're dealing -- at this
14 point --
15 (Crosstalk.
16 DR. FREEMAN: -- between mixed and small
17 fiber.
18 Giuseppe?
19 DR. LAURIA: There is something that's not
20 quite clear to me considering that the motor fiber
21 is okay, what is the difference between the
22 predominant and mixed?

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1 DR. FREEMAN: The difference between
2 predominant and mixed is what we are discussing
3 over here. So we are a saying mixed axonal
4 neuropathy will be somebody who has weakness. They
5 would be mixed. Eva is postulating that mixed
6 axonal neuropathy is loss of reflexes. So we're
7 trying to fill in the mixed axonal neuropathy pot,
8 which is to say -- now we're very clear on pure.
9 Let me be explicit.
10 DR. LAURIA: I'm sorry. Maybe it's me
11 that --
12 DR. FREEMAN: Let me be explicit. We're
13 very clear on --
14 DR. SINGLETON: I think Giuseppe was
15 confused. I think that we just said, Giuseppe,
16 that no weakness can be allowed in either --
17 DR. FREEMAN: Yes.
18 DR. SINGLETON: -- small fiber predominant
19 or mixed axonal neuropathy, or pure --
20 DR. FREEMAN: That's what Eva is saying.
21 Eva is saying that you cannot be in this class over
22 here -- this is clear. Right? This is basically

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1 the hard-nose criteria.
2 This is not so clear, and we're trying to
3 decide what the difference is between this and
4 this. And we have agreed that any of this bullet,
5 the second bullet, puts you over there. What we
6 have not agreed yet is on which aspects of these
7 are actually permissible and are allowed to keep
8 you in small fiber predominant.
9 DR. LAURIA: Any --
10 DR. FREEMAN: Let me just finish.
11 DR. LAURIA: Yes, I'm sorry.
12 DR. FREEMAN: Eva has suggested that
13 reflexes would move you down to mixed.
14 DR. FELDMAN: Loss of reflexes.
15 DR. FREEMAN: Loss of reflexes. Exactly.
16 DR. LAURIA: I still don't understand,
17 but --
18 DR. FREEMAN: Gordon?
19 DR. SMITH: So just a couple of points.
20 One, in Peter Dyck's kind of dress up the patients
21 and come to Rochester study, one of the changes we
22 made in the second year -- was to agree that absent

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1 reflexes were acceptable in people over 70. And
2 that was just one of the things that we agreed
3 upon, and it improved our accuracy substantially
4 and our reproducibility.
5 This is obviously not a small fiber
6 predominant population.
7 DR. FREEMAN: So can I just define this
8 accurately? And reproducibility --
9 DR. SMITH: Reproducibly.
10 DR. FREEMAN: -- would be saying somebody
11 has a neuropathy or not.
12 DR. SMITH: Or not, right.
13 DR. FREEMAN: I just want to be clear on
14 this --
15 DR. SMITH: So the reduced overdiagnosis of
16 neuropathy.
17 DR. FREEMAN: -- because there are two
18 issues over here, how easily non-neurologists can
19 elicit reflexes, and the other is defining
20 neuropathy based on reflexes.
21 DR. SMITH: So I bring that up just as a
22 data point, not arguing one way or the other about

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1 reflexes. But the second I wanted to bring up is
2 the issue of non-neurologists doing reflexes,
3 which -- I don't know whether I've got oncology on
4 the brain, but oncologists just seem fearful of
5 this.
6 DR. FREEMAN: And that's my concern. And
7 Vera Brill I think found that as well. I have
8 concerns about using reflexes at all, particularly
9 ankle reflexes, which I think most non-neurologists
10 find challenging.
11 Okay. I'm going to have some closure on
12 this quite quickly. So Nurcan, and then Bob
13 Dworkin.
14 DR. UCEYLER: I wonder if the already
15 existing criteria of Stewart 1992 and the Lacomis
16 2002 might be helpful in distinguishing small fiber
17 predominant and mixed axonal. So when we look at
18 this here, for instance, Stewart says included
19 patients with loss of vibratory sensation at the
20 toes absent ankle reflexes. If this is the case,
21 still the patient can be classified as small fiber
22 neuropathy.

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1 I think this is helpful; at the Lacomis site
2 a few years later, more significant indicators of
3 large fiber dysfunction, including decreased
4 proprioception at the toes, vibratory loss at or
5 above the ankles, and any distal wasting or
6 weakness, and generalized areflexia to be
7 exclusionary.
8 Is this helpful in any way? This is
9 something that we are using, for instance, in
10 clinical practice, and I find this very helpful
11 because ankle reflexes, as you say, this can be
12 lost after a certain age. Areflexia is something
13 different. Maybe this may help.
14 DR. FREEMAN: So just to make sure that all
15 of the views are on the table, there is the one
16 view that says, well, this is normal aging and yet
17 you can lose reflexes. Eva is saying there's
18 nothing normal about losing reflexes. And I think
19 we need to come to some consensus on that.
20 Bob? And I want to move this along because
21 this is why I put this for last. I had concerns
22 about this one.

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1 Let's go. Bob?
2 DR. DWORKIN: I'm sorry that I missed the
3 last three hours, but I was in a meeting with drug
4 company CEOs where ACTTION IMPACT were discussed,
5 and I obviously needed to be there.
6 So maybe I'm biased by the last three hours
7 with discussions about why drug companies are
8 leaving CNS, and in particular pain. And that was
9 the discussion for most of the two-hour discussion
10 of pain, which is how to get pharmaceutical
11 companies back into pain because they've been
12 fleeing pain because drug development is so
13 difficult.
14 But in the context of that discussion, I
15 look at this -- and maybe this is another naive
16 question. But does this inhibit drug development?
17 Are we slicing the pie too skinny so that if I was
18 a CEO and looking at this and thinking, okay, I'm
19 going to pursue Alzheimer's disease or major
20 depression because now I've got to figure out
21 whether my drug development program is pure SFN or
22 small fiber predominant, and that's going to be my

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1 label. And of course this makes the clinical
2 trials more difficult because, as Gordon was
3 saying, everyone's got to be trained to do a
4 sophisticated neurological exam.
5 If I'm off base here and there's no
6 potential here for inhibiting drug development,
7 then I retract my comments. But after my last
8 three hours, that's a concern I have about this
9 slight, very fine elegant slicing.
10 DR. FREEMAN: We have very much kept our eye
11 on the ball, and pharma has commented, and at the
12 end of every discussion, we've taken their views.
13 And the last thing on our minds is to inhibit drug
14 development. But I do take your point, and that's
15 really my stance on reflexes. I have concerns
16 about this.
17 I want to maybe just broaden this out a
18 little and say what do we think is acceptable in
19 the large fiber realm to create a mixed category
20 that skiers left can include in a clinical trial?
21 DR. SINGLETON: I'll offer a proposal. I
22 would say a very conservative proposal, that is

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1 queuing towards pure, is we would allow reduced but
2 not absent vibration at the toe, and we would not
3 allow reduced proprioception at the toe.
4 DR. FREEMAN: Reduced or absent?
5 DR. SINGLETON: I said we would not allow
6 reduced proprioception at the toe.
7 DR. FREEMAN: You would not allow. So
8 reduced vibration, but you would not allow any
9 reduction in proprioception.
10 DR. SINGLETON: Yes. But in return --
11 DR. FREEMAN: As we know, proprioception can
12 be done --
13 (Crosstalk.)
14 DR. SINGLETON: But in return for my
15 proposal, I want to make --
16 (Crosstalk.)
17 DR. FREEMAN: -- with excursions of 90
18 degrees and excursions of 10 degrees.
19 DR. SINGLETON: Haggling here. So in
20 return, I would say we want to either make -- I
21 think there's a real argument for making reflexes
22 agnostic. Like we're just going to leave them off

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

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

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

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1 So I think that you could include
2 potentially any of those patients in your study.
3 It depends on what your target is. But this is
4 much easier for me than just working towards what
5 I've had to most of the time up until now, which
6 was really idiopathic or pure SFN.
7 DR. FREEMAN: Okay. So I'm going to float
8 another balloon up before people respond, and I'm
9 going to say that we are going to say the
10 characteristics of small fiber predominant are the
11 following: decreased but not absent vibration. We
12 are going to see we do not include proprioception
13 or reflexes in this because of the fact that these
14 are two unreliable in the hands of non-neurologists
15 and that -- and this we haven't discussed, but I do
16 want to move things along a little -- that
17 absent -- and we do allow present but decreased
18 sural sensory action potentials, but absent sural
19 sensory action potentials will move you down into
20 the mixed.
21 Can I float that up and see what people
22 think about that? Gordon?

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1 DR. SMITH: I want to go back to Bob's
2 comment and the exchange. And I said yesterday I'm
3 ambivalent about the whole diagnostic validity of
4 small fiber neuropathy, and that ambivalence is
5 getting worse listening to this conversation. I
6 worry that we could run into taxonomic chaos,
7 because we'll have a separate taxonomy for painful
8 peripheral neuropathy for instance. So where does
9 our small fiber predominant neuropathy with pain
10 differ from painful neuropathy?
11 I think we just need to think about the
12 landscape
13 in which these exist. And I think this
14 conversation is good internally, and I think we can
15 certainly nest this in such a way so that pure
16 small fiber neuropathy is a subtype of small fiber
17 neuropathy. But I just want to point out that
18 there are these other taxonomies out there that we
19 need to keep in mind, so that we don't end up with
20 confusion from a regulatory or pharmaceutical
21 development perspective.
22 DR. FREEMAN: I think once we start

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1 discussing idiopathic, I think it will become
2 clearer.
3 DR. LAURIA: May I very quickly? Following
4 your comment, I agree with Gordon because this is
5 just a matter of defining the subgroup of patients,
6 but nothing prevents in a trial dealing with the
7 assessment of a new drug, a neuro analgesic
8 [indiscernible], to include all of them. You will
9 have then a more favorable postdoc analysis, for
10 instance, by the subgroup. So I think it's
11 DR. STEINER: But what are you indicating,
12 then?
13 DR. LAURIA: It's a painful neuropathy. If
14 a new drug wants to reduce the pain, the
15 neuropathic pain, do you think that it is really
16 the core of the fact that you're taking patients
17 with pure small fiber neuropathy or a patient with
18 a predominantly small fiber neuropathy, that will
19 be a never-ending discussion because pure small
20 fiber neuropathy could get an abnormal nerve
21 conduction study if you study the very distal
22 nerves.

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1 So I think it is just a matter of defining
2 within the group of this category of neuropathy how
3 they subgrouped in terms of predominant impairment
4 of the of the type of fibers.
5 DR. FREEMAN: I would echo that approach.
6 That here there's no doubt that in some patients
7 this is a moving target. They progress from pure
8 small to mixed -- to small fiber predominant to
9 mixed, and in other patients, they remain pure or
10 maybe remain at small fiber predominant. There's
11 no doubt that if you were to look at -- as David
12 implied, if you look at plantar responses, they may
13 be absent at some point along the way. If you were
14 to do, as somebody showed earlier -- Giuseppe
15 showed some sural nerve biopsies. You will see
16 small fiber loss.
17 We are creating diagnostic criteria and
18 defining the box. And I think it would be
19 certainly acceptable from my standpoint to say that
20 if you are looking at painful diabetic peripheral
21 neuropathy, you are looking at the complete
22 package, including mixed. And if you are looking

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1 at small fiber neuropathy, and in particular,
2 idiopathic small fiber neuropathy, this is what
3 we're talking about.
4 So that's my stance on it. Giuseppe?
5 Karin?
6 DR. LAURIA: That's what I was saying.
7 DR. FREEMAN: I know that. I'm agreeing with
8 you in another accent, that's all.
9 (Laughter.)
10 (Crosstalk.)
11 DR. RUSSELL: Roy, I agree with what you're
12 saying, but to further define that box, you may
13 want to recommend certain ways of actually
14 measuring vibration. So Nurcan [indiscernible]
15 earlier had mentioned there was a Rydel-Seiffer
16 tuning fork that you do have normative data. And I
17 have to tell you a lot of neurologists are very,
18 very poor at measuring whether vibration is
19 abnormal in older individuals.
20 There is also normative data as the
21 percentiles now published for the sural sensory
22 responses. So again, I would probably recommend we

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1 might want to consider using that particularly in
2 older individuals where it's more difficult to
3 determine cutoffs.
4 DR. FREEMAN: But before, Eva, I just want
5 to make sure that we so far are on the same page
6 with absent vibration moves you down to the mixed,
7 and absent sural sensory action potentials moves
8 you down to the mixed, and anything less than that
9 keeps you in the small fiber predominant.
10 Eva?
11 DR. FELDMAN: So I'm just confused why we're
12 even going to talk about nerve conduction studies.
13 I mean, if you think there's variability in the
14 ability of people to do ankle reflexes, what about
15 getting sural nerve amplitude? So my suggestion
16 would be if we're going to forget ankle reflexes,
17 we should forget nerve conduction studies also. I
18 don't think they necessarily need to be a part of
19 this.
20 DR. FREEMAN: Yeah. Okay.
21 MALE VOICE: That's a very good point.
22 DR. FREEMAN: But let me say something.

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1 What happens if they exist? Unfortunately,
2 particularly in the US, you cannot have a tingling
3 toe without having nerve conduction studies done.
4 What happens if --
5 DR. FELDMAN: This is in a Michigan
6 experience. One of our fellows looked at
7 individuals who come to us with an absent sural,
8 and we redo the study. In almost 40 percent of the
9 time, surals were present if there were ankle
10 reflexes. So again, it depends, but I just don't
11 think it should be part of this.
12 DR. FREEMAN: I understand. I take your
13 point.
14 Rob is the one that wanted this discussion.
15 How do you feel about Eva, that we make that
16 agnostic as well, and all we have is vibration?
17 DR. SINGLETON: It's easy. We'd all agree
18 that there are nerve conduction study abnormalities
19 that would be exclusionary, evidence of
20 demyelination for instance. So I think we have
21 to --
22 DR. FELDMAN: But do you have to have the

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1 nerve conduction studies? I just think we really
2 start getting down a slippery slide here.
3 DR. SMITH: Under a diabetes population, the
4 positive predictive value of nerve conduction
5 studies is very poor. This is the flip side of the
6 conversation we had about skin biopsies. So I
7 think requiring normal nerve conduction studies
8 doesn't make sense in that context, and then it
9 adds a great deal of complexity for something that
10 I think has already been [indiscernible] time.
11 DR. FREEMAN: So we certainly are not saying
12 normal, but we --
13 So Giuseppe, you've heard this discussion
14 over here. People are saying, essentially now,
15 small fiber predominant, all that we have left
16 because of the complexity of the assessments, all
17 that we have left is vibration. Karin? Giuseppe?
18 Your experience?
19 DR. LAURIA: I think that the nerve
20 conduction studies are part of the clinical
21 examination of a patient, and I think we have to
22 make an agreement --

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

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

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

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

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1 response is somehow different in a population with
2 pure or small fiber predominant, or if you have a
3 little bit more, large fiber involvement.
4 At the end of the day, that's the most
5 important. Do patients actually benefit from the
6 therapy independent of their clinical phenotype?
7 DR. FREEMAN: I think we're going to --
8 DR. SMITH: That's really critical. If you
9 want to be a lumper in this -- and we may be going
10 down the wrong path. So far, the one argument I've
11 heard for creating a set of criteria for pure SFN
12 is the sodium channel narrative.
13 Is there another argument for a distinct
14 pathophysiology for pure SFN? And if not, why are
15 we spending so much time worrying on that? Because
16 one can always create a trial specific to a group
17 that you think is enriched with people who have a
18 particular genotype.
19 DR. LEVINE: Can I just make one quick
20 point? I know I know all the difficulties that
21 exist in getting reliable sural responses, but I
22 think for the pharma companies in the room, it's

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1 important to know that there's not a single payer
2 in this country that will pay for small fiber
3 testing the biopsy without normal nerve conduction
4 studies. It is predetermined, Blue Cross, Aetna,
5 United. I'll give you the --
6 DR. FELDMAN: Not Michigan.
7 DR. LEVINE: Really? Because the payer
8 policies -- with our lab, we deal with all kind of
9 people --
10 (Crosstalk.)
11 DR. LEVINE: Really? It is widespread. I
12 will say that.
13 DR. FREEMAN: I'm going to go to Karin, but
14 just to answer Gordon's question, I want to be sure
15 that I understand what you're saying. The sodium
16 channel hypothesis, this applies not just to
17 patients who have polymorphisms, but the fact that
18 a sodium channel blocker, as Karin said, would be
19 effective in any small fiber neuropathy.
20 DR. SMITH: My question has to do with
21 whether we are oversizing it and focusing on pure
22 SFN. And it goes back to my ambivalence about the

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1 distinction between small fiber predominance.
2 DR. FREEMAN: So we know where you are.
3 DR. SMITH: Yeah, you know where I am. But
4 I think it's relevant to your point.
5 DR. FREEMAN: I do get the point. I think
6 we all do.
7 Karin?
8 DR. FABER: I have two points. One is also
9 a response to Gordon, is that we would never have
10 been able to publish sodium channels if we did not
11 have this rigid criteria for small fiber
12 neuropathy. So that's one. And that's also
13 something you have to take in mind when you develop
14 a trial.
15 The other thing is, if you decide which
16 group you want to include, it also depends on the
17 type of drug and the mode of action of the drug
18 that you will include. If it goes for sodium
19 channel blocker, then I don't think it makes a lot
20 of difference whether you include the entire group
21 or not. But for other drugs, this may be different
22 because the genetic background may be different.

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1 We don't know that.
2 So why isn't it possible to say, okay, we
3 have the group of small fiber neuropathy that
4 includes pure small fiber neuropathy and small
5 fiber predominant neuropathy? And between this,
6 you can discriminate. You have the risk of the
7 subgroup analysis, but on the other hand, it gives
8 you the opportunity to select one group for a
9 certain trial.
10 DR. FREEMAN: It certainly would move the
11 field forward.
12 I agree with that. My sense is that the
13 majority, if not everybody, agrees with that. Is
14 it okay to move forward? Is the majority -- I want
15 to see people nod or shake their heads. Eva's
16 nodding.
17 Is everybody on the page that Karin so
18 carefully -- and I know Gordon is not. But is
19 everybody else on the page that we can move
20 forward?
21 (Affirmative nods.)
22 DR. FREEMAN: I'm going to take that as a

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

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

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

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

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1 DR. FREEMAN: Anybody disagree then that in
2 order to do a clinical trial on a small fiber
3 neuropathy on patients who have the appropriate
4 symptoms, the appropriate signs, we don't need a
5 skin biopsy.
6 Chris?
7 DR. GIBBONS: I think you're sort of taking
8 two questions there. One is, does this biopsy move
9 you to confirmed or do you need that to enter a
10 trial? I think those are different questions.
11 DR. FELDMAN: That's what I was trying to
12 understand.
13 DR. FREEMAN: Let's go back a bit. For
14 example, even with those -- I showed earlier
15 NeuPSIG grading system, possible/probable for a
16 neuropathic pain trial. Gordon's point, a diabetic
17 neuropathic pain trial, probable is sufficient to
18 enter you a clinical trial.
19 The question over here is, is small fiber
20 different? Again addressing in some sense Gordon's
21 point, that is this an entity where because of the
22 grain greenness on the edge of the boundary, that

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1 we actually need to have confirmation in order to
2 enter the clinical trial, support in order to enter
3 the clinical trial. And that really is the
4 question. So in my mind, they actually are quite
5 closely connected. I accept the point that you are
6 making, but I think with this specific entity, they
7 actually blend into one.
8 DR. GIBBONS: In this case, I might
9 disagree. I would say symptomatically I think you
10 could absolutely enter into the probable. If
11 you're going for a disease modifying, then I think
12 you need confirmed.
13 (Voices stating agreed.)
14 DR. FREEMAN: Okay. This is really
15 interesting to hear. Certain, industry is really
16 very happy to hear this because it's a huge barrier
17 to recruitment, patients needing to have a piece of
18 skin removed. So Do others agree with this? I
19 mean, I'm not sure that I do.
20 DR. LEVINE: Isn't post-herpetic neuralgia
21 the analogy? We do those painful trials with --
22 DR. FREEMAN: No, it's not the analogy; it's

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1 a rash. It's a rash.
2 DR. LEVINE: But you may see them long after
3 the rash.
4 DR. FREEMAN: There's a history of a rash.
5 There's diabetes. There's HIV. This is my stance
6 on this, and that's the big difference with this
7 entity. And it really does address Gordon's point.
8 Yeah?
9 DR. SMITH: I'm curious why you're
10 comfortable in diabetes, outside of diabetes. Over
11 10 percent of Americans have diabetes and only half
12 of those have neuropathy. And I bet a lot of the
13 millions of Americans who have diabetes without
14 neuropathy, have metatarsalgia and plantar
15 fasciitis, and I further would posit that they're
16 probably more likely to have those things.
17 So I think it's worth being self-reflective
18 about why. I agree with Chris. I'm a little less
19 comfortable with it, but I think we're hiding
20 behind diabetes to create false comfort. If we're
21 comfortable with it and diabetic neuropathy, then I
22 would say we probably ought to be comfortable with

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1 it here.
2 DR. FREEMAN: I'm not that comfortable in
3 diabetic neuropathy to say how I feel, but I am
4 more comfortable when here -- and this is just my
5 view and I want to hear what others think. What
6 gives me the discomfort is that you are just
7 dealing with symptoms and signs, whereas diabetes,
8 I would say that in a clinical assessment of the
9 patient -- I'm just going to go clinical -- every
10 piece of information increases the probability that
11 you are coming to the right conclusion, and I don't
12 want to overweight the presence of diabetes, nor
13 the presence of HIV because there's no doubt
14 that -- as one of my German fellows once said, you
15 can have lice and fleas. Because you have
16 diabetes, it doesn't mean you don't have another
17 cause of a peripheral neuropathy. But over here,
18 we don't have any of that stuff that increases the
19 probability, and that's why I come down to the skin
20 biopsy; my stance on this.
21 I now want to hear what others think. Eva?
22 DR. FELDMAN: So I would definitely share

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1 your concern in a pure small fiber neuropathy. I
2 feel less so in the small fiber predominant because
3 then we have at least two signs, a large fiber and
4 a small fiber sign of neuropathy with decreased
5 vibratory sensation. But thinking about it, think
6 how many patients we have seen who we thought had
7 pure small fiber neuropathy who we biopsied, who
8 turned out to be at least -- their intraepidermal
9 nerve fiber density was quite robust. And then you
10 followed them along and realized they probably
11 didn't have a small fiber neuropathy, although
12 signs and symptoms were present for more than six
13 months.

14 DR. FREEMAN: Although some would say they
15 could still have it even though the intraepidermal
16 nerve fiber density was normal. But I think that,
17 as we discussed earlier, pharma would prefer to
18 exclude those patients and rather have something
19 more definitive.

20 David Herrmann?

21 DR. HERRMANN: I certainly agree that skin
22 biopsy should be on this, would be my preference,

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1 the primary measure -- supportive measure. It's
2 the way I practice, and it's the way I think these
3 trials should be designed. But one of the
4 questions is you're dealing with a relatively
5 small population of patients you who can enroll in
6 a trial, so what you want to do is avoid excluding
7 too many people who might be eligible.

8 So one question is if you do have a set of
9 tier 2 measures, let's say they are QST, let's say
10 QSART, what happens if you have a patient whose
11 epidermal nerve fiber density is on that 7th
12 percentile, but the QSART's abnormal and the QST's
13 abnormal? Those patients, I think most people
14 feel, with signs and symptoms have small fiber
15 neuropathy.

16 The point that Giuseppe made was that,
17 really, even as good as skin biopsy is, its
18 sensitivity is not perfect, and its specificity is
19 better but not perfect. So it's a question,
20 obviously you have to make some pragmatic decisions
21 when you design trials, and we may pragmatically
22 say, you know what, we put the QST in tier 2, we

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1 put QSART in tier 2, but from a practical
2 perspective, we cannot design a multicenter trial
3 with these kind of technologies. Then I think we
4 have to take them out of tier 2. But if we're
5 going to put them in tier 2, I would offer that you
6 could back these both as an alternative. I don't
7 know. I just put it out there.

8 DR. FREEMAN: We have Giuseppe, and then we
9 have Ahmet.

10 DR. LAURIA: Very brief. Actually, the
11 specificity is very high but it's by definition
12 because of the enormity. The sensitivity is not a
13 thing. We don't need to use the biopsy as a
14 screening tool for the population. So we need to
15 have that as a confirmatory test in terms of going
16 from the probable set into the supported set,
17 confirmed set.

18 DR. FREEMAN: There's a growing consensus.

19 DR. LAURIA: Yeah. The second point is
20 actually, I think that we should be feasible, and
21 we cannot exclude patients or centers dealing with
22 patients only because one tool is not available,

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1 because if we put all the tools together, we see
2 how the specificity remains high.

3 DR. FREEMAN: So I'm hearing so far -- and
4 just let me synthesize -- that of the confirmatory
5 supportive tests, we have tier 1 and tier 2 tests.
6 Skin biopsy is tier 1, that it is a confirmatory
7 test, and for clinical trials, we want to be
8 careful about excluding tests that others don't
9 have, that investigators don't have.

10 Eva? Sorry. Where were we? It was Ahmet?

11 DR. HOKE: I was going to comment to reflect
12 on Chris' comments. I think the use of skin
13 biopsies is gonna depend on whether you're
14 developing symptomatic therapy, in which case you
15 really don't care what a skin biopsy shows as long
16 as I'm convinced the patient as neuropathy based on
17 history and exam. But if you're doing a
18 disease-modifying trial, I think I would like to
19 see changes in pathology because it's something
20 that is the most objective measure that can be
21 quantified, whereas all the others, you'll have
22 trouble quantifying.

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1 DR. FREEMAN: So why it does matter -- and
2 maybe answer your question directly -- is that the
3 drug developers are actually looking at an entity,
4 looking at a disease. They are looking at small
5 fiber neuropathy, idiopathic small fiber
6 neuropathy. So as Gordon implied, they're not just
7 looking at painful neuropathy. They are looking to
8 develop a drug specifically for small fiber
9 neuropathy. So what our goal over here is, to
10 define the boundaries of that entity. So I think
11 the same applies for disease modifying as it does
12 for, and that's why I think --
13 DR. HOKE: But I'm not sure if that's
14 what -- I mean, maybe the pharma people can
15 comment. I wouldn't be trying to get a designation
16 for idiopathic peripheral neuropathy for
17 symptomatic treatment only because to me, you're
18 like shoehorning yourself into a very small --
19 DR. FREEMAN: Let's not -- drug development
20 is a complex business.
21 DR. HOKE: I would go after pain. You're
22 making this into symptomatic.

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1 DR. FREEMAN: I appreciate it. I appreciate
2 your views. You can discuss that with Deb
3 afterwards.
4 DR. STEINER: But what if the target is pain
5 in a patient population with small fiber
6 neuropathy? There are two issues. One is that in
7 a proof-of-concept study, we want to make sure
8 we're enrolling the right population. The other is
9 what are we going to get on a label, but what
10 population are we looking at?
11 DR. FREEMAN: I'm going to cut this
12 discussion.
13 DR. HOKE: [Indiscernible] --
14 DR. FREEMAN: Ahmet, let's stop. This is
15 not why we're here. Perhaps, Deb, you can meet
16 with Ahmet afterwards and maybe bring the CEO of
17 Biogen in, and he can tell you how you should be
18 running your business.
19 Any other comments on -- there was some
20 stuff at the back there. Karin, any views?
21 Anybody else want to comment?
22 Let me maybe outline where we stand at the

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1 moment, that skin biopsy is considered a
2 confirmatory test, that this is an objective test,
3 and that it does define the bounds of this entity.
4 I want to get a sense as to whether this is
5 supported by the majority, and I want to get a
6 feeling as to where those dissenters stand on this.
7 (Nods from audience.)
8 DR. FREEMAN: So I've seen nods. Karin,
9 nod. Eva, so you satisfied? Yeah. Rob, are you
10 satisfied? Anne Louise? Ahmet? Not really.
11 (Laughter.)
12 DR. FREEMAN: Michael, I'm sure, yeah. He's
13 nodding very vigorously.
14 Gordon?
15 DR. SMITH: I want to make Ahmet feel
16 better. It's part of my conciliatory role now. To
17 some extent, this is a paper tiger, right? So
18 we're going to create probable criteria that are
19 based on signs and symptoms. So for epidemiology,
20 maybe that works, and it might be for a particular
21 neuropathic pain agent, depending on the putative
22 mechanism, that might work. However, in a trial

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1 that's targeting sodium channels where there's data
2 from a very selective group of pure small fiber
3 neuropathy, the company may want to go with
4 whatever we're calling confirmed or supported.
5 So to some extent, this isn't our dark
6 problem. We're creating levels of certainty that
7 then can be deployed by pharma in a way that fits
8 their development most appropriately.
9 DR. FREEMAN: I think that is actually fair.
10 I don't think I would disagree with what you're
11 saying. Anybody, before we take closure on this,
12 any additional points?
13 Chris?
14 DR. GIBBONS: I wasn't sure if we actually
15 got confirmation or disagreement on with two second
16 tier tests.
17 DR. FREEMAN: No, we haven't discussed the
18 second tier tests yet, at all.
19 So skin biopsy, I'm going to say we're ready
20 to move on. I've got two additional questions with
21 skin biopsy, and that is do we need to specify
22 laboratories. Eva made the point about nerve

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1 conduction studies. I think we've all seen many
2 skin biopsies that were misinterpreted, misread,
3 David Herman, misperformed. And then the next
4 point, and address both of these, is how long ago?
5 Six months, One year, 10 years? What's acceptable?
6 So let's open that up for discussion.
7 DR. LEVINE: On your first point, I was
8 trying to do this through the AAN last year and
9 just made no progress over the last 12 months. But
10 a number of commercial pathology labs are now doing
11 the 5 micron thin section through a Ventana machine
12 and spitting it out. It's being done all across
13 the country.
14 So I think there should be two issues in the
15 first question. One is specifying the technique,
16 so that the technique is at least consistent among
17 labs. The second question about specifying labs is
18 complicated. I think a central lab is always a
19 good idea for a trial. We could recommend and,
20 again, the drug company would choose. But I think
21 we do need to say it needs to be the thick sections
22 and frozen --

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1 DR. FELDMAN: Joint Commission accredited.
2 DR. LEVINE: Joint Commission accredited,
3 yeah, exactly. So I think some basic credentials
4 and basic techniques that we could specify would be
5 helpful there.
6 DR. FREEMAN: Okay. Giuseppe?
7 DR. LAURIA: The number of years you're
8 running it probably is not very useful. I would
9 consider qualified probably or I would suggest a
10 lab which is part of a quality control program,
11 which is I think important, interesting, that can
12 be created.
13 DR. FELDMAN: Joint Commission.
14 MALE VOICE: That's a U.S. based.
15 DR. HERRMANN: There are also different
16 accrediting agencies. There's CAT, there's Joint
17 Commission, so I'd just be a little broad with
18 that, but definitely demonstrate quality assurance.
19 DR. FREEMAN: So I think we'll be somewhat
20 vague as far as that is concerned. We will I think
21 specify technique, and we will talk about cutoff
22 values, normative data. And then we'll have to

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1 talk about how long ago, six months. One year, two
2 years?
3 DR. OAKLANDER: One year.
4 DR. FREEMAN: A year from Anne Louise.
5 Do I hear six months? Karin, six months.
6 Do I had three months?
7 DR. LEVINE: So you're saying if they've had
8 it within the last 12 months, they don't need
9 to --
10 DR. FREEMAN: That's what Anne Louise we
11 says. Karin said six months.
12 DR. SMITH: We dealt with this with Topspin,
13 and we decided not to accept outside biopsies for
14 the various reason Todd talked about. And we
15 talked about do we get the slides and look at them.
16 And ultimately -- and we can all name companies,
17 but some of the most prevalent providers of this in
18 the United States do a terrible job. And as I
19 think David mentioned, we routinely see people who
20 had very abnormal biopsies at another place, and we
21 repeat them in the lab, and it's normal.
22 So I wonder whether this is even a road we

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1 want to go down.
2 MALE VOICE: Quality [inaudible - off mic]
3 with expert labs.
4 DR. FELDMAN: With the same [inaudible - off
5 mic]?
6 DR. FABER: But I think that for me the six
7 months is when the biopsy is done by ourselves or,
8 for example, by Giuseppe, then it's acceptable.
9 DR. SMITH: Yeah, that I'm comfortable with.
10 But the idea that we're going to create a false
11 sense of security using any accredited laboratory
12 value I think is a problem.
13 DR. FREEMAN: I think in Biogen's defense,
14 they are taking a very rigorous -- I think it's
15 been argued too rigorous approach to this, but I
16 think it's perfectly appropriate in that they have
17 readers, and then they have a central confirmatory
18 reader. And I think that that's a very rigorous
19 approach to this.
20 Chris, then Christian David Herrmann.
21 DR. GIBBONS: So I guess I want to step back
22 to ask, are we defining this in a taxonomy

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1 standpoint? In other words, you need a biopsy
2 every six months to maintain --
3 DR. FREEMAN: No, no, no, no.
4 DR. GIBBONS: -- to maintain your diagnosis.
5 DR. FREEMAN: No, no, no, no. We're not
6 seeing that at all. We are saying somebody --
7 DR. GIBBONS: Just for a clinical trial
8 standpoint, yes, but for a taxonomy standpoint --
9 DR. FREEMAN: We are just doing inclusion
10 criteria, no taxonomy, no outcomes. We are just
11 doing entrance criteria.
12 DR. GIBBONS: But just to play devil's
13 advocate --
14 DR. FREEMAN: I just want to make sure that
15 everybody understands. Somebody comes to James's
16 center. He fulfills all of the criteria for a
17 small fiber neuropathy, the signs, the symptoms,
18 and he had a biopsy done in Anne Louise Oaklander's
19 lab, which was done seven months ago. Does he need
20 a repeat biopsy? That's the question, or done 13
21 months ago, does he need --
22 DR. FELDMAN: So could I suggest if the

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1 biopsy is abnormal, he does not; if the biopsy is
2 normal, he does? And then you just pick --
3 DR. FREEMAN: But that's the question. If
4 it's abnormal --
5 DR. FELDMAN: If it is abnormal, and those
6 who are most expert can say if it's 6 months or 12
7 months, and we can move on because we only have
8 about 15 minutes, and we're going to lose the
9 Europeans who are the other tests.
10 DR. FREEMAN: I want to do the biopsy while
11 the Europeans are here, but thank you.
12 (Laughter.)
13 DR. GIBBONS: I still want to clarify. So
14 if James sees the patient a year before, fulfills
15 everything, a year later they see me.
16 DR. FREEMAN: He's in front of him.
17 DR. GIBBONS: Right.
18 DR. FREEMAN: He's had a biopsy. Very
19 simple. He's in front of him. He's had a biopsy.
20 This is something that really is important for
21 Biogen, for Heikki. He's in front of him. He has
22 a small fiber neuropathy, clinically. He had a

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1 biopsy a year ago, Eva's point about
2 normal/abnormal. Yes?
3 DR. FELDMAN: One year.
4 DR. FREEMAN: One year. Are we okay with
5 one year? I think we're okay with one year.
6 DR. HERRMANN: Can I just make one comment?
7 DR. FREEMAN: Yep.
8 DR. HERRMANN: As much as we want to
9 separate out for trial purposes diagnosis entry
10 criteria, if you're going to do a skin biopsy,
11 you're going to follow that as an outcome. And you
12 can't take a baseline biopsy from six months ago or
13 a year ago and substitute it for a baseline biopsy.
14 You're going --
15 DR. FELDMAN: Not for baseline.
16 DR. RUSSELL: This is for inclusion
17 criteria.
18 DR. FREEMAN: This is inclusion criteria.
19 (Crosstalk.)
20 DR. HERRMANN: Then you have to specify if
21 it's only inclusion to make a diagnosis. But if
22 you're going to use skin biopsy as --

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1 DR. FREEMAN: We are only talking about
2 inclusion criteria.
3 DR. HERRMANN: But if you're going to use
4 that biopsy as an endpoint, you're going to do --
5 DR. FREEMAN: We are not talking about
6 endpoints.
7 DR. SMITH: The problem, Roy, is it's not
8 Anne Louise's lab that's the issue, and you know
9 who I'm thinking about and a few others. The
10 problem is if we go down this route, if Biogen is
11 going to take comfort in those biopsies, we're
12 going to have to come up with some sort of system
13 that I think is going to be impossible to say whose
14 skin biopsies do we trust and not trust.
15 DR. FREEMAN: Well, Biogen's approach is you
16 do the biopsy and you send it to Giuseppe, send it
17 to Karin, and send it to Michael.
18 DR. SMITH: I can give you an example. I'll
19 tell you what happened at ARUP, where the stain
20 failed. And they reported out -- and I probably
21 shouldn't be saying this publicly -- severely
22 abnormal biopsies for a year. And it was only when

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1 we started looking at them, we realized that the
2 stain wasn't working, and it can be hard to sort
3 out. It's a risky thing.
4 DR. FREEMAN: We understand that. So I
5 think we can word this reasonably enough.
6 Let's move on, and I think we now can talk
7 about the so called tier 2 test, QST and autonomic
8 testing. And I'm going to shelve corneal confocal
9 microscopy for just a second. Let me hear where
10 people stand on QST. How does this fit in?
11 DR. RUSSELL: Roy, the problem again here
12 is, if you don't have to have tier 1, but you can
13 include the patient if they're only in tier 2, then
14 you run this problem that I mentioned earlier, that
15 you have problems with sensitivity and
16 reproducibility of the test.
17 DR. FREEMAN: So let me maybe articulate it
18 a little differently. James is saying that tier 2
19 has no role in supporting the diagnosis.
20 DR. RUSSELL: Essentially, yes.
21 (Laughter.)
22 DR. FREEMAN: So QST is irrelevant to this.

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1 The other approach to this is saying that QST is
2 actually part of the sensory examination, and could
3 have abnormal warm and cold thresholds, and that
4 would be equivalent to the hyperalgesia, allodynia,
5 and pinprick that we spoke about, which would be
6 another way of looking at QST. And we often say it
7 is an extension of the clinical examination, and it
8 certainly fits in.
9 FEMALE VOICE: It's not feasible.
10 DR. FREEMAN: Feasible. Where is that
11 coming from?
12 FEMALE VOICE: Are we going to ask people
13 [inaudible = off mic].
14 DR. FREEMAN: Okay. But we're not saying
15 it's obligatory, but we are saying that if it is
16 done by a reputable laboratory, that is acceptable.
17 That's another approach to it.
18 So the one approach is James' approach, has
19 no place, and we can word it politely. The other
20 is -- this fits in as an -- there are certain tests
21 that are extensions of the clinical examination,
22 perhaps are better sensory tests, and this is part

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1 of the examination.
2 DR. HAROUTOUNIAN: Evidence wise, when it's
3 done appropriately, I think the data supporting
4 those two thresholds of warm detection and cold
5 detection are pretty reasonable. So the question
6 is -- again, I would generally recommend against
7 the other things, heat pain, cold pain that is
8 before the field. With those two thresholds, I
9 think --
10 DR. FREEMAN: That was clear from the data.
11 DR. HAROUTOUNIAN: We can have a note that
12 the data are pretty supportive if it's considered
13 to be --
14 DR. FELDMAN: Could I ask Simon a question
15 in case there are cases where skin biopsies are not
16 doable? Do you believe, based on the data, that it
17 could be a tier 1, and for a confirmatory test, it
18 could be either skin biopsy or an abnormal QST?
19 DR. HAROUTOUNIAN: I think so. We should be
20 careful in defining what the healthy controls or
21 the normal values are. But if we define that, I
22 think that it's -- I would vote for yes.

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1 DR. FREEMAN: So really there's the James'
2 view, has no place at all. It's my suggestion that
3 it could be an extension of the, of the exam and
4 this Simone's view was saying that this is exam,
5 and Simon's view is saying that this is equal
6 weight with the pathology.
7 DR. HAROUTOUNIAN: I'm not saying equal, but
8 again, if the biopsy is not available as a
9 potentially weaker option, I think the data are
10 pretty reasonable.
11 DR. RUSSELL: The one problem with this is
12 that if you use handheld devices -- and there are
13 several handheld devices out there. They are
14 notoriously unreliable. So the problem I see here
15 is that you're going to get a trial run somewhere
16 in the world where they're going to come up with
17 some handheld device, and they're going to say this
18 is abnormal, and therefore this is a small fiber
19 neuropathy.
20 Now, if they really did sit down and they
21 followed all the rigorous criteria for using a
22 sensory testing device, then one might consider

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1 that perhaps a little bit more useful. But if you
2 can't actually take a skin biopsy and send it to a
3 central lab to get it processed, then I'm not sure
4 you're really going
5 to have the ability to perform quantitative sensory
6 testing using the most robust devices and in the
7 correct way. That's my concern.
8 DR. FREEMAN: So these guys are going to be
9 able to say, well, we don't want to have
10 quantitative sensory testing. But let me just for
11 argument's sake say that this is done with the
12 right equipment, in the right way, done absolutely
13 perfectly, and we will actually have to prescribe
14 exactly how this is done.
15 Given that idealized circumstance, where do
16 you think this should lie, as tier 2 or part of the
17 examination as an extension of the examination;
18 another point, or as tier 1? And think about that
19 while I have Chris respond.
20 DR. GIBBONS: So I would support it as part
21 of the examination. I think that could be an
22 appropriate direction. I think another one to

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1 consider would be amongst tier 2, CCM, QST, and
2 QSART; 2 of 3 abnormal would be convincing,
3 assuming all the quality --
4 DR. MALIK: I think you really are missing
5 something if you're not going to have functional
6 assessment of the fibers because I know there are
7 difficulties with QST and sudomotor, but it's a
8 functional aspect. And I see patients, honestly,
9 that have had a perfectly normal skin biopsy and
10 yet have functional deficits. So I think it has to
11 be in there. You can't just throw them out.
12 DR. FREEMAN: So Chris has made a proposal
13 of grouping the three so called tier 2 tests, each
14 of which requires very, very specific performance
15 requirements, as if you have 2 of those 3, then you
16 can move up one tier, and that is supportive,
17 whereas skin biopsy is in and of itself an
18 acceptable supportive or confirmatory diagnosis.
19 There were some other hands back over there.
20 Gordon?
21 DR. SMITH: So I'm curious the frequency
22 with which I'm QST is abnormal in an individual

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1 who, to use Roy's expert neurologist, finds a
2 completely normal bedside sensory examination. And
3 this goes to your idea of using this as an
4 extension. And I don't know those data, and it
5 sounds like you guys do.
6 DR. HAROUTOUNIAN: I think roughly 30 to 40
7 percent of studies didn't confirm a difference
8 between small fiber neuropathy in healthy controls.
9 DR. SMITH: No. So what I'm asking is, if I
10 see a patient who has symptoms of neuropathy, they
11 have burning feet, yet I find a normal pin
12 sensation or even normal bedside thermal sensation
13 using disks, how often is QST abnormal for those
14 domains?
15 DR. UCEYLER: I don't think that they are
16 systematic.
17 DR. FREEMAN: So far where we are, we are
18 not assessing thermal sensation at all.
19 DR. SMITH: That's right, pain sensation,
20 yeah.
21 DR. FREEMAN: Bear that in mind.
22 So Giuseppe, you give it equal weight. You

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1 give QST equal weight with skin biopsy in your
2 criteria, as do you, Karin.
3 DR. LAURIA: Again, if you need to define
4 what is the condition that was the other
5 tool -- it's a functional test, so it's different;
6 it's not the same thing. But it is a way to define
7 whether a class of fiber works normally or not. So
8 if we are there, I think that we should agree on
9 the fact that the biopsy has a higher power on
10 that, but again, we should do so in a most feasible
11 way. And other tools in tier 2 should be
12 considered such as QST, CCM. I think they've shown
13 very good results, very precise results.
14 So the discussion I think would be if you
15 are going to the tier 2, since the power and
16 actually the specificity, which is different in
17 this case, is not that much for the QST, and you
18 want to define the entry criteria for the trial, if
19 the biopsy is normal, would you rely on the
20 abnormal QST or you would need two normal
21 examinations at tier 2?
22 DR. FREEMAN: I think this is where we are

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1 at the moment, and I want to get some consensus.
2 So there are two options. The one is -- and this
3 is assuming QST is available with a good
4 instrument, perfectly performed, patient is alert,
5 conscious, motivated, that it will be an extension
6 of the exam. It will provide thermal assessment as
7 part of the exam. So that will be one of the four.
8 That's one possibility. And the other is
9 that it moves down to tier 2, and we have the
10 proposal that I think came from Chris, 2 out of the
11 3 tier 2's need to be positive in order to give you
12 support confirmation.
13 Yes, Simon?
14 DR. HAROUTOUNIAN: One note. So we were
15 mentioning those 4 or 3 tier 2 criteria. There
16 were other tests that were performed in smaller
17 amount of studies with initially promising results.
18 DR. FREEMAN: There were many centers --
19 (Crosstalk.)
20 DR. HAROUTOUNIAN: My question is, if a
21 company does a phase 2 trial, a small one, but they
22 have ability to do LDI flare, or chips, or laser,

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1 is there a role to one of those indicators --
2 (Crosstalk.)
3 DR. FREEMAN: Laser disk potential is not
4 available in the U.S., chips, almost nobody has it.
5 And we can discuss how those should be grouped at
6 the end, but another story. But I don't think
7 those are part of the table.
8 Yep. David?
9 DR. HERRMANN: We have the flexibility
10 though for the person designing the trial to say,
11 look, we are quite interested in function without
12 particular agent. We are less interested in an
13 effect on epidural nerve fibers. And while we can
14 specify that our preferred criteria include a
15 primary, we can do Chris's option of having two of
16 these second-tier measures that might be more of
17 interest in a particular trial situation.
18 DR. FREEMAN: I like that. I like that
19 notion, that we leave -- I'm fine with either of
20 those two options. I want to get a majority.
21 So I think we really are -- we've just got
22 to come down to a decision over here, whether it

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1 should be an extension of the clinical examination
2 or whether it should be 2 of the 3. And certainly
3 function is autonomic and function is QST, and both
4 of them need to be performed perfectly.
5 DR. RUSSELL: So Roy, I guess what the issue
6 is, the only reason why I would think you would
7 need tier 2 criteria is if you believe that a
8 center or a trial for some reason would not be able
9 to use the interpretable nerve fiber density as
10 tier 1. So in other words, this will be a
11 substitute for tier 1.
12 I find that kind of hard to understand why
13 that would be the case, but if you were to do that,
14 then you could include the QSART. I prefer your
15 earlier idea that the quantitative sensory testing
16 would be one of the things that you could use to
17 try to make your examination a little bit more
18 accurate.
19 DR. FREEMAN: I'm not disagreeing with you,
20 but I want to clarify why it might be of value.
21 And that was the point I think made by David
22 Herrmann, that, one, we're assessing dysfunction,

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1 which may be abnormal before we are assessing
2 structure; and two, it looked like from his data we
3 are assessing, at least with the autonomic side, a
4 different population of fibers.
5 Am I articulating what you said?
6 DR. HERRMANN: And again, I'm a proponent of
7 skin biopsy fundamentally, but I think they can be
8 differentially involved in these patients. So I
9 think that there are issues with this. I think if
10 it's going to be used, the technical aspects and
11 the pitfalls have to be very clearly delineated,
12 but it may be option. And I don't think we need to
13 be too prescriptive. It's a second tier,
14 second-line option for certain trial designs.
15 DR. FREEMAN: To me, I don't have a sense of
16 consensus at all. Two options, I need to ask for a
17 show of hands.
18 Who thinks that this should be an extension
19 of the clinical examination, that it's part of the
20 menu, that we will have thermal thresholds as part
21 of what we will call tier 2, perhaps possible,
22 probable -- we're in the probable. That's the one

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1 possibility, so extension of the clinical exam, who
2 thinks -- and this is purely QST, so not tier 2,
3 but it's QST as part of an extension of the
4 clinical exam.
5 Option number 1, who thinks that it should
6 be a tier 2, and we have the 2 out of 3 menu of
7 possibilities that is optional for the pharma. And
8 before give this to vote, it would be helpful to
9 hear what pharma thinks about this.
10 Have you understood the menu?
11 DR. GIBBONS: Could it be both?
12 DR. FREEMAN: Well, we can always -- yeah,
13 anything can be anything I suppose.
14 DR. GEWANDTER: What if it's a clinical
15 extension, is it going to be mandatory? Like is it
16 going to be like we have to have this like as part
17 of our [inaudible - off mic]?
18 DR. FREEMAN: No.
19 MALE VOICE: So it needs to be both.
20 DR. FREEMAN: Let's hear. Deb, what do you
21 think?
22 DR. STEINER: I would be fine with it being

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1 both, and I've said that we want prescriptive
2 guidelines. But the more flexibility there are in
3 the guidelines so that we can make a steady work
4 and operationalize it on a larger multicenter
5 level, the better. So if there were a tier 1 and
6 tier 2 approach, that would be optimal.
7 DR. FREEMAN: Okay. This is like in a movie
8 where the audience actually decides how the movies
9 gets to end.
10 (Laughter.)
11 DR. FREEMAN: I like this; can it be both?
12 Well, what do you think, Heikki, can it be both?
13 DR. MANSIKKA: Yeah. I think the previous
14 comment -- it's good to have the flexibility, and I
15 think there is ambiguity on the data that what is
16 actually -- I mean data doesn't show us either way
17 or the other, so I think therefore there should be
18 flexibility around this.
19 DR. FREEMAN: Steven?
20 DR. SAINATI: I agree that that flexible
21 approach makes sense.
22 DR. FREEMAN: Okay, flexibility. The

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1 Italians and the Netherlands who are about to
2 leave, are you okay with this kind of approach?
3 Where do you guys lie? You've thought more about
4 this than most of us.
5 DR. LAURIA: I think we can support the
6 second option.
7 DR. FREEMAN: Tier 2.
8 DR. FELDMAN: Yeah.
9 DR. FREEMAN: And are you okay with the 2
10 out of 3?
11 DR. FELDMAN: Yes.
12 DR. FREEMAN: So you would say that a
13 positive corneal confocal microscopy result
14 combined with, let's say, abnormal QST, one of the
15 thermals is equivalent to a skin biopsy.
16 DR. LAURIA: In a patient with a probable
17 condition, probably not.
18 DR. FREEMAN: So in terms of possible,
19 probable, definitely tier 1, tier 1, tier 3, are we
20 okay?
21 DR. FELDMAN: What happened to QSART?
22 DR. FREEMAN: Oh, okay. That was one of the

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1 tier 3. I thought that was included as part of
2 tier 3, QST and CCM.
3 MALE VOICE: QSART.
4 DR. FREEMAN: Sorry. Did I say -- those
5 three anyway. I haven't had lunch yet, unlike you
6 guys.
7 So those three are okay? Are we okay with
8 that?
9 Does anybody want to comment about QSART?
10 And I think with QSART, it needs to be perfectly
11 executed, as does QST, and I assume -- and I know
12 least about the CCM as Rayaz leaves.
13 DR. MALIK: Before I go, you definitely have
14 to include it, okay?
15 (Laughter.)
16 DR. FREEMAN: My suggestion is that you
17 don't go yet.
18 DR. FELDMAN: [Inaudible - off mic].
19 DR. FREEMAN: Should I raise the elephant in
20 the room about CCM?
21 DR. FELDMAN: No, no. As Rayaz knows, I
22 just haven't been completely convinced as a

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1 clinical endpoint.
2 DR. FREEMAN: Eva, as an endpoint?
3 DR. FELDMAN: And that really is based on
4 seeing our data. That's the data Rayaz and I have
5 together in our NIH trial, and seeing Rob and
6 Gordon's data. And I just think it's something
7 that requires further exploration before we say
8 it's a definitive trial endpoint.
9 DR. FREEMAN: And I have to say --
10 DR. FELDMAN: But it isn't fair because
11 Rayaz is leaving. That's the reason I wanted to do
12 this sooner.
13 (Crosstalk.)
14 DR. FREEMAN: The only negative thing I have
15 to say about him is that he is a Manchester United
16 supporter.
17 (Laughter.)
18 MALE VOICE: Oh, they're a great team.
19 DR. FREEMAN: I must say I echo Eva's point.
20 Rayaz knows where I stand on this. I do think it
21 might be nonspecific, but let's -- so we've said 2
22 out of 3. I think we do need to have this

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1 discussion.
2 DR. OAKLANDER: We submitted a clinical
3 trial grant to NINDS [inaudible - off mic].
4 DR. FREEMAN: NINDS has nixed lots of grants
5 with CCM, without CCM.
6 DR. FELDMAN: That has nothing to do with
7 CCM.
8 DR. GIBBONS: I want to weigh in just from a
9 slightly different perspective. I'm also not
10 comfortable with CCM, but at the same time, I think
11 I'm no less comfortable with it than QST or QSART,
12 which I think have their own problems. I think it
13 still, in conjunction with these others, gives us
14 support.
15 DR. FREEMAN: Do we have enough? Jen, who's
16 chatting over there, do we have enough to word this
17 appropriately? Does anybody leaving want to add
18 anything to this, including Rayaz?
19 DR. LAURIA: I'm leaving, so make it nice
20 [inaudible - off mic].
21 (Laughter.)
22 DR. FREEMAN: Can we word this appropriately

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1 to -- yeah?
2 DR. SMITH: I'm questioning, and someone
3 made this point yesterday, and I can't remember who
4 it was. We have a set of tier 2 tests that I bet
5 the majority in the room, an overlapping Venn
6 diagram is uncomfortable with each one individually
7 in some way or another.
8 Does a combination of two of these tests
9 that we're just not very excited about actually add
10 additional validity or is it just making us
11 comfortable with it?
12 DR. FREEMAN: Are you multiplying the
13 discomfort? I think that's the challenge.
14 DR. SMITH: Or are we hiding the discomfort?
15 DR. FREEMAN: Yes.
16 DR. SMITH: Someone made this point
17 yesterday, and I can't remember who, the data to
18 drive our --
19 DR. FELDMAN: I just don't think we have
20 enough data to include CCM.
21 DR. FREEMAN: Are we talking CCM or --
22 DR. FELDMAN: I've been trying to be

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1 convinced otherwise for many, many years, but I
2 really do think it's still -- it's simply not there
3 yet. This is an opinion, but it's not an opinion
4 just based on emotion. I mean, it really is an
5 opinion based on data, in fact, and Rayaz knows
6 that. That's the reason he commented.
7 DR. FREEMAN: And I think none of us are
8 hiding this from Rayaz.
9 David Herrmann?
10 DR. HERRMANN: QSART's localizing; QST
11 isn't. But at least those are being assessed
12 somewhat in the distribution of -- the stimulus is
13 being applied in the distribution of where patients
14 are experiencing maximal symptoms, for what that's
15 worth.
16 DR. FREEMAN: I have growing comfort with it
17 as a surrogate measure, growing comfort. I'm not
18 entirely comfortable, but I share that view, and I
19 don't know as much about the data.
20 So I think we're not going to resolve this
21 here. Let us word this in a way that perhaps
22 satisfies everybody. I think as we've allowed

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1 people to ventilate a little bit, it's become clear
2 that there's not as much comfort with the technique
3 as all that.
4 Anybody want to add anything to the
5 discomfort -- to the discussion?
6 (Laughter.)
7 DR. FELDMAN: Are we saying -- [inaudible -
8 off mic]?
9 DR. FREEMAN: Well, we are saying that there
10 are this group of tests, and we will word it
11 appropriately to say that there are issues with all
12 of these tests, and they are different issues, and
13 that there are challenges with including these,
14 what we are calling tier 2 tests, in a clinical
15 trial for X, Y, and Zed reasons. I think I can
16 work with this.
17 DR. FELDMAN: Are you going to say 2 of the
18 3 equate a tier 1? I thought David made a really
19 good point -- I guess he left -- but the idea that
20 if someone is really interested more in function
21 and really doesn't care about the INFD, they would
22 want that as their inclusion criteria. I hadn't

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1 thought of it that way, but it was a very nice
2 point.
3 DR. FREEMAN: And I think it's a very
4 reasonable point.
5 So certainly, there are the two,
6 quantitative sensory testing and autonomic testing.
7 Again, very few centers can do these with
8 sophistication.
9 DR. FELDMAN: I agree.
10 DR. FREEMAN: To some extent, in a clinical
11 trial -- which is really why we're here -- I think
12 this is not as big an issue as all that. And I
13 think we can deal with this I think quite
14 reasonably. And I'm not sure that we should have
15 the two of the three, and perhaps word it in the
16 way that David suggested rather than move two or
17 three of them, move up.
18 DR. FELDMAN: So include all three of them
19 with a measured discussion.
20 DR. FREEMAN: Exactly.
21 DR. FELDMAN: I think that's a fair
22 approach.

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1 DR. FREEMAN: Okay. So one or two more
2 areas of discussion. Thanks so much for staying.
3 I want to define the idiopathic. And idiopathic
4 means that we've excluded all causes of neuropathy,
5 and clearly there would be very few arguments about
6 including these three: plasma glucose, B12, and
7 perhaps a little argument about with and within
8 without metabolites, and using serum protein,
9 immunofixation, electrophoresis. I think no
10 arguments about that.
11 Let me just get a show of hands from the
12 neurologists in the room for Biogen doing the trial
13 for Kromasil doing the trial for Aptinex. Should
14 they do B12 metabolites? What's the decision tree?
15 Chris?
16 DR. GIBBONS: Yes.
17 DR. FELDMAN: I don't know the data. Are
18 there data there to support that?
19 DR. GIBBONS: For methylmalonic acid?
20 DR. FELDMAN: I mean, rather than --
21 DR. FREEMAN: High methylmalonic acid, where
22 the cutoff should be excluded, is what Chris is

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1 saying.
2 Brian's view is what?
3 DR. FELDMAN: B12.
4 DR. FREEMAN: B12 alone. Gordon?
5 DR. SMITH: The way we handle this is B12,
6 and then for borderline B12, follow up with
7 metabolites. And then I guess the question
8 is -- we've sort of slipped through the prediabetic
9 state.
10 DR. FREEMAN: Oh, no. We haven't slipped.
11 DR. SMITH: Okay. You're going to come back
12 to that?
13 DR. FREEMAN: We have not.
14 DR. SMITH: I agree with Eva.
15 DR. FREEMAN: What are you agreeing with?
16 What are you saying?
17 DR. SMITH: B12.
18 DR. FREEMAN: B12 only. In a borderline --
19 DR. SMITH: Then metabolites.
20 DR. FREEMAN: Metabolites. And how do you
21 deal with metabolites?
22 DR. SMITH: I've hoped well.

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1 (Laughter.)
2 DR. FREEMAN: Let's see how you do it. So
3 an elevated methylmalonic acid.
4 DR. SMITH: Yes, someone with a borderline
5 B12 with an elevated MMA is out.
6 DR. HOKE: Where is the data to say that
7 those are actually B12 responsive small fiber
8 neuropathy patients? A lot of these, I treated
9 them, and they don't improve.
10 DR. SMITH: As I mentioned yesterday, the
11 way we're handling this in one trial is that
12 patient, we supplement. They come back I think
13 three months later, and if there's no
14 change -- maybe 3 or 6 months. If there's no
15 change in their phenotype, we assume that this was
16 an irrelevant or non-related abnormality, and then
17 we enroll them. And then for the other trial,
18 we're a little more restrictive.
19 DR. FREEMAN: Bear in mind that you want to
20 err on the side of specificity in a clinical trial
21 and this is different to clinical practice.
22 DR. SMITH: And the one where we're allowing

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1 it, these are diabetic patients, so they were
2 hiding under the cover of diabetes.
3 DR. FREEMAN: All right. And I think with
4 the autonomic, we say that we want to exclude a
5 specific cause, and the only obvious cause is the
6 acetylcholine receptor antibody.
7 Anne Louise?
8 DR. OAKLANDER: These are the AAN guidelines
9 for [inaudible - off mic].
10 DR. FREEMAN: Okay.
11 DR. OAKLANDER: [inaudible - off mic].
12 REPORTER: I'm not getting you --
13 MALE VOICE: You have to turn the mic on.
14 DR. OAKLANDER: I don't know why it turns
15 off.
16 These are the AAN guidelines for evaluation
17 of sensory polyneuropathy, not for small fiber
18 neuropathy. And while there's a robust literature
19 linking M proteins to demyelinating
20 polyneuropathies, I'm not aware of a literature
21 linking it to small fiber polyneuropathy.
22 DR. FREEMAN: Well, yes and no. I mean

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1 there is at least an association with M spikes and
2 autonomic neuropathy. And I would say that you
3 don't want in any kind of peripheral neuropathy
4 trial to have patients who have a paraproteinemia.
5 It would be, to me, intuitively obvious.
6 Let's move on to the others that perhaps are
7 to a larger extent associated with small fiber
8 neuropathy, and I've left out HIV. What should we
9 do?
10 Gordon, perhaps you can weigh in on this.
11 This was your topic. What should Biogen do in
12 their clinical trial? How many of these should
13 they do? What should they not? Just go through,
14 you said B6 should be done to look at toxicity.
15 DR. SMITH: No. I said no, no, no, no, no,
16 no, no, no, no, no, no, no, no and no.
17 (Laughter.)
18 DR. FREEMAN: So I just want to be clear on
19 that. You would say that a clinical trial can be
20 done without doing a metabolic screen, without
21 checking renal function, without checking liver
22 function, without TFTs?

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1 DR. SMITH: Yeah. No. Joking aside, I
2 think doing basic metabolic and CBC is a prudent
3 thing to do. But in terms of checking ANA, and sed
4 rate, ACE and so forth, I would say no.
5 DR. FREEMAN: Okay. Even given the large
6 Netherlands predisposition, a prevalence of sarcoid
7 in their series, you think that is --
8 DR. OAKLANDER: We looked at ACE. In our
9 2016 paper, we looked specifically at ACE because
10 it was so often abnormal. And those patients were
11 tested -- the ACE-positive patients were tested for
12 sarcoid. None of them had it. ACE is positive.
13 We checked at MGH. There's like a 30 percent rate
14 of ACE positivity among all the ACE tests run at
15 MGH.
16 DR. FREEMAN: Okay, we get it. Anybody who
17 would think that any of these, including HIV,
18 should be done as an assessment?
19 DR. RUSSELL: Roy, can't you just leave it
20 open that specific causes of neuropathy should be
21 excluded and leave it up to the judgment of the
22 investigators?

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1 DR. FREEMAN: We can certainly --
2 DR. RUSSELL: Because otherwise, you're
3 going to drive yourself crazy. I mean, you've got
4 to exclude celiac disease. You've got to exclude
5 this and --
6 DR. FREEMAN: I'm totally fine with that.
7 (Crosstalk.)
8 DR. RUSSELL: You've got to exclude this and
9 [indiscernible.]
10 DR. FREEMAN: I think that that's absolutely
11 acceptable.
12 Chris?
13 DR. FELDMAN: I agree, James.
14 DR. GIBBONS: There is a bundled question
15 with this, and you're implying that part of the
16 clinical trial, I think you're going to be required
17 to hit multiple ones, LFTS, CBCs --
18 DR. FREEMAN: And they will. They will
19 certainly do that.
20 (Crosstalk.)
21 DR. GIBBONS: That will be part of the
22 trial --

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1 DR. FREEMAN: They don't want to give their
2 drug to patients who have renal failure, liver
3 failure, all of those things.
4 DR. FREEMAN: Right. But the question
5 ultimately, is that going to be the exclusion
6 criteria for small fiber neuropathy? And it seems
7 like no.
8 DR. FREEMAN: Okay. I think we're all on the
9 same page with this. The elephant in the room is
10 this one, and I'm going to just float something up
11 in the interest of time, and that is to say we
12 don't know the relationship between small fiber
13 neuropathy
14 in its various forms and the prediabetic state. We
15 don't know whether it's causative, we don't know
16 whether it's associated, we don't know whether it's
17 the fact that it is present in one-third of the
18 U.S. population, and you are bound to see some
19 patients with it.
20 I know there are arguments on both sides of
21 the equation. The epidemiology, as Gordon
22 mentioned, are not perfect -- as Rob mentioned, the

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1 epidemiology is not perfect. My floating balloon
2 would be to say that this is pure small fiber
3 neuropathy. This is a mixed small fiber
4 neuropathy. This is small fiber sensory
5 predominant neuropathy in a patient with impaired
6 glucose tolerance. That would be my suggestion,
7 and there's yet another discussion, which will be
8 as to whether we can just look to fasting plasma
9 glucose and hemoglobin A1C, or whether we need to
10 use the 2-hour postprandial glucose.
11 So the balloon is that we will say this is
12 what the patient has, more neuropathy in one, two,
13 or three flavors, or without impaired glucose
14 tolerance.
15 How does that sit?
16 DR. LEVINE: I think that's a great idea,
17 And I would try to word it even a little more
18 strongly because if we've got three pharma
19 companies here and more pharma companies getting
20 into this field, it would be a huge waste of
21 potential data not to capture this. So I think we
22 capture it, but we don't necessarily have to

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1 exclude somebody on the basis of IGT because we
2 don't know that that's necessarily causative. so I
3 agree.
4 DR. FREEMAN: Okay.
5 DR. SMITH: I don't think you need to do a
6 glucose tolerance test. It would be great to have
7 data. And if our pharma colleagues would like to
8 do it, we'd be very excited to have it. But I
9 think the real question is not prediabetes, and
10 from my perspective, I don't think you need to do a
11 2-hour glucose tolerance test to determine if
12 someone in whom you don't have clinical suspicion
13 of diabetes has diabetes.
14 So I think that's sort of the second; can
15 you get by with a fasting plasma glucose for an
16 A1C, and I would say yes to those/
17 DR. FREEMAN: I think most of us would agree
18 with that.
19 DR. OAKLANDER: Our 2016 paper supported
20 that.
21 DR. FREEMAN: Anybody disagree? Anybody
22 says it's obligatory to do a glucose tolerance

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1 test?
2 DR. FELDMAN: Well, the ADA no longer says
3 it's obligatory. So I think the ADA now new
4 guidelines is not obligatory. So you can just --
5 DR. FREEMAN: This is newer than 2016?
6 DR. FELDMAN: Yes. No, they just came out
7 with an addendum in 2017. I believe I have it on
8 this computer, where I think you can just use
9 F -- actually, I think it was just A1C.
10 DR. FREEMAN: Oh, really?
11 DR. OAKLANDER: We should follow the ADA
12 guidelines.
13 DR. FREEMAN: Yes, I think that will make
14 everybody happy.
15 DR. FELDMAN: I'll get that from Rodica and
16 sent it to you.
17 DR. FREEMAN: That would be great.
18 So all that remains really is the special
19 criteria for an immune-mediated small fiber
20 neuropathy and then additional discussion.
21 Todd, you want to take us there?
22 DR. LEVINE: Yeah. I don't have an answer.

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1 I think the difficulty is, if you start doing
2 enough tests, you will find some things that are
3 abnormal, like ACE levels and ANAs and SSAs in a
4 significant percentage of these people, and it
5 doesn't necessarily mean that they have that
6 disorder. So it's a question of how you define it.
7 In someone with known sarcoid who develops a small
8 fiber neuropathy --
9 DR. SMITH: Let's go with -- we're in the
10 idiopathic world. My take on it --
11 DR. LEVINE: Is any testing needed to
12 exclude --
13 DR. FREEMAN: What I'm asking -- and it's a
14 very simple question. And the reason why I don't
15 have a slide, despite
16 you sending me those slides, is I don't have an
17 onset because I'm not sure that we are there yet,
18 and I want to be sure that you are --
19 DR. LEVINE: I think you can just say -- I
20 would exclude patients with known autoimmune
21 disease.
22 DR. FREEMAN: Okay. So in the patient with

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1 known autoimmune disease, you are designing a
2 clinical trial with an immunomodulatory agent. Is
3 there anything special that you would do? Karin
4 Faber made the point yesterday -- and she's gone
5 now -- saying that in her clinical trial with IVG
6 she's doing at the moment, it's the same old stuff.
7 She's not doing anything special to increase the
8 probability of a response.
9 Are you in concurrence with that?
10 DR. LEVINE: No. So again, the one that
11 Chris and I are working on, although we can argue
12 about whether Pestronk's antibodies mean anything,
13 we're specifically choosing patients that have one
14 of those two auto antibodies.
15 DR. FREEMAN: Of the antibodies, yeah.
16 DR. LEVINE: Now again, it may or may not
17 work; that may not mean anything. But I think if
18 you're trying to design a trial for an autoimmune
19 disease, or with immunomodulatory therapy and
20 presumed autoimmune disease, you need some
21 evidence, and your paper as well.
22 DR. OAKLANDER: Yeah.

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1 DR. FREEMAN: What do you think, Anne
2 Louise?
3 DR. OAKLANDER: Well, I don't think you
4 should be giving immunomodulatory therapies to
5 people unless you think they have -- unless they
6 have an immune cause.
7 DR. FREEMAN: Are you telling us that no
8 patient with a small fiber neuropathy, without a
9 known autoimmune disease, should get IVIG? Is that
10 what you're saying, I a clinical trial?
11 DR. LEVINE: Or some evidence of an
12 autoimmune disease.
13 DR. FREEMAN: Some evidence.
14 DR. OAKLANDER: So here are things that I
15 think. And it's very imperfect, so I'm not saying
16 anything cast in stone. But what everybody uses as
17 evidence is, number one, presence of a systemic --
18 DR. FREEMAN: I just want to be clear. We
19 are excluding. We are dealing in the idiopathic
20 world, so there's no --
21 DR. OAKLANDER: How about doing an SSA/SSB?
22 I mean, Sjogren's is so common.

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1 DR. FREEMAN: No, because those are not
2 idiopathic. Those are small fiber neuropathy due
3 to Sjogren's.
4 DR. OAKLANDER: Right, but that's what I
5 meant. Should we include SSA? I thought we were
6 voting on what blood tests.
7 DR. FREEMAN: You voted, and we said -- I
8 want to be clear with the question.
9 (Crosstalk.)
10 DR. OAKLANDER: I don't understand the
11 question.
12 DR. LEVINE: Are you asking should patients
13 with idiopathic small fiber neuropathies be
14 enrolled in autoimmune or immunomodulatory
15 therapies/
16 DR. FREEMAN: It's not even that. It
17 actually is you decide that there may be an
18 immunological cause of an idiopathic small fiber
19 neuropathy. You want to set up a clinical trial.
20 You're an IVIG company, and you want to do a
21 clinical trial. And you can do one of two things.
22 You can take the current fiber approach and say we

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1 just don't know at this point; we are going to
2 treat every idiopathic peripheral neuropathy
3 patient in a clinical trial. Or you can say, okay,
4 I want to increase the likelihood of a response, so
5 I want to have these entry criteria: rapid onset,
6 severe symptoms; some immunological marker, which
7 is not a disease, but may or may not be an API
8 phenomenon; something, want to do a skin biopsy and
9 see inflammatory markers.
10 I'm throwing up what could be possible ways
11 to increase the probability of response time,
12 giving you the potential to enrich your clinical
13 trial. That's what I'm really saying. What is
14 your enrichment strategy or are we not there yet?
15 DR. LEVINE: Well, we don't have any data
16 for it, but I think something close to the table
17 that I tried to present yesterday with all the
18 variables that you just mentioned gets us close.
19 DR. OAKLANDER: And I would add prior
20 response to immunotherapy to the list. If a
21 patient comes in and said, "Doc gave me a Medrol
22 dose pack for something else, and Oh my God, my

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1 neuropathy was really improved."
2 DR. FREEMAN: Okay. Eva and James.
3 DR. RUSSELL: Roy, can I just actually read
4 the 2018 ADA criteria so everyone's clear about
5 this?
6 DR. FREEMAN: Two thousand and what?
7 DR. FELDMAN: Eighteen.
8 DR. RUSSELL: 2018. "Diabetes may be
9 diagnosed based on plasma glucose criteria, either
10 the fasting plasma glucose or the 2-hour plasma
11 glucose value during 75-gram oral glucose tolerance
12 test or A1C c criteria, which you've got up there.
13 Generally, fasting plasma glucose, 2-hour plasma
14 glucose during the 75-gram oral glucose tolerance
15 test and the A1C are equally appropriate for
16 diagnostic testing."
17 DR. FELDMAN: Right. So those are the new
18 criteria. So that's why I'm saying we can just
19 use A1C.
20 DR. FREEMAN: So that's pretty much this,
21 isn't it?
22 (Crosstalk.)

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1 DR. RUSSELL: You can use any of those.
2 DR. FREEMAN: I don't think it's actually
3 changed.
4 DR. RUSSELL: It hasn't.
5 DR. FREEMAN: So it's any one of these
6 three.
7 DR. FELDMAN: So we can just use that.
8 DR. FREEMAN: Go back to the question that
9 we were discussing. Is there -- and this is I
10 think pretty much my last point -- is there any way
11 that we should suggest that an immunomodulatory
12 trial could be enriched or are we not there yet?
13 DR. HAROUTOUNIAN: I think it's very trial
14 specific, so I don't think it should be in our core
15 criteria, but we can certainly suggest researchers
16 who are doing trials in disease-modifying -- those
17 kinds of agents, that they can consider reaching
18 their trials by those parameters.
19 DR. GIBBONS: Certainly one of the
20 challenges you're asking and we're sort of facing
21 is that many of the presumed problems may not yet
22 have been identified. So as new antibodies come on

1 board that we think are pathogenic, that would make
2 sense, and that would be part of the trial
3 question. But I think if there is a presumption of
4 associated immunomodulatory mechanism, then yes.

5 DR. FREEMAN: So I'm hearing or at
6 least -- and part of this is my sentiment that
7 we're not there yet and that we can suggest, to
8 tease that, are in the wings and an approach. But
9 there is nothing definitive yet about an
10 immunomodulatory trial.

11 DR. LEVINE: I know you keep saying this, so
12 I know you're going to yell at me. But I think in
13 this section, in talking about trial design, we
14 have to talk about objective outcome measures. So
15 autonomic testing biopsies --

16 FEMALE VOICE: Agreed.

17 DR. LEVINE: -- we've got to make that --

18 DR. FELDMAN: But that's not what we're
19 doing at this meeting.

20 DR. LEVINE: No, I know.

21 DR. FREEMAN: There's no doubt, of course.

22 Todd, I'm going to yell at you.

1 DR. LEVINE: See? Told you.

2 (Laughter.)

3 DR. LEVINE: At least I was prepared.

4 DR. FREEMAN: And on that note, unless
5 anybody has anything else to add, I think --

6 DR. FELDMAN: I want to thank you because
7 you have actually herded cats. And we actually
8 have I think a fairly good consensus, which I
9 wasn't sure we were going to be able to reach. So
10 thank you, Roy. I mean that, very much.

11 (Applause.)

12 DR. FREEMAN: This has been really
13 interesting. I've learned an enormous amount. My
14 dog just bit his dog walker yesterday, but other
15 than that, I would say --

16 (Laughter.)

17 Adjournment

18 DR. FREEMAN: -- it hasn't been herding
19 cats; it's been herding dogs.

20 (Whereupon, at 3:01 p.m., the meeting was
21 adjourned.)

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