

*ACTION - CONCEPT MEETING ON  
SMALL FIBER NEUROPATHY*

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*April 5, 2018*

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1 associated with the presidency.  
2 (Laughter.)  
3 DR. FREEMAN: So, Bob, it's a pleasure.  
4 Presentation - Robert Dworkin  
5 DR. DWORKIN: Now that we've gotten my  
6 political affiliation out of the way --  
7 (Laughter.)  
8 DR. DWORKIN: -- I'd like to welcome all of  
9 you on behalf of the ACTTION public/private  
10 partnership to this meeting. I think this is going  
11 to be a really interesting and exciting meeting.  
12 And I just want to spend a couple of words for any  
13 of you who may not be familiar with ACTTION,  
14 talking about really what ACTTION is.  
15 The acronym ACTTION stands for Analgesic,  
16 Anesthetic, and Addiction Clinical Trial  
17 Translations, Innovations, Opportunities, and  
18 Networks. ACTTION is a public-private partnership  
19 that was established by the FDA, the U.S. Food and  
20 Drug Administration, in 2010. And I don't see any  
21 of them in the room, but the people who are really  
22 responsible for launching this and then shepherding

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1 this public-private up today are Bob Rappaport, who  
2 many of you know, who's the director of that  
3 division at the FDA for 15 or 16 years, and then  
4 his successor, Sharon Hertz. And the person who  
5 takes care of ACTTION on day-to-day basis is  
6 Allison Lin. I wish all three of them were here,  
7 but I don't see them, because ACTTION and all of us  
8 wouldn't be here without the efforts of the three  
9 of them.  
10 FDA's notion of ACTTION was to set up a  
11 public-private partnership with multiple  
12 stakeholders, and I think we've succeeded with  
13 that. We have representation from major  
14 professional societies, including the AAN, but also  
15 rheumatology, pain, anesthesiology, et cetera,  
16 organizations.  
17 There is great participation from industry,  
18 academic experts, patient advocacy organizations,  
19 and I'm sure I'm leaving other government agencies,  
20 NIH, CDC, DEA, and SAMHSA. That was the FDA's  
21 notion of a public-private partnership -- and I  
22 hope I'm not leaving anybody out -- and I think

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1 that's occurred.  
2 The mission of ACTTION -- and I'm sure this  
3 isn't the exact wording, and this was really the  
4 FDA's intent from the start -- was to do whatever  
5 is necessary to accelerate the development of  
6 improved therapeutics in what is now four different  
7 therapeutic areas. It was originally just pain,  
8 and then expanded to include anesthesia and  
9 sedation; also addiction medicine, treatment of  
10 addiction; and finally disease modification in  
11 peripheral neuropathy. So those are the four  
12 different therapeutic areas that ACTTION has  
13 ongoing activities in.  
14 It's important to emphasize, we don't really  
15 address whether this or that drug, or device, or  
16 class of therapeutics is efficacious or safe and  
17 tolerable. So we don't do what Cochrane  
18 collaboration does, which is systematic reviews of  
19 literature or treatment guidelines.  
20 What the focus of all of ACTTION's  
21 activities really is, is to improve the kind of  
22 pathway I guess from preclinical research to

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1 getting a drug on the market, the sort of  
2 translational pathway. At the start, we didn't  
3 have very many activities in preclinical research.  
4 We've really ramped that up recently and have a  
5 whole effort ongoing now involving rigor and  
6 reproducibility of preclinical research.  
7 So what are the kinds of things that ACTTION  
8 focuses on? Meetings, studies, reviews of the  
9 literature relevant to inclusion/exclusion criteria  
10 in clinical trials; outcome measures for clinical  
11 trials; the right way of analyzing clinical trial  
12 data; for example, what do you do about imputing  
13 missing data, which is a very timely issue.  
14 Interpretation of clinical trial data;  
15 diagnostic criteria; actually developing improved  
16 outcome measures. Maybe I already said that; and  
17 also a number of studies where we've examined how  
18 clinical trials get reported in the literature and  
19 various inadequacies or shortcomings in the way  
20 that clinical trials and their results are  
21 reported. So those are the kinds of activities  
22 ACTTION has undertaken over the past, what, seven

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1 or eight years.  
2 For any of you who are interested, the funds  
3 have come from two contracts from FDA and two  
4 cooperative agreements. We're currently in the  
5 second year of a five-year cooperative agreement  
6 and towards the end of a five-year contract that we  
7 hope will be renewed next year. The FDA contracts  
8 and FDA cooperative agreements give us different  
9 kinds of prerogatives, so it's nice to have both a  
10 contract and cooperative agreement simultaneously.  
11 In addition to funds from FDA, we get unrestricted  
12 support from industry, and we also have a little  
13 bit of philanthropy and a little bit of royalties  
14 from outcome measures that have been published  
15 under the auspices of ACTTION.  
16 So I want to end these remarks by just  
17 saying that we're very proud that ACTTION has now,  
18 since it was launched in 2010, published over 80  
19 articles in peer-reviewed major journals, journals  
20 that you are all familiar with: neurology,  
21 anesthesiology, pain, Journal of Pain. So we are  
22 very proud of that milestone. I think it's about

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1 85 publications as of this morning.  
2 If you're interested in any other  
3 information about ACTTION, the website is really  
4 quite comprehensive, and it's ACTTION with two  
5 T's.org. I want to answer any questions, so if you  
6 have any questions, raise your hand. But before I  
7 leave the podium, I want to say that the CONCEPT  
8 consortium, which is responsible for the disease  
9 modification in the peripheral neuropathy component  
10 of ACTTION, has been led by Roy and Jen Gewandter  
11 for the last five or six years, and I just think  
12 they've done a fantastic job. And without Roy and  
13 Jen's efforts, we wouldn't be here. And I'm sure  
14 this is going to be a great meeting because of all  
15 the work they've put into it.  
16 So thank you very much, welcome, and does  
17 anybody have any questions about ACTTION or what it  
18 does?  
19 (No response.)  
20 DR. DWORKIN: Thank you.  
21 Presentation - Roy Freeman  
22 DR. FREEMAN: Thanks, Bob, for setting up

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1 the meeting.  
2 What I want to do is to in the next -- I  
3 have been given 45 minutes, and it will be far, far  
4 less, so we can get the meeting going -- is really  
5 set the stage for what's going to proceed over the  
6 next two days.  
7 Now, for those of us in the field, it is a  
8 very exciting time for small fiber neuropathy. The  
9 small nerve fibers for decades were regarded as  
10 invisible, inaccessible, unmeasurable. But over  
11 the past maybe 10, 20 years, suddenly they have  
12 emerged from darkness, and now almost every  
13 neurology department has somebody there who is  
14 capable of assessing, measuring, and is interested  
15 in these small nerve fibers. But as a consequence  
16 of those years of darkness, the entity, the  
17 disease, small fiber neuropathy, was poorly  
18 understood, poorly studied. Patients who had the  
19 disease were inadequately treated, and that has  
20 changed dramatically.  
21 Now for the first time we have target-based  
22 therapies addressed at patients who have small

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1 fiber neuropathy, a very, very exciting change.  
2 And this change is in large part due to the  
3 emergence of structural and functional measures to  
4 address the small nerve fibers, both the small  
5 sensory nerve fibers and the autonomic fibers. And  
6 I think it is because of that, that we are here  
7 today.  
8 I want to very briefly touch on what  
9 CONCEPT is. As you may have gathered, somebody in  
10 the ACTTION framework is a lover of misspelled  
11 acronyms --  
12 (Laughter.)  
13 DR. FREEMAN: -- or perhaps just has a  
14 typewriter with a sticky key.  
15 CONCEPT is the Consortium on Clinical  
16 Endpoints and Procedures for Peripheral Neuropathy  
17 Clinical Trials. This emerged, as Bob  
18 suggested -- Bob Rappaport has been a driving force  
19 for ACTTION and all of the subsidiaries under  
20 ACTTION, and some years ago, he raised awareness of  
21 the fact that there is no drug approved in the  
22 United States for axonal peripheral neuropathy.

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1 And if I were to envision what CONCEPPT is about,  
2 it is to provide the framework -- and I think Bob  
3 touched on this briefly -- the framework for the  
4 development of drugs for axonal peripheral  
5 neuropathy so those patients who have those  
6 devastating diseases that are a consequence of  
7 axonal peripheral neuropathies, we'll have  
8 therapies to address them.

9 When I say we, the co-director Jen Gewandter  
10 and I have taken a field of dreams kind of approach  
11 to it, that we want to provide the framework, and  
12 hopefully as a consequence of that, from academia,  
13 from industry, we will have the drugs to treat  
14 these devastating diseases.

15 To touch very briefly on some of the  
16 activities over the past couple of years, we have a  
17 series of papers that, as Bob mentioned, have been  
18 published here on Measurement Tools for Peripheral  
19 Neuropathy, again, establishing the framework; one  
20 on the Content Validity of Symptom-Based Measures,  
21 which was published in Muscle and Nerve; a  
22 manuscript in preparation with Chris Gibbons and

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1 Jen Gewandter on clinician related sign measures  
2 for peripheral neuropathy; just published in  
3 Neurology last year, an overview with  
4 chemotherapy-induced peripheral neuropathy clinical  
5 trials; and a manuscript, which has received the  
6 first set of very good reviews and I'm sure will be  
7 published in Neurology on clinical trial design for  
8 the prevention of chemotherapy-induced peripheral  
9 neuropathy.

10 So that's where this stands at the current  
11 point, and then finally -- oh, how could I forget?  
12 Just last year, we had a meeting at the end of the  
13 year, a number of the audience members were there,  
14 on developing the taxonomy for diabetic peripheral  
15 neuropathy. I should not use the word  
16 "developing," "refined" because we are building on  
17 the shoulders of giants. There are several  
18 taxonomic approaches to diabetic peripheral  
19 neuropathy, but we wanted to modernize this for the  
20 future, and we are hoping that at least two  
21 manuscripts will come from that meeting.

22 Finally, the present meeting, and Simon

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1 Haroutounian is working on a systematic review on  
2 clinical trials and inclusion/exclusion criteria,  
3 up until this point in time, on small fiber  
4 neuropathy. And we hope to come out of this  
5 meeting with a case definition, inclusion/exclusion  
6 criteria, for small fiber clinical trials. And  
7 that really is our charge today. We will stray  
8 from that charge just a little on either side, but  
9 if I were to think of what we at the end of the  
10 meeting want to accomplish, it will be that.

11 So let me now begin to talk a little about  
12 the roadmap for the meeting. And you have your  
13 agendas in front of you. What I want to do in the  
14 next couple of minutes is just touch on what I  
15 think the issues are where perhaps there will be  
16 some areas of controversy. And this I hope will be  
17 one in which there is no controversy at all. We  
18 will begin by discussing the epidemiology and the  
19 dimensions of the problem. Rob Singleton will be  
20 doing that. He will be discussing national  
21 differences. He will be talking about impaired  
22 glucose tolerance, the epidemic that exists around

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1 the world and how that fits in to our concepts of  
2 the epidemiology of small fiber neuropathy.

3 Then at another point, but I think it gels  
4 very nicely with the epidemiology, Gordon Smith  
5 will be talking about the laboratory workup for  
6 small fiber neuropathy, what do we need to do? How  
7 much is enough? When do we define a peripheral  
8 neuropathy, and here in this case specifically,  
9 small fiber neuropathy, as idiopathic? What  
10 combinations of tests are necessary? What about,  
11 again, the neuropathy at the meeting we had in  
12 December? We decided it should be called the  
13 neuropathy associated with, carefully chosen, not  
14 caused by, impaired glucose tolerance.

15 Does this mean that every patient in a trial  
16 for small fiber neuropathy needs to have a glucose  
17 tolerance test? Because the epidemiology or the  
18 prevalence of impaired glucose tolerance is so  
19 vast, is it just that we have a very common  
20 disorder associated occurring in conjunction with a  
21 less common disorder, and these are not causal?

22 Is idiopathic peripheral neuropathy

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1 compatible with impaired glucose tolerance or are  
2 these two different entities? As we've learned, we  
3 will talk about the various polymorphisms or even  
4 inherited disorders for Reye's disease that are  
5 associated with small fiber neuropathy.  
6 Do we consider a patient with a sodium  
7 channel polymorphism as having idiopathic small  
8 fiber neuropathy or is this a new discrete entity  
9 and we should no longer consider this small fiber  
10 neuropathy? And what about a patient who had a  
11 potential cause of a small fiber neuropathy? For  
12 example, B12 deficiency. It was treated a number  
13 of years ago. Can a patient like this enter a  
14 clinical trial? Is this an idiopathic small fiber  
15 neuropathy or are patients like that excluded from  
16 clinical trials?  
17 We have now entered the molecular era with  
18 small fiber neuropathy, and a question that must be  
19 asked is, is it obligatory now in this era to  
20 genotype every patient that enters a small fiber  
21 neuropathy trial? Do we need, in conducting a  
22 clinical trial, to balance or stratify

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1 randomization based on the genotype? What are the  
2 therapeutic implications? Are different drugs  
3 going to work or not work in patients who have  
4 different genotypes?  
5 How do we tie the beautiful, elegant work  
6 that comes from the Netherlands, comes from Italy,  
7 with this study that was done from the PNRR? It's  
8 a different methodology. It's a registry study,  
9 but is discordant with the results that come from  
10 Italy, and I'm sure this will be an area of Italy  
11 and the Netherlands. I'm sure this will be an area  
12 of discussion.  
13 All of us in the field have been challenged  
14 by patients who appear in our clinics either having  
15 been treated, or on treatment, or desirous of  
16 treatment with immunomodulating therapy, and we  
17 will be addressing the question is there an  
18 immune-mediated small fiber neuropathy. If so,  
19 what is the clinical phenotype? Are there  
20 biomarkers, diagnostic biomarkers, for this  
21 disorder? Are there predictives of treatment  
22 response for this disorder? And we have a number

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1 of experts in the audience who will be discussing  
2 this.  
3 Finally, or almost finally, we have a number  
4 of questionnaires in various stages of development.  
5 Some of these may be screening questionnaires, some  
6 of these may be diagnostic questionnaires, some of  
7 these may be phenotype-defining questionnaires, and  
8 these will be discussed as well.  
9 One of the important questions is do we in  
10 these clinical trials need disease-specific  
11 questionnaires or are the general sensory pain  
12 questionnaires, autonomic questionnaires,  
13 sufficient at this point in time? And in terms of  
14 thinking of the framework, this is a very important  
15 part of the framework.  
16 The focus of the meeting is going to be on  
17 inclusion criteria, and one of the important  
18 questions with inclusion criteria is, is a skin  
19 biopsy actually necessary for inclusion enrollment  
20 in a clinical trial? Now, all of us in the field  
21 are totally aware that this is a benign procedure.  
22 Many in the audience have pockmark legs from

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1 repeated skin biopsies --  
2 (Laughter.)  
3 DR. FREEMAN: -- and are very aware that  
4 this is, as we say in the field, a benign  
5 procedure. However, there is the consensus out  
6 there that somewhere between a liver transplant and  
7 a heart transplant lies a skin biopsy --  
8 (Laughter.)  
9 DR. FREEMAN: -- and we have members of  
10 industry in the audience, and it is a barrier to  
11 clinical trial inclusion. And there's no doubt  
12 that those who are in the drug development business  
13 would love it if we could say, well, this is a very  
14 reasonable substitute for skin biopsy. And indeed,  
15 Giuseppe Lauria, who is sitting at the back very  
16 quietly, in his disease-defining criteria said two  
17 of the following three, and only one of those three  
18 was skin biopsy. So it is using those very widely  
19 used criteria to define small fiber neuropathy  
20 possible to exclude skin biopsy. But if we decide  
21 that skin biopsy is objective and it is obligatory,  
22 can it be done by everybody?

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1 Now, as I mentioned, there are many  
2 laboratories around the country, widespread  
3 availability of skin biopsies, to assess  
4 intraepidermal nerve fiber density. Is one  
5 laboratory the same as another? And what about the  
6 patient in a clinical trial who had intraepidermal  
7 nerve fiber density assessed 6 months ago, 1 year  
8 ago, 2 years ago? When is the cutoff? When has  
9 too much time elapsed since the last biopsy?  
10 What about QST? Is QST in there, another  
11 one of the criteria that is used very frequently in  
12 clinical trials, or in cohort studies, intervention  
13 studies? Is QST necessary? Not everybody has the  
14 \$30,000 computer-aided QST equipment. Can one just  
15 use a structured clinical examination for small  
16 fiber neuropathy or even just a structured clinical  
17 examination in general, or just a clinical  
18 examination?  
19 What about bedside QST? My group and a  
20 number of the groups have attempted to come up with  
21 a simple, quantified sensory examination using very  
22 simple equipment that can, perhaps for those who do

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1 not have the \$30,000 equipment, allow them to do  
2 that quantitative sensory testing.  
3 Autonomic testing. David Herrmann has  
4 published two articles on autonomic testing or  
5 autonomic test results as criteria for small fiber  
6 neuropathy, and conclusions of this work are that  
7 this is the holy grail. It increases sensitivity  
8 without decreasing specificity. Is this something  
9 that we should be more insistent of including in  
10 the diagnostic criteria for small fiber neuropathy?  
11 And the new kid on the block, corneal confocal  
12 microscopy, where does this fit in? How do we use  
13 it as inclusion and exclusion criteria?  
14 How about the exclusion criteria? And I'll  
15 touch on just two of them. Nerve conductions  
16 studies, again thinking of those people that are in  
17 the business of drug development. Does every  
18 patient who enters a small fiber neuropathy  
19 clinical trial need to have nerve conduction  
20 studies in order to exclude any large fiber  
21 dysfunction?  
22 Again, referring to Giuseppe's criteria,

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1 they were quite fitting with his character, very  
2 hard-nosed, rigid, and in those criteria excluded  
3 all signs and all features of large fiber  
4 neuropathy, including the necessity of having nerve  
5 conduction studies being normal. Nerve conduction  
6 studies, for those who are not in the field, of  
7 course only assess large fibers. And what about on  
8 the clinical examination? Do we permit in a  
9 clinical trial any large fiber dysfunction?  
10 Well, there's more than enough to talk  
11 about. As I present all of this, I'm not sure that  
12 we are going to have nearly enough time, but we  
13 will of course do the best we can.  
14 Let me, before getting things underway, give  
15 some housekeeping rules. The usual, keep your cell  
16 phones quiet. Microphones are voice activating.  
17 Please speak directly in the microphone. State  
18 your name before speaking. This is kind of  
19 important. The meeting is going to be recorded,  
20 and there will be a transcription, which will help  
21 us write the paper or papers afterwards, so please,  
22 the people transcribing will not recognize voices,

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1 accents, so please state your name, and we will  
2 remind you as the meeting goes on.  
3 Sign in if you haven't done so. Lunch is in  
4 the Dupont Room, the conference level. You see the  
5 internet access code. Restrooms are located  
6 outside of the meeting room to the left. And  
7 Valorie and team -- who have done a fantastic job,  
8 and just in case I don't thank them at the end of  
9 the meeting, I think we all recognize what a  
10 wonderful job they've done so far -- they are  
11 available for assistance at the registration desk.  
12 Well, that's all I have to say at this  
13 point. One last thing to say. For those of you  
14 who have not been at meetings like this before,  
15 they are highly interactive. There is no firewall  
16 between the audience, the panel, and the speakers.  
17 Everybody is expected to -- it's part of the price  
18 of entry -- participate very actively no matter  
19 where you are sitting in the room.  
20 So we expect a very exciting and interactive  
21 meeting, which then brings me to the first speaker  
22 of the day, which is going to be Rob Singleton, who

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1 will be talking about the epidemiology.  
2 Presentation - Robinson Singleton  
3 DR. SINGLETON: Thanks, Roy.  
4 It's really very exciting to be asked to  
5 present to you, to this group, something about the  
6 epidemiology of small fiber neuropathy. Let me  
7 just say that I can thank Roy, but I can also kind  
8 of curse him because this turns out to be a very  
9 difficult subject, and we're going to talk a little  
10 bit about why it's so difficult. And Roy's touched  
11 on some of these aspects already, but I think we'll  
12 just kind of stumble through this for the next  
13 25 minutes, and then we'll take questions. Let me  
14 say, I have no conflicts of interest to disclose.  
15 I started this really as a series of  
16 questions that I wanted answered. And let me just  
17 state right out in the front that basically I have  
18 failed in answering any of these questions for you,  
19 so you will have --  
20 (Laughter.)  
21 DR. SINGLETON: -- just take that for what  
22 it's worth. But we'd like to know what fraction of

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1 all neuropathies we consider as small fiber  
2 neuropathy. What does that mean? And this comes  
3 back to Roy's point, that the definition of small  
4 fiber neuropathy is critical to answering this  
5 question. What are the most common causes of small  
6 fiber neuropathy? I think we'll focus on this  
7 aspect most intensely over the course of this talk.  
8 Recognize that a large fraction, some  
9 unclearly defined fraction, of small fiber  
10 neuropathy or neuropathy in general remains  
11 idiopathic despite very careful efforts to  
12 phenotype these patients.  
13 Do these patients have a distinct prognosis?  
14 Do they have different implications for their  
15 treatment? I think that's crucial for us to  
16 understand in order to understand what's the market  
17 for the treatment of small fiber neuropathy. We  
18 want to be able to include those patients. Do they  
19 have a different natural history than other  
20 patients? In the same way, we need to know whether  
21 pain makes a difference in terms of patients'  
22 response to this. Is there anything different

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1 about the biology of patients who have painful  
2 versus non-painful neuropathy?  
3 Let me just start with the working  
4 definitions that I used when I went through this  
5 because I think they're important. First of all,  
6 I'm going to talk about neuropathy. That is what I  
7 mean when I say systemic, length-dependent,  
8 typically, injury to peripheral nerve.  
9 There's this obvious distinction between  
10 small fiber predominant neuropathy in which  
11 features of small fiber dysfunction are a prominent  
12 portion. Basically, in the literature it means  
13 painful. So if you have pain, that's a marker for  
14 small fiber neuropathy that is one of the easiest  
15 things to recognize versus a pure small fiber  
16 neuropathy in which, as we'll come around to  
17 talking about, Karin Faber and her group have  
18 really focused on. This is only involvement  
19 spinothalamic sensory features.  
20 Let me just say, Chris, this is a talk about  
21 somatic sensory injury, and I'm leaving it to you  
22 to discuss autonomic abnormalities. But the idea

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1 that neuropathy is rigorously defined as affecting  
2 spinothalamic fibers but not dorsal column fibers,  
3 and that you've done something to prove that you  
4 don't have that large fiber involvement, I think  
5 that really is a very separate animal in terms of  
6 its epidemiology.  
7 Just to illustrate a couple of these  
8 concepts, if you look at the causes of neuropathic  
9 pain, some of the most important ones aren't  
10 actually neuropathy. They are zoster, and cancer  
11 associated pain, and spinal cord injury. These  
12 take up more than half of the defined causes of  
13 neuropathic pain. So we have to decide what is it  
14 that we want to focus on. For this meeting, I  
15 think we're talking about length-dependent  
16 neuropathy.  
17 Another issue is that racial diversity and  
18 geographic diversity of neuropathic pain is  
19 enormous, so this large epidemiologic inquiry about  
20 the report of neuropathic pain of all types  
21 suggests dramatic differences across age and across  
22 ethnicities.



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1 Here is my working list of relevant causes  
2 of small fiber neuropathy in no particular order in  
3 terms of their frequency or prevalence. I think  
4 all of you are very familiar with these, and we'll  
5 touch on some of the ones that are particularly  
6 common.

7 Type 2 diabetes is certainly the obvious  
8 800-pound gorilla of small fiber neuropathy. In  
9 all of these, as I go through them, one of the  
10 things I couldn't find is like a list of  
11 neuropathies and their prevalence. So as part of  
12 my preparation for this, I've actually done an  
13 attempt, just looking back at the literature, to  
14 create that list for us. So we'll talk for these  
15 about the prevalence of each causative entity, the  
16 frequency of neuropathy associated with that  
17 causative entity, and then some guesstimate on my  
18 part about what fraction of those neuropathies, say  
19 for diabetes, are actually small fiber predominant.

20 Again, to just keep things manageable, I've  
21 really focused these numbers on the United States  
22 and the prevalence here, but I recognize that over

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1 the world, there are very different prevalences,  
2 and we'll touch on that in some other causes of  
3 neuropathy.

4 Here, diabetes is a dramatic problem. The  
5 lowest estimates now are about 31.5 million  
6 Americans, or 14 percent, have diabetes, type 2  
7 diabetes. My guess is that a quarter of those  
8 patients have a clinical small fiber neuropathy  
9 phenotype in which pain is a prominent feature. So  
10 that gets us to an overall burden of about  
11 8 million patients with type 2 diabetes who have  
12 neuropathy.

13 This is just to point out that the  
14 prevalence of diabetes and therefore neuropathy  
15 varies widely in countries across the world but  
16 also populations within the United States. Off the  
17 top because it's a smaller prevalence is well-to-do  
18 white Americans who have a diabetic prevalence of  
19 around 6 percent. But if you scroll down here to  
20 black Americans or Pima Indians, you get into half  
21 of the population of those ethnicities, even seeing  
22 more. And you can see it here, that between

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1 diabetes and impaired glucose tolerance, two-thirds  
2 of patients are Pima Indians.

3 Prevalence depends on the type of diabetes  
4 you have of course, it depends on the duration of  
5 diabetes, and it depends on how old you are. These  
6 are not surprising in any way. But this just  
7 illustrates the concept that the longer you have  
8 diabetes, the older you are, the more likely you  
9 are to have a neuropathy in this setting.

10 This is not quite epidemiology, but it's  
11 crucial. Neuropathy is expensive, and diabetic  
12 neuropathy is one of the best characterized of  
13 neuropathies in terms of the burden on patients.  
14 This study, which looked at 112 patients in the  
15 United States with painful neuropathy associated  
16 with diabetes, tried to estimate both the direct  
17 costs in terms of clinical care for these patients  
18 each year, and then also indirect costs as measured  
19 by loss of work productivity, basically. They  
20 characterized patients in terms of the severity of  
21 their neuropathy and found that even moderate  
22 severity cost about \$15,000 a year in that

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1 combination of direct and indirect costs.

2 I think Roy asked me to give this talk in  
3 part so I could talk about pre-diabetes metabolic  
4 syndrome and its service as a risk factor for  
5 peripheral neuropathy and small fiber neuropathy.  
6 Multiple lines of epidemiologic data suggest  
7 there's a causative association between the  
8 features of metabolic syndrome and injury to small  
9 unmyelinated nociceptive fibers.

10 One of the earliest lines of that  
11 epidemiologic evidence is looking at patients who  
12 have idiopathic neuropathy and finding that a  
13 greater proportion than we would expect have  
14 metabolic syndrome features. Probably the best of  
15 these epidemiologic studies were done by  
16 Dr. Noterman and her colleagues in Utrecht.

17 Here in the upper left, you'll see looking  
18 at all-comers with painful or non-painful sensory  
19 neuropathy who remain idiopathic after a basic  
20 evaluation, there was a significant increased risk  
21 of meeting definitions for metabolic syndrome.  
22 Then down to the lower right is that same data but

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1 shown with each feature of metabolic syndrome  
2 broken out, then comes the same thing that there is  
3 this increased risk.  
4 A second line of evidence comes from looking  
5 at patients who actually have diabetes, examining  
6 the features of metabolic syndrome and seeing how  
7 those contribute to risk for neuropathy. In the  
8 neuro-diab studies of type 1 diabetics, this looked  
9 at patients who had type 1 diabetes, followed them  
10 for up to 7 years, and then by doing an analysis  
11 that took out age and glucose control looked at  
12 other features of metabolic syndrome in order to  
13 look at the relative risk for developing new  
14 neuropathy in those type 1 diabetes patients. You  
15 can see that each feature of metabolic syndrome add  
16 some increased risk to the development of  
17 neuropathy over this period of time for this  
18 carefully performed study.  
19 We've done kind of the same thing in a much  
20 better characterized group of patients with  
21 diabetes. We've taken patients, about 225  
22 patients, with diabetes and followed them, a third

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1 of whom had neuropathy at the beginning. We  
2 followed those patients for up to 8 years in order  
3 to see how features of metabolic syndrome  
4 influenced risk for development of neuropathy and  
5 progression of neuropathy. Here again, you can see  
6 that these features of metabolic syndrome are  
7 predictive of progression of neuropathy and the  
8 presence of neuropathy independent of glucose  
9 control.  
10 I guess a last area of epidemiologic data  
11 comes from looking at treatment. So if you  
12 intervene in patients who have diabetes or pre-  
13 diabetes, does that make some difference to their  
14 neuropathy and to their neuropathy risk? The  
15 STENO 2 trial is one of the largest studies that  
16 took a comprehensive approach to control of  
17 metabolic syndrome risk factors in type 2 diabetic  
18 patients and found that there was a reduction in  
19 risk primarily for cardiovascular endpoints, but  
20 there is a little bit of microvascular data,  
21 including some autonomic testing that suggests an  
22 effect on peripheral nerves and on small fiber

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1 nerves.  
2 I would be remiss if I didn't at least point  
3 out that we now have a really rich set of animal  
4 models that recapitulate the clinical features of  
5 small fiber neuropathy in the period of metabolic  
6 syndrome before diabetes, and these can be used  
7 both to characterize that neuropathy, to look at  
8 the biology of those small fibers, and to show that  
9 if you intervene by changing the biology, the  
10 metabolism in these mice, you can have an influence  
11 on the severity of neuropathy on the progression to  
12 neuropathy for these rodents. I think these models  
13 are good enough now that they have the opportunity  
14 to serve as a real translational entry way to human  
15 treatments and how we use them.  
16 The most specific and the least convincing,  
17 I think, of thee epidemiologic mechanisms or  
18 epidemiologic studies for prediabetic metabolic  
19 syndrome is to look at patients who have these  
20 different aspects of glucose control and directly  
21 measure how many of them have small fiber  
22 neuropathy. Dan Ziegler has probably done this

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1 best in my mind. He looked at 200 controls in 200  
2 patients with various levels of abnormal glucose  
3 control and found that there was an excess number  
4 of patients who had both neuropathy and also  
5 neuropathic pain as patients stepped from controls  
6 to diabetes.  
7 A much larger study done by Brian Callaghan  
8 looked at 2400 patients in the Health ABC study and  
9 found that, basically, each additional factor of  
10 metabolic syndrome added about 1 percent to your  
11 risk for neuropathy.  
12 I think Roy's CONCEPPT meeting in December  
13 really helped us to begin addressing how we should  
14 consider patients with prediabetes. As Roy  
15 mentioned, we came to the understanding that we  
16 should talk about this as an association. It's I  
17 think one of multiple risks for small fiber  
18 neuropathy that should be considered when  
19 considering the cause of neuropathy in these  
20 patients.  
21 Moving on to type 1 diabetes, this is the  
22 much less common cause of neuropathy, but still

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1 probably 400,000 patients in the United States have  
2 a small fiber neuropathy associated with their type  
3 1 diabetes.  
4 I just want to put in a plug here for the  
5 rare but perhaps underrecognized treatment-induced  
6 neuropathy in diabetes that Chris Gibbons and Roy  
7 Freeman have helped us to recognize in patients who  
8 have diabetes and have too rapid a correction of  
9 their hyperglycemia.  
10 Now I'm going to get into neuropathies that  
11 clearly are associated with small fiber injury,  
12 which have a different distribution across the  
13 world, which I think need to be recognized as  
14 important causes globally but challenging targets  
15 for treatment.  
16 Neuropathy associated with HIV infection,  
17 the overall prevalence is about 0.8 percent across  
18 the world. Different studies found a widely  
19 disparate frequency of neuropathy associated with  
20 HIV from 9 to more than 60 percent of patients.  
21 Risk factors are ones very similar to diabetes and  
22 pre-diabetes in the sense that duration of HIV and

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1 older age predicts the development of small fiber  
2 neuropathy in these patients.  
3 We're kind of working our way in order of  
4 prevalence, and this is quite a diverse list. But  
5 chemotherapy-induced polyneuropathy is a  
6 surprisingly common cause of painful small fiber  
7 neuropathy. It's very difficult, I think, to get  
8 at the true prevalence of this disease because it's  
9 complicated. The best estimates are that 485 out  
10 of every 100,000 patients will have new -- or  
11 people will have new cancer diagnosis in a given  
12 year; 171 of those patients in any given year. So  
13 there's some residual survivors who make up the  
14 prevalence, and that number varies widely. It  
15 might be as much as 5 percent of the population who  
16 are cancer survivors in this setting.  
17 Roughly 20 percent of patients who have  
18 cancer have a cancer that's treated with  
19 chemotherapy that may be neurotoxic. So you take  
20 that number and then work partly from Noah Kolb  
21 that looks at the frequency of neuropathy in  
22 patients who received chemotherapy. That number is

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1 surprisingly high, 40 to 50 percent of patients.  
2 So that gets us to this overall burden of perhaps a  
3 million patients who are at risk for small fiber  
4 neuropathy associated with their chemotherapy over  
5 time.  
6 Hepatitis -- this is B, but C as well -- has  
7 a significant burden of illness, about 230,000  
8 patients in the United States. Leprosy, just to  
9 illustrate a disease that has a dramatic difference  
10 across the world as a risk, there was a time when  
11 we talked about leprosy as the most common cause of  
12 neuropathy in the world. Those days are gone.  
13 Recognize -- it's kind of hard to read  
14 here -- the risk across countries is spectacularly  
15 different, according to your exposure. In the  
16 United States, that risk really is on the order of  
17 less than 10 cases per 100,000, and most of those  
18 are immigrants in the United States, rare cases of  
19 international travel, and then there is beginning  
20 to be an indigenous risk for leprosy that comes  
21 from armadillos, that I discovered as I read about  
22 this, so Texas, be cautious. Clearly, 90 percent

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1 of patients who have leprosy express a neuropathy.  
2 One of the challenges is knowing for any given  
3 illness how frequently neuropathy occurs in that  
4 illness.  
5 The talk really after mine is about the  
6 genetics of small fiber neuropathy, so I'm going to  
7 touch very lightly on these topics. At least for  
8 hereditary sensory and autonomic neuropathies,  
9 these are super rare, but there has been increasing  
10 interest in sodium channelopathies. And we're  
11 going to hear a lot about this I think in the next  
12 couple hours, so I'm not going to talk much about  
13 it, except to just point out that this is an  
14 example of how difficult it is to get a true  
15 prevalence for these genetic disorders.  
16 Nav 1.7 coded genetic defects are the cause  
17 for some extremely rare gain-of-function  
18 neuropathies, including the scarily named  
19 paroxysmal extreme pain disorder. If you want to  
20 pick something you don't want to have, this is  
21 probably it. And loss of function causes  
22 insensitivity to pain in some patients.

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1 We know that gene defects in these sodium  
2 channels cause neuropathy, but the idea that there  
3 might be gain-of-function mutations -- that there  
4 are gain-of-function mutations that cause a more  
5 generic small fiber neuropathy is something that  
6 really has been explored.

7 I'm sorry, Karin, for getting the C in your  
8 name wrong there.

9 DR. FABER: That's okay.

10 DR. SINGLETON: The initial studies, very  
11 small groups found that maybe more than a quarter  
12 of patients who had otherwise idiopathic neuropathy  
13 might have these defects. Subsequent studies have  
14 found, and larger groups have found, much slower  
15 frequencies, and I'm sure we're going to hear about  
16 this.

17 Again, I feel like I'm stealing thunder from  
18 whoever gets to talk about the registry, but in the  
19 most very recently published data about patients  
20 from the peripheral neuropathy research registry,  
21 there was nearly -- this graph that I created down  
22 here on the lower right, nearly identical frequency

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1 of rare SCN9A mutations across patients with and  
2 without pain, who are either idiopathic or had  
3 diabetes; so really no difference in the frequency  
4 of these mutations that help us understand why some  
5 patients have pain and others do not.

6 I'll just finish by talking for a second  
7 again about efforts to very rigorously look at  
8 patients who have pure sensory neuropathy. And  
9 again, the work by Dr. Faber and Ingemar Merckies'  
10 very recently published paper have done an  
11 excellent job of taking patients with small fiber  
12 neuropathy, looking at those who have pure  
13 neuropathy, examining how that diagnosis is made  
14 with either quantitative sensory testing or nerve  
15 fiber density abnormalities, doing a very  
16 comprehensive list of tests that look for the  
17 etiology of small fiber neuropathy, and then  
18 reporting that distribution.

19 So in this study of 921 patients, you can  
20 see this distribution in which immunologic  
21 abnormalities, genetic abnormalities, or metabolic  
22 abnormalities feature most prominently. But one

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1 clear take-home message for me was that more than  
2 half of the patients who underwent this analysis  
3 didn't find any obvious recognizable cause for  
4 neuropathy.

5 DR. FELDMAN: Rob, could you go back to the  
6 previous slide? I haven't seen this paper yet.  
7 Does that say, though, that -- what does TTT stand  
8 for here, in the bottom?

9 DR. FABER: Temperature threshold testing.

10 DR. FELDMAN: Thermal threshold, so --

11 DR. SINGLETON: It's a small fiber QST  
12 measure.

13 DR. FELDMAN: So you have like  
14 normal -- like on the right, over 600 people have  
15 normal skin biopsies but abnormal thermal --

16 DR. SINGLETON: That's right.

17 DR. FELDMAN: I think this turns out to be  
18 really important, is we --

19 DR. SINGLETON: Very important. I'm sure  
20 we're going to get around to talking -- this is  
21 back to Roy's point, that we need to decide --

22 DR. FELDMAN: Right.

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1 DR. SINGLETON: -- are quantitative sensory  
2 measures sufficient to diagnose small fiber  
3 neuropathy. What's the role there for that test?  
4 And amongst quantitative sensory testing, which  
5 ones are adequate. I think those are absolutely  
6 questions to discuss.

7 DR. FELDMAN: That's actually a really  
8 interesting -- those data.

9 DR. SINGLETON: I think one reason I wanted  
10 to bring this up is that this result shows us how  
11 much referral bias affects these distributions.  
12 This is incredibly, carefully done work, but it  
13 still represents an ultra tertiary care analysis of  
14 small fiber neuropathy. And compared to population  
15 studies, it gets a very different result in terms  
16 of what is the most important cause of neuropathy.

17 An earlier study that Dr. Faber did, in  
18 which there was a much smaller group, found that  
19 sarcoidosis was actually more common in their  
20 population than diabetes as a cause for small fiber  
21 neuropathy, and that's because there are  
22 sarcoidosis referral centers, so the patients who

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1 come in the door have that much more often. So I  
2 think we just have to be very cautious about how  
3 referral bias affects our evaluation of the  
4 epidemiology.  
5 DR. FABER: Again, I add one thing, and  
6 that's we hardly find any diabetics because they  
7 are not referred to us, so that's very simple.  
8 DR. SINGLETON: Exactly.  
9 DR. FABER If they have a small fiber  
10 neuropathy, they're not going to send them to our  
11 center, so we cannot state anything about diabetic  
12 small fiber neuropathy in these patients.  
13 DR. SINGLETON: Right. And I'm not in any  
14 way criticizing this. I think that that's  
15 beautiful work. But I think when we review the  
16 literature in order to think about the population  
17 prevalence or the epidemiology of these small fiber  
18 neuropathies, we can't rely too heavily on the data  
19 that comes from very careful evaluation in tertiary  
20 care centers because it gives us a false idea about  
21 those prevalences.  
22 DR. FABER: I do think what you can say is

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1 which tests are useful. If you find a patient with  
2 a small fiber neuropathy, for example, you can  
3 steal that out of these data. So some tests are  
4 not useful or do not give any additional  
5 information, and then you can leave it out. For  
6 example, testing for Fabry's disease is useless if  
7 you don't have any other signs compatible with  
8 Fabry. You will never find it.  
9 DR. SINGLETON: Dr. Smith and I have done  
10 that same sort of analysis, but just less  
11 beautifully than you, in examining the utility of  
12 different tests. And I think that should inform  
13 our decisions about inclusion criteria.  
14 Yes, Dr. Oaklander?  
15 DR. PELTIER: And it really depends on what  
16 the cause is. It's Amanda.  
17 DR. SINGLETON: You have to raise your hand  
18 if you want to talk.  
19 DR. PELTIER: But it really depends on the  
20 cause of neuropathy because, for example, sudomotor  
21 testing is very sensitive in diabetic and glycemic  
22 related tests and HIV, but not very good with

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1 idiopathic sensory predominant small fiber  
2 neuropathy. So it really depends on your etiology,  
3 what you're thinking of as to what tests you should  
4 include.  
5 DR. SINGLETON: I agree. Thank you. That's  
6 an important concept. I think one goal we should  
7 have is to consider tests that have the opportunity  
8 to be sensitive across causes of small fiber  
9 neuropathy.  
10 Dr. Oaklander?  
11 DR. OAKLANDER: So in our paper on this  
12 topic, which I think was in 2016, we pulled in the  
13 cost data. And I think it was called -- what was  
14 it called? I forget. But the point is we're all  
15 scientists, and we're all excited by these obscure  
16 diseases, but it's naive not to include cost  
17 considerations. So we went and actually tracked  
18 down the reimbursement codes for these diagnostic  
19 tests. For instance, diabetes neuropathy alone,  
20 which we all agree is a huge thing, what's the  
21 relative value of 2-hour GGT versus fasting alone  
22 versus A1c versus random?

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1 So let's consider cost more in our  
2 discussion for value as well.  
3 DR. SINGLETON: Yes, Gordon?  
4 DR. SMITH: I just want to amplify that.  
5 Brian Callaghan has done I think really beautiful  
6 work looking at healthcare utilization surrounding  
7 neuropathy diagnosis. And it turns out that  
8 drivers and the large data sets are really things  
9 that we're not going to even talk about today,  
10 which are MRI scans, brain MRI scans for small  
11 fiber neuropathy, which I think we can agree we  
12 don't need. So maybe that's our first consensus.  
13 I think when we start thinking about do we  
14 need normal nerve conduction studies, do we require  
15 skin biopsy and these sorts of things, I think it's  
16 really important to differentiate the need in a  
17 clinical trial setting versus common clinical  
18 practice because those things really do  
19 cumulatively drive healthcare testing costs for  
20 neuropathy evaluation.  
21 DR. SINGLETON: Just to finish the things I  
22 had to say, this represents, for these diseases, my

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1 guess at the minimum prevalence of small fiber  
2 neuropathy in the United States for these diseases  
3 listed in order of overall disease burden. I did  
4 this in part because I think it's important to  
5 recognize just how important this is in aggregate  
6 as a problem to be addressed.

7 The second thing I want to say is important  
8 lines that are missing from my table are genetic  
9 causes of neuropathy. It's really hard to define  
10 the prevalence, and I don't think that a true  
11 population study of prevalence for sodium  
12 channelopathies or other causes of neuropathy has  
13 been done. And then idiopathic neuropathy is -- in  
14 my experience, in other people's experience, it  
15 represents a third or a half of patients who have  
16 small fiber neuropathy. What's the magnitude of  
17 that if we step away from the burden -- sorry, from  
18 the bias of referral patterns? We just don't have  
19 a number for that, that I can tell.

20 These really are challenges and take-home  
21 points for me, that the prevalence of small fiber  
22 neuropathy depends critically on our definition.

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1 And that's why we're having this conference, is to  
2 discuss what that definition should be so that we  
3 can decide what's inside and what's outside of the  
4 tent of our neuropathy in this case. The metabolic  
5 causes probably greatly outnumber other etiologies  
6 when we look at population studies, and that the  
7 true prevalence of idiopathic small fiber  
8 neuropathy remains really poorly defined.

9 So the things that I think we need are a  
10 population based epidemiology of idiopathic  
11 neuropathy that's based on unbiased referral  
12 patterns. I think Brian Callaghan, again, is the  
13 person who has exemplified this work of looking at  
14 large databases in order to try and find this in a  
15 population. I think we should be thinking about  
16 how as a group we can amplify that work in order to  
17 be even more powerful to get a true idea about  
18 this.

19 We need prospective studies that follow  
20 patients with small fiber neuropathy and other  
21 common neuropathies to see whether there's a  
22 difference in fate or response to treatment if you

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1 have a painful or non-painful neuropathy. And then  
2 we need additional studies that look at patients  
3 with idiopathic neuropathy to discover the  
4 importance of sodium channelopathies and other  
5 genetic influences on neuropathy because almost  
6 certainly, a significant portion of patients who  
7 have idiopathic neuropathy now have a genetic  
8 influence that we just haven't recognized yet.

9 So with that, I'll take questions. Yes,  
10 Gordon?

11 DR. SMITH: I wanted to ask a question that  
12 I think -- I might as well get it out of the way  
13 now, and that is my concern about conflation of  
14 painful neuropathy with small fiber neuropathy.  
15 Your beginning and I think your epidemiology of  
16 diabetic neuropathy kind of does that. The numbers  
17 to me look like you took the percentage of people  
18 who have diabetes, who have neuropathy, and then  
19 said but half of those have small fiber neuropathy.  
20 That's really painful neuropathy, and it may be  
21 even lower. Most patients who have painful  
22 neuropathy have some degree of large fiber

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1 involvement, and this goes to really the boundaries  
2 of what small fiber neuropathy represents.

3 I don't know if this is the time we should  
4 talk about it, but I just wanted to bring it up  
5 because it certainly impacts the epidemiology.  
6 It's different to say the epidemiology of painful  
7 neuropathy is X from saying small fiber neuropathy  
8 is Y. That's a bad metaphor.

9 DR. SINGLETON: I have an opinion, but I  
10 think you're absolutely right.

11 I don't know. Roy, maybe this is an hour's  
12 worth of talk on Friday afternoon, to talk through  
13 this question.

14 DR. FREEMAN: No. Clearly, this is a  
15 critical topic. I'm not sure that we -- and I  
16 think it's hanging over the session. I think it's  
17 exemplified by the course that Chris is now  
18 directing, and I think it really exemplifies just  
19 how interesting this entity has grown. We began  
20 this course maybe 10 years ago, and 20 people  
21 showed up. And the course was entitled Small Fiber  
22 Neuropathy: Sensory, Autonomic, or Both.

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1 Now the course is oversubscribed. We  
2 haven't resolved the issue of definition quite yet,  
3 but I think this is a critical point, and perhaps  
4 we need to begin to refine the way we talk about  
5 this, the way we write about it, and the way we  
6 think about this. And obviously, every clinical  
7 trial will need to do this, and I think it's an  
8 important focus. And hopefully by the end of the  
9 meeting, we will have come away with more discrete  
10 criteria for differentiating those different parts  
11 of the small fiber neuropathy spectrum.  
12 DR. SINGLETON: Chris?  
13 DR. GIBBONS: I think the point that Gordon  
14 raised is perfect, and I actually want to throw out  
15 another disease we don't even actually talk about,  
16 Parkinson's disease. We see this really small  
17 fiber neuropathy that's totally asymptomatic, quite  
18 frequently if you look for it, but we don't talk  
19 about it. So just kind of, again, keeping that  
20 theme going.  
21 DR. SINGLETON: Again, reviewing this  
22 literature, there is fairly convincing evidence

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1 that patients with Lou Gehrig's disease have a  
2 decrease in their nerve fiber density. Should w  
3 consider that small fiber neuropathy? I think not,  
4 but the harder you look --  
5 MALE VOICE: That's for diabetes --  
6 DR. SINGLETON: -- the more people you  
7 include.  
8 DR. OAKLANDER: It's up to us. The field  
9 needs guidelines, and we're the people.  
10 DR. SINGLETON: That's right.  
11 Yes, Dr. Herrmann?  
12 DR. HERRMANN: I think another issue I would  
13 say is the issue of age. When people get 75, 80,  
14 85, I think it gets harder and harder. We always  
15 sort of dance around the issue of neuropathy of  
16 aging versus just normal findings for age. And I  
17 think at a certain point, in terms of clinical  
18 trial design, I think at a certain point everyone's  
19 losing small fibers. So if you have a density of X  
20 at age 83, we call that maybe normal for age, but a  
21 person who's 20 years younger has neuropathy.  
22 I think thinking about how to think about

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1 the older individual with small fiber signs and  
2 abnormal skin biopsies I think will be important  
3 because at some stage we may want to exclude people  
4 above a certain age because I'm not sure we can  
5 really define a small fiber neuropathy entity in  
6 those patients well and distinguish that from  
7 normal aging.  
8 DR. SINGLETON: I agree. But one thing I  
9 would say is a crucial piece of our definition  
10 needs to be clinical impact; that is you need to  
11 have symptoms. You need to complain of those  
12 symptoms. You need to have some consequence for  
13 your function. If you don't have those things,  
14 then I don't think that's neuropathy.  
15 Okay. Roy looks like he might want me to  
16 stop talking.  
17 (Laughter.)  
18 DR. SINGLETON: Thank you, Roy.  
19 (Applause.)\_  
20 DR. SINGLETON: So a couple of things.  
21 There will be plenty of time for questions.  
22 There's a one-hour panel, so if you still have

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1 questions to ask Rob, and if Rob still wants to  
2 keep talking, he'll have another round.  
3 It's a pleasure to introduce Karin Faber  
4 from Maastricht Netherlands, who, as you've heard  
5 several times already this morning, allowed the  
6 field to take a giant step forward by defining,  
7 together with the group from Milan and the group  
8 from Yale, the molecular biology that underpins  
9 some patients who previously we thought, or perhaps  
10 still have thought, of as having small fiber  
11 neuropathy; and specifically by defining  
12 gain-of-function mutations in Nav 1.7, and then  
13 later 8 and 9. And it's wonderful to have Karin  
14 here.  
15 Presentation - Karin Faber  
16 DR. FABER: Thank you very much, Roy. It's  
17 a big honor to be invited here and to talk here  
18 about the genetics of small fiber neuropathy. And  
19 as Roy already pointed out to me, the most  
20 important thing is whether we should include  
21 genetics or not. So if I would answer this, then I  
22 would be on very quickly, but I will talk a little

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1 bit more about a background as well. I don't have  
2 any conflict of interest, but we have some grants  
3 from the European Union and also from a national  
4 foundation on neuromuscular research, and I'm on an  
5 advisory board for Biogen, Vertex, and Chromocell.  
6 A small fiber neuropathy, as you already  
7 heard, is a disorder in which the small nerve  
8 fibers, the A delta and the C fibers, are affected.  
9 And you can have a lot of debate, so far as clear  
10 from the discussion we had, whether this is pure  
11 small fiber neuropathy or whether you should have  
12 predominantly small fiber neuropathy. And this  
13 leads to often very severe pain in combination with  
14 autonomic symptoms.  
15 There are a lot of conditions, as Rob  
16 already told, that can be associated with small  
17 fiber neuropathy, and associated does not  
18 necessarily mean it causes neuropathy; that might  
19 be something different. But indeed, the list is  
20 growing and growing like in our peripheral  
21 neuropathies. When we started working on small  
22 fiber neuropathy, we thought, well, how does it

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1 come that all these patients have the same symptoms  
2 and so many underlying conditions or causes could  
3 have been some kind of -- well, one  
4 pathophysiological pathway?  
5 That's when we started looking into the  
6 sodium channels, and the sodium channels seemed a  
7 logical way to go. You know that the first  
8 description of a locus on chromosome 2 was in 2001  
9 for primary erythromelalgia, and then in 2004, the  
10 gene SCN9A coding for the Nav 1.7 was discovered in  
11 primary erythromelalgia. And later in the same  
12 year, also the electrophysiological properties were  
13 described by the lab of Steve Waxman.  
14 In 2006, also mutations in SCN9A were  
15 described in paroxysmal extreme pain syndrome,  
16 which is another painful disorder. That's when we  
17 thought, well, maybe this could also play a role in  
18 small fiber neuropathy, and we included patients  
19 with the typical clinical picture of small fiber  
20 neuropathy in combination with an abnormal  
21 temperature threshold testing, as well as an  
22 abnormal skin biopsy. So those were very strict

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1 criteria for patients with idiopathic small fiber  
2 neuropathy. And indeed, in a number of these  
3 patients, we found a mutation in SCN9A.  
4 The electrophysiological properties in these  
5 mutations were described. And as you may know, but  
6 I'm not sure whether everybody knows, you can test  
7 electrophysiology using patch clamp analysis, and  
8 there are two ways of doing this. You can have a  
9 voltage clamp analyze this, and that's testing the  
10 channel function, so meaning you test  
11 depolarization, repolarization, and inactivation.  
12 And you can also use the current clamp analysis,  
13 and with this you test the excitability of the  
14 channel. So it means that the resting membrane  
15 potential can change, or the current threshold can  
16 change, or you can have an increased spontaneous  
17 firing or an increased firing frequency.  
18 Indeed what we saw was that in these  
19 patients you saw abnormalities in  
20 electrophysiological properties, so there was an  
21 impaired slow inactivation. For example, in this  
22 mutation, you can see that in C, the current

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1 threshold was lowered and also the resting membrane  
2 potential was different, meaning the potential was  
3 more depolarized. And in F, you can see that the  
4 firing frequency is higher in the patient with the  
5 mutation, and also there's more spontaneous firing  
6 compared to the wild-type channel.  
7 This is another family, and this family  
8 taught us a lot, and that's why I'm showing this.  
9 It's a family in which we saw the proband, and you  
10 see a picture of him here. And he showed  
11 complaints compatible with erythromelalgia, so red  
12 hands and feet, extremely painful, but he also had  
13 severe autonomic symptoms, which is not compatible  
14 with erythromelalgia but more with small fiber  
15 neuropathy. And he also had very small hands and  
16 feet and also legs and arms.  
17 You can believe it or not, but these are  
18 also normative values for your hands and arms and  
19 whatever part of your body you can think of, and  
20 this was really abnormal. Then his father and  
21 other brother, also affected, had the same clinical  
22 phenotype, including the small hands and feet,



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1 while his unaffected brother and mother did not  
2 have any symptoms. We now know that he has two  
3 daughters that are now 5 and 7 years old. They  
4 have the same mutation, and they also have the same  
5 clinical phenotype, including pain.  
6 This is the electrophysiology of this  
7 patient, and you can see there are marked  
8 differences with the wild-type channel. I'll come  
9 to this mutation later on to show you something  
10 else that is important.  
11 SCN9A is also associated with a lot of  
12 function mutation, meaning that these patients have  
13 a congenital inability to experience pain. This  
14 may sound fantastic, but it leads to severe  
15 problems, I think even worse than the  
16 hyperexcitability.  
17 The Nav 1.7 channel consists of alpha  
18 subunit and one or more beta subunits. It is  
19 preferentially expressed in dorsal root ganglia and  
20 sympathetic ganglia neurons and their actions. It  
21 is encoded by the SCN9A. Now compiling this, you  
22 can say, well, you have the wild-type channel

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1 that's on the right, and then you have the loss-of-  
2 function mutation that's a widespread mutation, and  
3 the channel function is absent.  
4 In small fiber neuropathy, what we see is  
5 gain of function. These mutations are located in  
6 domain 1 and 2, and they show an impaired  
7 inactivation. If you have the patients of the  
8 family with the G856D, the small hands and feet,  
9 they have also an impaired inactivation but also an  
10 increased opening of the channel. In primary  
11 erythromelalgia, you can also see the mutations in  
12 domain 1 and 2, and they have an increased opening  
13 and an impaired deactivation and paroxysmal extreme  
14 pain disorder. There's also a gain of function,  
15 and these are mainly located in domains 3 and 4,  
16 and there's impaired fast inactivation.  
17 This may seem very clear. You have distinct  
18 groups, but of course, unfortunately, it's not  
19 always like this. So what we see is that it is  
20 more or less like a spectrum. The paroxysmal  
21 extreme pain disorder is at one end of the  
22 spectrum, but especially for the small fiber

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1 neuropathy and the primary erythromelalgia, we see  
2 patients that have an overlapped syndrome between  
3 the two. The gain-of-function mutation is  
4 important in that these are missense mutations, and  
5 it is an autosomal dominance inheritance. And the  
6 loss-of-function mutations can be nonsense, a  
7 frame-shift or splice-site mutations, and these are  
8 autosomal recessive inherited.  
9 Now that we know a lot about these  
10 mutations, we also realize that there's a lot that  
11 we don't know. For example, there is large  
12 phenotypic diversity. For example, the I228  
13 mutation is a mutation in which patients within the  
14 same family have a very distinct phenotype. For  
15 example, one brother and one sister. The first  
16 started with pain in the face and the other with  
17 more distal pain, more like a picture that we know  
18 of the lengthy pain in neuropathy. And also  
19 another patient, there's pain on the scalp, and  
20 both had the same mutations.  
21 We were able to find also  
22 hyperexcitability -- not we, but the lab of Steve

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1 Waxman -- in the trigeminal neurons. With that,  
2 you can explain it, but we don't know why one  
3 patient has one phenotype and the other has the  
4 other phenotype. So that's still not completely  
5 clear.  
6 We also know that there is a variable  
7 expression of the mutation. Some patients have  
8 severe autonomic symptoms, while others have hardly  
9 any autonomic symptoms. This was nicely  
10 demonstrated also with electrophysiology, but we  
11 simply do not know why some mutations do cause  
12 autonomic symptoms and others do not.  
13 Then these mutations are partly penetrant.  
14 There's a large variation in age of onset of  
15 symptoms, so some are very young but there are also  
16 patients that exhibit symptoms after they are 40,  
17 or 50, or 60, and some may even not have any  
18 symptoms at all. We don't know at this point. We  
19 simply don't know what is the cause of this.  
20 Also, if you look, for example, the first  
21 mutation, that was one of the mutations that was  
22 described in the Annals paper, and you can see that

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1 the frequency in our SFN cohort is very low, and  
2 also for the other mutation, it is higher than in  
3 the general population. But we don't know exactly  
4 how this is working, and one can argue, well, are  
5 these disease-contributing variants or are these  
6 risk factors? And I will come to this later on in  
7 the presentation. What we know is that also in the  
8 lab of Steve, they did testing on neurite  
9 outgrowth, and what they saw is, especially in the  
10 I228M mutation, so the second one, there was a  
11 reduction in neurite outgrowth.  
12 If you treat these cells with a sodium  
13 channel blocker carbamezapine, you can see that the  
14 neurite outgrowth turns back to normal. So this is  
15 reversible, and the same is true when you inhibit  
16 the sodium calcium exchange. What is very  
17 important is, for example, in this G856D -- this is  
18 also published -- if you have these cells in  
19 culture for 18 days, you don't see axonal  
20 degenerations. So that's figure A and B.  
21 DR. FELDMAN: I was going to say what cells?  
22 I was asking --

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1 DR. FABER: It's A and B. So A is the wild  
2 type and on B is the mutated channel.  
3 If you then depolarize these cells for  
4 4 days, that's C and D, you don't see anything  
5 happening. So there's no axonal degeneration. If  
6 you cause metabolic stress by impairing glycolysis,  
7 that's E and F, you don't see anything also for  
8 4 days. If you combine it, then you can see that  
9 in the patients with the G856D mutation, or in the  
10 channels, you see marked axonal degeneration.  
11 So it means that the mutation in itself does  
12 not cause in this experiment axonal degeneration,  
13 but it is pathogenic. It contributes to axonal  
14 degeneration given certain circumstances. So it  
15 may be that you call it a risk factor. It may be  
16 that you call it a multi-hit model or whatever, but  
17 there is something going on.  
18 What is really important is that we realize  
19 that not every variant we see is contributing to  
20 the disease. You have to be very careful by  
21 stating that every variant is pathogenic because  
22 it's not, and that requires a very thorough workup,

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1 including the functional analysis, in silico  
2 testing. But in silico testing on its own is not  
3 enough I think, so you have to have a good family  
4 history, if possible; the functional testing, good  
5 clinical phenotyping. All these things are really  
6 important.  
7 To make things even more complicated, there  
8 are also polymorphisms that are quite frequent,  
9 some of them, that also have an influence on the  
10 channel function, and these probably influence pain  
11 perception; so not being pathogenic, but it can  
12 also have an influence.  
13 We also described gain-of-function mutations  
14 in Nav 1.8 and Nav 1.9 that also contribute to  
15 small fiber neuropathy. Of course there may be  
16 other genes. I thought this may be important  
17 because there was already discussion on the  
18 frequency of mutations, et cetera. In our own  
19 group of over 1500 patients, we have 1140 patients  
20 with a pure small fiber neuropathy, and we found  
21 patients with potential pathogenic mutation in  
22 SCN9A, 10A and 11A between 10 and 15 percent, and

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1 that's quite constant over the years now. The  
2 first publication was a very small group, but this  
3 is quite constant.  
4 We also studied the PROPANE study of which  
5 Giuseppe Lauria is the coordinator, looking at the  
6 role of sodium channels in painful small fiber  
7 neuropathy but also in diabetic neuropathy. I  
8 think important here is that you can see that these  
9 percentages are more or less the same as in our  
10 own population, which is much larger, but you can  
11 also see that there's a difference between the  
12 painful diabetic neuropathy and the idiopathic  
13 small fiber neuropathy. And this means that you  
14 cannot simply say that these are the same. I think  
15 these are distinct groups and that you need to look  
16 at them separately.  
17 This is also underlined by this paper that  
18 was already discussed in which 278 idiopathic  
19 neuropathy, of which partly was painful, and  
20 diabetic neuropathy also 77 percent painful, and  
21 the number of gain-of-function mutations was  
22 extremely low, and there were no differences

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1 between painful and non-painful groups in the  
2 previously reported gain-of-function mutation.  
3 This means that painful neuropathy is not the same  
4 as painful diabetic neuropathy, and it's also not  
5 the same as idiopathic small fiber neuropathy, the  
6 genetic meaning anyway.  
7 From the same PROPANE study, this is a work  
8 in progress. If we go to the group that we have  
9 now analyzed, the German painful diabetic  
10 neuropathy population, you can see that we found 51  
11 variants that were unique for the painful  
12 phenotype. This needs to be further analyzed, but  
13 there are differences between the painful and the  
14 non-painful group.  
15 Of course this leads to a lot of questions  
16 that remain unanswered. For example, the penetrant  
17 is caused by a difference in genetic background;  
18 what are really causes and what are contributors or  
19 risk factors, and what is the role of mutations in  
20 other genes or the genetic background? Is there a  
21 role for sodium channels in other painful  
22 neuropathies? We simply do not know at this point,

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1 or maybe if other genes and also of course  
2 therapeutic options. We do know that sodium  
3 channels play a role in small fiber neuropathy, and  
4 that it is important to make the diagnosis based on  
5 an integrated approach and that other genes or the  
6 genetic background might play an important role,  
7 and this may also be key to targeted treatment.  
8 My main assignment was, well, what do we do  
9 with this in terms of trial design? At this point,  
10 I think there are too many questions open to say,  
11 well, you have to analyze only patients with this  
12 mutation or that mutation. Should you include gene  
13 mutations in the trial design, it really depends on  
14 the kind of trial you are aiming for.  
15 For example, if you want to do a sodium  
16 channel blocker in a trial, it makes sense to do a  
17 secondary subgroup analysis on patients with  
18 mutations and patients without a mutation. For  
19 other trials, it doesn't make any sense at this  
20 point I think to do that, and there is so much more  
21 that we need to know before we can do any really  
22 strong suggestions regarding this.

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1 DR. FREEMAN: Thanks. Thank you very much.  
2 (Applause.)  
3 DR. FREEMAN: Any questions for Karin right  
4 now? Just know that there will be time  
5 [inaudible - off mic].  
6 DR. UCEYLER: Karin, thanks for this very  
7 nice talk. Just to come back to the numbers you  
8 gave about the prevalence of mutations in your  
9 large group of patients with small fiber  
10 neuropathy, one that you showed with 1,000 and more  
11 patients, did I get it right? It is around 10 to  
12 15 percent you would say that are positive.  
13 These are sodium channel mutations?  
14 DR. FABER: Yes.  
15 DR. UCEYLER: All of them, and not other --  
16 DR. FABER: No. These are only the sodium  
17 channel mutations.  
18 DR. UCEYLER: Okay. That's very  
19 interesting. We also are looking at the genetics  
20 in our patients in the last years. For instance,  
21 in a group of around 60 patients, I would have  
22 maybe 4 to 5 with a mutation. One of those would

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1 be sodium channel and 3 to 4 really other genes,  
2 which is also important not only to focus on the  
3 sodium channels. But this is really all sodium  
4 channel, right.  
5 DR. FABER: The analysis for the other genes  
6 that we are testing is following.  
7 DR. UCEYLER: If I may add another short  
8 comment, coming back to your paper you presented in  
9 2012, the Annals paper, very beautiful, where you  
10 had a higher number and where you had selected the  
11 patients. So these were those who had reduced  
12 further density and pathological QST, right, and  
13 had all sodium channel mutations.  
14 This is very interesting. In our hands,  
15 interestingly, those with the channel mutations are  
16 mostly those who have normal fiber density and also  
17 normal QST when we use the DFNS criteria, which I  
18 always find very logical because you have the  
19 mutation. In the neuron, the exaggerability  
20 changes. Why should fiber density change, and why  
21 should thermal perception change? But very  
22 interesting, and I think something to be discussed

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1 later on.  
2 DR. FABER: In our group, it doesn't make  
3 any difference. We check that as well, whether  
4 there's a difference in abnormal skin biopsy with  
5 or without a mutation, but the percentages are the  
6 same.  
7 DR. GIBBONS: Hi. Chris Gibbons. I think  
8 the work is spectacular. I think one of the things  
9 that we're always struggling with as we sort of  
10 trickle down from where the initial research comes  
11 and where it ultimately ends up, obviously the  
12 paper that was just referred to with the PNR group  
13 had a very different frequency of mutations and of  
14 unclear relevance. And I think to some of us, when  
15 we look at these in our own populations, the  
16 frequency with which we may find these mutations  
17 seems to be very different than what's reported.  
18 And it may be, again, a bias in terms of referrals,  
19 et cetera. But then when we do find the mutations,  
20 it seems to have nothing to do with at all what we  
21 would traditionally think of as a neuropathy.  
22 I'd be curious to see what others'

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1 experiences with this are, but I know it's one of  
2 the challenges in putting this together. And I  
3 wasn't sure if you heard feedback yet from other  
4 groups around the world on this.  
5 DR. LAURIA: If I may, I had a comment. The  
6 point is that these are -- let's call them variants  
7 because we don't actually know what they are. We  
8 know that there are some variants compared to our  
9 controls. The second thing is that it's a  
10 matter -- this has been a quite large targeted NGS  
11 approach, and of course it depends on the filtering  
12 that you do. So we have filtered patients based on  
13 some clinical criteria and some molecular biology  
14 criteria, and in this way, we came up with a number  
15 of variants which can segregate into different  
16 phenotypes, also comparing idiopathic and diabetic.  
17 But in any case, it is clearly a little bit  
18 more complex, and, again, the message it's  
19 carrying, has been delivering, is that likely there  
20 is a kind of background or susceptibility, which  
21 can cluster a subgroup of patients based on the  
22 frequency of some variants in the different genes

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1 and coding for only the sodium channels that we  
2 have analyzed, that we have material to analyze  
3 many other genes.  
4 DR. FREEMAN: Can I ask a question? I want  
5 to just follow up on the question that  
6 [inaudible - off mic] asked. I had a similar  
7 response when I saw that slide, and I will be more  
8 specific. Have you actually looked at loss of  
9 function mutation in the potassium channel?  
10 DR. FABER: Well, not at this point.  
11 DR. LAURIA: We have loss of function only  
12 in some patients we've found with the expected  
13 phenotype of congenital insensitivity to pain.  
14 Actually, we have found in one case a loss of  
15 function that was not pathogenic. The protein was  
16 nothing, and we did a test on [indiscernible]. So  
17 actually, so far, as far as I know, there  
18 isn't -- all the variants that are related to pain  
19 are amino acid substitution.  
20 DR. FREEMAN: Because as you know, there are  
21 immune mediators -- [inaudible - off mic] on the  
22 potassium channel syndrome [inaudible - off mic].

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1 DR. BELL: Can I just ask one more question,  
2 Roy, before we move on?  
3 Karin, hi. Josh Bell from Biogen. I just  
4 have a quick question for those of us in the drug  
5 development business. So you showed a lot of data  
6 on the involvement of multiple sodium channels in  
7 the proposition of pain, the SCN9A, 10A, and 11A.  
8 Based on all the work that you've done, would you  
9 say that it is more advantageous to develop a drug  
10 that targets multiple sodium channels, inhibiting  
11 each one to X percentage, or would you rather have  
12 one really good drug that inhibits one particular  
13 sodium channel?  
14 DR. FABER: Well, this is a wild guess of  
15 course, but I think that if you hit one sodium  
16 channel and do it really good, that it should work.  
17 DR. BELL: That would better than --  
18 DR. FABER: So Nav 1.7 and Nav 1.8, they  
19 work in tandem, so if you block one, you will also  
20 influence the function of the other. My guess  
21 would be that if you have a good Nav 1.7 blocker or  
22 a very good Nav 1.8 blocker, that you will

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1 influence pain irrespective of whether you have a  
2 mutation or not.  
3 DR. BELL: You would rather have a drug that  
4 works like that than one that has a 30 to  
5 40 percent inhibition of each one of those Nav  
6 channels?  
7 DR. FABER: Yeah, I think so.  
8 DR. BELL: Okay.  
9 DR. FREEMAN: I think that's a topic for the  
10 panel. Can you wait, David, for the panel?  
11 DR. HERRMANN: I'll ask it during the panel.  
12 DR. FREEMAN: It's a pleasure to introduce  
13 Ahmet Hoke from Johns Hopkins. He has in many ways  
14 driven the peripheral neuropathy research registry  
15 and will talk about the results of that study and  
16 put it in the context of what Karin has just spoken  
17 about.  
18 Ahmet?  
19 Presentation - Ahmet Hoke  
20 DR. HOKE: Thank you.  
21 As Roy mentioned, we've set up a  
22 collaboration a number of years ago with Roy, and

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1 later Gordon and Rob also joined this consortium,  
2 which is funded by the Foundation for Peripheral  
3 Neuropathy. We call it the Peripheral Neuropathy  
4 Research Registry, and this is, really, a natural  
5 history study focusing on distal symmetric  
6 polyneuropathy patients, primarily axonal  
7 neuropathy patients. And we had 4 disease  
8 categories that we enroll patients in this cohort:  
9 idiopathic, diabetic, HIV, and chemotherapy-induced  
10 neuropathies. This specifically excluded known  
11 inherited neuropathy patients, as well as  
12 autoimmune neuropathies.  
13 We collect detailed histories, standardized  
14 examination, and there's a minimum data set for  
15 labs, nerve conduction studies, and skin biopsies.  
16 We collect blood for future genomic and biomarker  
17 studies, and out of this cohort, a number of years  
18 ago -- I think they first approached us about four  
19 years ago now -- Bristol-Meyers-Squibb wanted to  
20 access this data set and collect blood for looking  
21 at -- but the main goal of their study was to  
22 identify a genetically defined subpopulation of

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1 peripheral neuropathy patients, whether they could  
2 then test specific Nav 1.7 inhibitors.  
3 Obviously the rationale is already there,  
4 and Karin already went over this, including their  
5 studies. BMS basically obtained the identified  
6 blood samples from the registry and did sequencing  
7 of Nav 1.7, 1.8, and 1.9. These are patients who  
8 had peripheral neuropathy. And I think every  
9 patient in this cohort had evidence of neuropathy  
10 either by nerve conduction studies or by skin  
11 biopsies, abnormal skin biopsies. Patients with  
12 normal nerve conduction studies and normal skin  
13 biopsies were not included in this cohort.  
14 The comparison to Karin's first paper is  
15 highlighted here. The BMS study was really a  
16 little bit untargeted in the sense that we took  
17 all-comers, all idiopathic and diabetic neuropathy  
18 patients in the cohort at that time. Right now,  
19 our numbers are about 1500 patients, but when these  
20 blood samples were taken, we had about 500  
21 idiopathic and diabetic neuropathy patients in the  
22 cohort.

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1 The idea was to correlate potential  
2 gain-of-function mutations or loss-of-function  
3 mutations with either clinical diagnosis of painful  
4 neuropathy versus non-painful and also to correlate  
5 the incidence of these mutations or variants within  
6 pain in each category. Within this group, they  
7 also looked at a subpopulation of patients who  
8 would have been labeled as idiopathic small fiber  
9 neuropathy because they had normal nerve conduction  
10 studies but abnormal skin biopsies.  
11 In our cohort -- and I think this reflects  
12 what Rob and Karin also mentioned -- a majority of  
13 the patients in the idiopathic group have painful  
14 neuropathy, and perhaps this also reflects the  
15 referral bias. Even among the diabetic patients, a  
16 large population had painful neuropathy. One other  
17 thing is -- and I'm sure other people have also  
18 noted this -- in our cohort, patients with painful  
19 symptoms in a given disease category tend to be  
20 much younger than the older patient populations.  
21 Within this cohort, they basically  
22 identified a number of genetic variants out of that

<p style="text-align: right;">Page 81</p> <p>1 450 subjects that was distributed across all three 2 sodium channels. The idea was to look at rare 3 mutations. Most of these coding variants resulted 4 in amino acid changes in all three groups. And one 5 of the things that came out of this study was that 6 these rare mutations, some of the patients actually 7 had multiple mutations; that they're not just 8 unique to one patient that only has mutation 9 Nav 1.7 but not the others. We had one patient 10 that had rare mutation in all three of them, 11 actually disease-causing mutations. They looked 12 carefully at these variants, and basically they 13 were distributed across the whole protein domains. 14 And again, these are all considered the rare 15 mutations that are less than 5 percent in the 16 general population. 17 Let me go back. Four of these rare 18 mutations were actually reported as the 19 gain-of-function mutation that Karin also 20 mentioned, [indiscernible] change in others. 21 When you look at these, quote/unquote, "know 22 gain-of-function" mutations across the whole</p>	<p style="text-align: right;">Page 83</p> <p>1 history questionnaire, the patients are asked about 2 their pain status, and if they said no pain, then 3 they're considered non-painful neuropathy. There 4 was no enrichment across all three Nav channels. 5 Within the idiopathic neuropathy patient 6 population, looking to see if there was any 7 enrichment, again, there was no enrichment in this 8 cohort of idiopathic peripheral neuropathy 9 patients. Again, looking at the rare and missense 10 mutations in the idiopathic small fiber neuropathy 11 patient -- this is a subpopulation of the 12 idiopathic peripheral neuropathy patients, and 13 again, there is no enrichment. 14 Then they looked at the haplotype groups 15 across all three genes, and again, they didn't see 16 any enrichment in painful versus non-painful 17 neuropathy, and there was no difference in 18 comparison to the reference population. And again, 19 there was no enrichment in the idiopathic subgroup. 20 In summary, this data set didn't really show 21 any enrichment in the U.S. population of these rare 22 gain-of-function mutations or even other rare</p>
<p style="text-align: right;">Page 82</p> <p>1 population, it was present only in about 3 percent 2 of the cohort that we had. These were primarily in 3 Nav .7, partly because that's where most of the 4 publications have been. Even though I mentioned 5 that there are some patients who had complex 6 mutations with multiple -- most of the patients in 7 the cohort had single, rare variants in the Nav .7 8 They then compared these non-synonymous, 9 low-frequency variants to reference populations, 10 and they were very similar, and again, similar 11 results with the other sodium channel mutations. I 12 think this is where perhaps the data from this 13 cohort differs from Karin's and maybe Giuseppe's 14 data set. These mutations were similar to the 15 general population. The only one that was 16 different was that in the Nav .17 [ph] mutations, 17 the frequency was slightly higher than the 18 reference populations. 19 Then they looked at the enrichment of these 20 rare Nav mutations in painful versus non-painful 21 categories. And again, this was basically 22 patient-reported classification, so in the patient</p>	<p style="text-align: right;">Page 84</p> <p>1 mutations in either idiopathic neuropathy patients 2 or in idiopathic painful neuropathy patients. So 3 based on this, I know BMS basically stopped their 4 Nav channel inhibitor program perhaps partly based 5 on these results. 6 It's going to be interesting how this plays 7 out, whether these are really druggable targets or 8 not. The data from families is very convincing, 9 but whether it's in the general population and are 10 there other modifiers that make these more disease 11 relevant will need to be seen. I'll stop. I think 12 this is my last slide. 13 Amanda? 14 DR. PELTIER: As part of your study, did you 15 have a chance to collect DNA from any of the family 16 members of the patients to figure out whether or 17 not those variants were -- I mean -- 18 DR. HOKE: That's a very good question. As 19 part of the -- 20 DR. PELTIER: You've been hanging out with 21 Jim [indiscernible] for too long. 22 DR. HOKE: -- we're not collecting blood</p>

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1 from the family members. As I was listening to  
2 Karin's talk, I was thinking actually if we could  
3 go back to the patients that have been identified  
4 in this cohort with the gain-of-function mutations  
5 and look at the family members -- obviously, I need  
6 to write a separate [indiscernible] before that.  
7 (Laughter.)  
8 DR. FREEMAN: Can I ask something? This is  
9 just [inaudible - off mic] -- carefully done study  
10 as Karin and others have done and a registry study.  
11 MALE VOICE: Roy, mic.  
12 DR. FREEMAN: Okay. What I was saying is  
13 there's an enormous difference between a registry  
14 study and a very carefully study done by academic  
15 centers who are devoted to a study. But even so,  
16 looking at the data you showed -- and I think it  
17 was four slides back, how many subjects of the 440  
18 or so do you think came very close to replicating  
19 the kind of patients that they have reported? And  
20 it looked to me like there were only 10 on the  
21 slide that you showed.  
22 So what I'm asking is patients who had a

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1 pure small fiber neuropathy, normal nerve  
2 conduction studies, no large fiber modality  
3 dysfunction, abnormal skin biopsy, and some other  
4 measure or some other criterion for small fiber  
5 neuropathy.  
6 DR. HOKE: Can you put the slides back? I  
7 just want to go back to the --  
8 DR. FREEMAN: It's about three slides back,  
9 the slide that prompted the question.  
10 DR. HOKE: Within the idiopathic -- yes.  
11 The pure small fiber neuropathy patients in this  
12 cohort is probably smaller than the reports  
13 of -- like Karin's large study with just a pure  
14 thousand patients with small fiber neuropathy.  
15 DR. FREEMAN: There are many reasons why  
16 there might be differences. I wondered whether one  
17 of them might be a type 2 error.  
18 DR. HOKE: Possible. We're looking at  
19 all-comers of idiopathic neuropathy patients and  
20 all-comers of diabetic neuropathy patients. That  
21 was BMS' interest, do you want to treat the tiniest  
22 population versus is this really applicable to the

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1 large patient population of painful neuropathies  
2 across different etiologies. That was the main  
3 reasons for this study.  
4 DR. FREEMAN: David?  
5 DR. HERRMANN: I do think, though, this  
6 probably speaks to differences in genetic  
7 background because I know at our center, we have,  
8 over the last maybe 5, 6, 7 years -- since  
9 next-generation sequencing has been available,  
10 we've taken every patient who's been younger with  
11 an early onset neuropathy, pure small fiber, normal  
12 medial plantars, normal surals, and with a clinical  
13 syndrome with or without the abnormal fiber  
14 density, and I've not found one pathogenic mutation  
15 in the sodium channels.  
16 So clearly, these patients and families are  
17 there, but I think what you'd probably could do to  
18 supplement your numbers of pure small fiber  
19 neuropathies -- across several centers in the  
20 United States that have been doing similarly -- you  
21 could probably aggregate some of the data to get a  
22 larger number of patients who really match the

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1 European experience. And it may just be that there  
2 are different genetic backgrounds that are at play  
3 here.  
4 DR. FREEMAN: Karin?  
5 DR. FABER: I think that one issue that is  
6 not mentioned, and it's very important, is you  
7 really have to look at your filtering criteria  
8 because if you select variants with a frequency of  
9 less than 5 percent, that's not a rare variant. I  
10 mean, that's really a big issue I think because we  
11 select variants that are less than 1 percent or  
12 even less than 0.1 percent. So if you're looking  
13 for rare variants, then those are rare variants,  
14 but 5 percent or 4 percent, that's not a rare  
15 variant. That's a frequent variant.  
16 DR. HOKE: They looked at both -- the  
17 analysis was done both looking at those variants  
18 that are less than 5 percent plus the reported  
19 gain-of-function mutations from your papers. And  
20 even if you look at just those patient populations,  
21 the numbers were much smaller obviously, and there  
22 was really no enrichment in those mutations in

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1 painful versus non-painful.  
2 DR. FABER: That indeed could be something  
3 like a different genetic background.  
4 DR. LAURIA: Also the difference in how the  
5 painful and non-painful have been defined because  
6 all the times it's very difficult because someone  
7 may say zero pain or painless is a non-clinical  
8 meaningful pain and so on.  
9 DR. HOKE: In our cohort, it's a very simple  
10 question. "Do you have pain attributable to your  
11 neuropathy?" And if the patient says no, then they  
12 are basically classified as non-painful. If they  
13 say yes and then they report is it 1 to 10, and the  
14 frequency and duration and so forth -- that's the  
15 classification of painful versus non-painful in our  
16 cohort. Obviously, probably do you want to  
17 consider a patient who says, yes, I have pain but  
18 it's only 1 or 2. Is that really painful versus  
19 the ones who say I'm in pain all the time and rates  
20 as 10?  
21 DR. OAKLANDER: One thing I've noticed is  
22 that a lot of these rare patients who come in who

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1 have these mutations, I know they have it or I'm  
2 very strongly suspicious of it before I do the  
3 genetic testing. We're in the ivory towers, a lot  
4 of us. Our recommendations are going to be read by  
5 people all over the world and physicians who don't  
6 have access to genetic testing, so I think we also  
7 have to think carefully about what the role is of  
8 expert clinician opinion.  
9 If somebody comes in with a strong family  
10 history and red burning feet, and they respond to  
11 mexilitine, you have to -- I mean, it's good to do  
12 it if you can do it. I'm in favor of genetic  
13 testing, but I don't know that that you have to do  
14 it before you treat somebody.  
15 DR. HOKE: I would actually argue that with  
16 the cost of genetic testing coming down, I'm in  
17 favor of testing every patient that comes before I  
18 even do an EMG or skin biopsy. It's much cheaper.  
19 DR. OAKLANDER: Of course.  
20 (Laughter.)  
21 DR. OAKLANDER: I agree a hundred percent.  
22 Of course, we all do. But we also have to look at

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1 the reality that the insurance companies do not  
2 agree with that statement.  
3 DR. HOKE: I haven't had a single patient's  
4 genetic testing rejected. Cost to the patient is  
5 only a hundred bucks for doing whole exome  
6 sequencing.  
7 DR. FELDMAN: We should really talk about  
8 that because we have many more insurance issues in  
9 Michigan.  
10 DR. FREEMAN: I'm speechless after that  
11 comment.  
12 (Laughter.)  
13 DR. OAKLANDER: So who here has insurance  
14 issues with ordering genetic testing for neuropathy  
15 patients?  
16 (Show of hands.)  
17 FEMALE VOICE: Huge.  
18 DR. OAKLANDER: Who has no insurance issues?  
19 (Laughter.)  
20 DR. OAKLANDER: So my point is we want  
21 global recommendations and we want to be useful in  
22 other --

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1 (Crosstalk.)  
2 DR. FREEMAN: On that note, let's take a  
3 break  
4 DR. HOKE: -- countries, and we can't assume  
5 that everybody has access to genetic testing.  
6 (Whereupon, at 10:01 a.m., a recess was  
7 taken.)  
8 DR. FREEMAN: As we begin, what I would like  
9 is for all of the speakers to come up to the front  
10 to form the panel. Oh, no. We're not at the panel  
11 yet, are we?  
12 One of the important roles of the chairman  
13 is to actually look at the schedule. Before I  
14 introduce the next speaker, one housekeeping  
15 announcement to make. And that is, as you know,  
16 there is free internet access, and the free  
17 internet access is for 35 individuals. If you were  
18 to do a prevalence of individuals in the room, you  
19 would recognize that there are 29 individuals in  
20 the room, and yet many people trying to log onto  
21 the internet are unable to do because we appear to  
22 have more than 35 people attempting to log on,



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1 which means if you were to do the math, some people  
2 are logging on more than once on more than one  
3 device.  
4 So what we request is one device, one  
5 person, if you can manage that, which is a  
6 democratic principle.  
7 (Laughter.)  
8 DR. FREEMAN: And having set that in motion  
9 and talking about voting more than once, let me  
10 introduce Todd Levine, who will be discussing I  
11 think one of the more controversial aspects of the  
12 meeting, and that is immune factors in small fiber  
13 neuropathy. I think probably there was some  
14 subliminal, subconscious aspect over here wanting  
15 to avoid all controversy, that I decided to skip  
16 this talk.  
17 Todd, please?  
18 Presentation - Todd Levine  
19 DR. LEVINE: Well, thank you guys for having  
20 me today. This is really going to be a lot of  
21 small anecdotal case series because, unfortunately,  
22 we don't have any good trials. But I think we'll

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1 sort of highlight the fact that many of us here  
2 from our patients treating small fiber neuropathies  
3 with immunomodulatory therapy is something that  
4 they want. I think for the clinicians in the room,  
5 we are looking for those patients that we can help,  
6 so this is a group of patients that we really try  
7 to identify.  
8 I think the beginning and the end of this,  
9 we'll sort of make the point as some of the earlier  
10 talks did, but I think unless we get accurate and  
11 smaller definitions of these disorders, we'll never  
12 really going to be able to find anything that works  
13 for the groups as a whole.  
14 A couple of disclosures, I work, by  
15 consultants and from the grant support, with some  
16 of the IVIG companies, so Shire, Grifols, and CSL,  
17 and also with Octapharma and with NuFACTOR home  
18 infusion company. And then I have a financial  
19 interest in Corinthian Reference Lab, which  
20 provides skin biopsy testing.  
21 We don't have great case series for small  
22 fiber neuropathies, in part because it depends on

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1 how you define it. So is it abnormal skin  
2 biopsies? Is it clinical? Is it QSTs? This is a  
3 paper from a few years ago that looked at  
4 mixed-fiber neuropathies both in South America,  
5 which is the column on the right, and North America  
6 on the left, and really kind of highlights the  
7 point that at least in North and South America  
8 among mixed fiber neuropathy, about 20 percent are  
9 probably immune-mediated. I think if you wanted to  
10 throw a dart at a board and said what percentage of  
11 small fiber patients are probably immune-mediated,  
12 20 percent would probably be a good starting point  
13 because, again, we don't have great data.  
14 The cryptogenic here is listed as only about  
15 a quarter of the cases in both groups, and then the  
16 hereditary varies probably depending on how you  
17 actually define inherited neuropathies,  
18 polymorphisms versus pathogenic mutations, but the  
19 number I kind of wanted to highlight is the 20  
20 percent number.  
21 That really kind of brings us to a broader  
22 question, which is what the hell is an

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1 immune-mediated neuropathy? And this is where we  
2 have a problem from square one. So I was going to  
3 actually just use this case to demonstrate that we  
4 don't even know what a neuropathy is or what an  
5 etiology of a neuropathy is.  
6 There's a 62-year-old female, 25-year  
7 history of diabetes, 3-year history of neuropathic  
8 symptoms. So is that diabetic neuropathy?  
9 Probably. Well, what if they had gotten  
10 chemotherapy five years ago because she had breast  
11 cancer? What if her family history's got 3 first-  
12 degree relatives? Is that inherited or is that  
13 diabetic?  
14 What if she took Levaquin 10 days before the  
15 symptoms began? Is that a toxic neuropathy or a  
16 diabetic neuropathy? Or are a lot of our  
17 neuropathies actually caused by multiple causes,  
18 which is what actually I would believe, and that we  
19 don't really know the etiology of any of these  
20 neuropathies? And this is as good as it gets,  
21 right? Twenty-five-year history of diabetes,  
22 that's as good as we can do. Now we're going to

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1 try to talk about immune neuropathies, and we're  
2 not going to do as well.  
3 How do we define a neuropathy as potentially  
4 immune mediated? These are my thoughts, and I'm  
5 sure we could probably add to it. The first is a  
6 clinical presentation. So that would be the  
7 pornography analogy, right? You know it when you  
8 see it.  
9 (Laughter.)  
10 DR. LEVINE: That's fair. I mean, we're  
11 clinicians. That's what we're supposed to do.  
12 What about acute onset? So somebody who's fine and  
13 2 days later, they've got diffused neuropathic pain  
14 everywhere, that seems to suggest that, but why  
15 couldn't that be toxic? We don't know that either.  
16 When it comes to the mixed fiber  
17 neuropathies, we've relied a lot on  
18 electrophysiology, and we'll talk about that a  
19 little bit. That can be helpful. It can also be  
20 very misleading. And then in the mixed fiber  
21 neuropathies, we used to rely on pathology. So  
22 some of the earliest descriptions of CIDP from

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1 Peter Dyck's group was based on actually doing  
2 vesicular nerve biopsies and seeing the  
3 inflammation in the nerve.  
4 Again, in some of the neuropathies, you have  
5 to look at changes in the CSF, C-elevated protein,  
6 and those kinds of abnormalities. More and more,  
7 we'd like to rely on the presence of neural  
8 autoantibodies, but we don't know the sensitivity  
9 or the specificity of those antibodies.  
10 What about associated autoimmune diseases?  
11 We'll talk a bit about that. If a person's got  
12 Sjogren's, does that mean their neuropathy is from  
13 Sjogren's or is it an idiopathic neuropathy and  
14 they just happen to have Sjogren's?  
15 The last one is the really challenging one.  
16 What about response to therapy? Can you define a  
17 neuropathy as immune mediated because they get  
18 better with IVIG or prednisone? Well, maybe, but  
19 what about the placebo effect? And I'll kind of  
20 show you a bit of that as well.  
21 This is a paper, actually after a lot of  
22 attempts, I just got published. And I'll throw it

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1 out there and you guys can attack it during the  
2 open session if we want. But my first point is  
3 that I don't think we can call this small fiber  
4 neuropathy anymore. We heard that a little bit  
5 this morning. I like the idea of small fiber  
6 predominant neuropathy because all neuropathies  
7 that cause pain, the pain's mediated by the small  
8 fibers; we know that, or pure small fiber  
9 neuropathy.  
10 But even within that, if you see enough of  
11 these patients, they look very different. So I've  
12 tried to propose that we break it out into four  
13 different groups. One is the small fiber sodium  
14 channel patients, so they have clear genetic  
15 defects in their sodium channels. They look very  
16 different than our other patients. You can  
17 identify them. They often have the  
18 erythromelalgia. Then you've got the small fiber  
19 mediated painful neuropathy patients. That's most  
20 of the patients we're sort of talking about. But  
21 that now really overlaps -- and I'll show you some  
22 data -- in this kind of more widespread pain

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1 disorder, so fibromyalgia for example. We know a  
2 significant percentage of those patients have small  
3 fiber dysfunction.  
4 Glenn Lopate's group at Wash U presented  
5 patients that only have muscle cramps and no  
6 neuropathic symptoms, that have small fiber  
7 neuropathy. So all of those sort of lump together  
8 and I think need to be split out because I think  
9 their clinical differences are probably telling us  
10 something. And then you have autonomic dysfunction  
11 on the other end. And then the problem is these  
12 overlap in a variety of different ways with  
13 different Venn diagrams. So obviously, some  
14 patients with painful neuropathy also have the  
15 autonomic symptoms and vice versa, but not always,  
16 and that may be telling us something different  
17 about their pathology.  
18 Let's start a little bit with the mixed  
19 fiber neuropathies. The classic immune neuropathy  
20 is Guillaine-Barre. We all accept this is an  
21 immune-mediated neuropathy. But the patient comes  
22 in a day after their symptoms begin. Their nerve

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1 conduction studies may be normal. Their CSF may be  
2 normal. If a patient was exposed to campylobacter,  
3 it may be axonal, so demyelinating and autoimmune  
4 are not synonymous. That's not the same process.  
5 Most of the patients with Guillaine-Barre  
6 don't have identifiable autoantibodies. They don't  
7 have to have a preceding illness. So we make the  
8 diagnosis of Guillaine-Barre clinically. Again, we  
9 know it when we see it, and we treat it. Everybody  
10 accepts that fact. Right? They don't say, oh no,  
11 your nerve conduction studies are normal on day 2;  
12 you can't give that person IVIG. Clinically we  
13 know it because we see it.  
14 So it makes it very difficult now when we  
15 start to go to other syndromes when we don't have  
16 quite as good a clinical course. So let's talk  
17 about small fiber neuropathies. Again, these are  
18 small series, I understand, but we'll talk about  
19 really good data to not so good data.  
20 So your classic Guillaine-Barre patient  
21 shows up. You know it when you see it. Here are  
22 two patients that were presented this year.

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1 Patients had acute onset preceded by an infection,  
2 diffused hyperreflexia, albuminocytologic  
3 association. They got IVIG. One got steroids.  
4 But most important, in the study, they took their  
5 sera, transferred it to a mouse model, and there  
6 were transient alterations in the thermal pain  
7 response.  
8 It's very difficult to argue that this is  
9 not an immune-mediated small fiber neuropathy.  
10 Now, we're not going to have most of this data for  
11 most of our patients, but this argues it does  
12 exist. We just may not have all the things at our  
13 disposal, particularly the mouse model, every time  
14 that we see a patient.  
15 So how about this case? This was a case  
16 that was published two years ago of a girl who got  
17 a vaccine, and beginning 9 days after the vaccine  
18 developed a diffused painful neuropathy. So skin  
19 biopsy was abnormal, everything else was normal,  
20 and they called this, again, a post-vaccination  
21 acute small fiber neuropathy. Probably, not as  
22 good a case as the one I just showed you before,

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1 but you go, "Yeah. I kind of buy it."  
2 Then what about this series from 10 years  
3 ago where they took patients that had acute onset  
4 small fiber neuropathies? They had abnormal QSTs  
5 in skin biopsies, and they gave them steroids, and  
6 they got better, but it was all a length-dependent  
7 neuropathy. Are you convinced that that's immune  
8 mediated? Probably a little less so than the first  
9 two I showed you, but it could be, but we just  
10 don't know.  
11 So when it comes to mixed fiber  
12 neuropathies, again, we've got the  
13 electrophysiology. We don't have the  
14 electrophysiology for small fiber studies. But the  
15 reason I've put this up here is in that first  
16 slide, you've got a long latency -- I think it's a  
17 median -- and the connection velocity is 31. Here  
18 you've got really impressive temporal dispersion.  
19 Here you've got conduction block.  
20 So that's three different examples of  
21 different types of demyelination. We tend to lump  
22 them all together and say, yes, that's evidence of

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1 a demyelinating neuropathy. This is most likely  
2 acquired when you see these types of changes, and  
3 therefore, acquired demyelinating neuropathy means  
4 that this is an immune-mediated process.  
5 The problem is we have -- actually I should  
6 say 20. We have 20 different sets of criteria for  
7 figuring out how much conduction block temporal  
8 dispersion with our prolongation latencies and  
9 velocities you need, and none of them are really  
10 all that good. Again, they help us, but they're  
11 not really that good.  
12 Then even more importantly are a growing  
13 number of case reports of inherited neuropathies  
14 where you can have proximal weakness, conduction  
15 blocks, and patchy load conduction velocities; not  
16 the findings that you would expect to see in the  
17 inherited neuropathies, but they can occur. So  
18 even our nerve conduction studies, which we think  
19 of as the most helpful for small fiber  
20 neuropathies, turned out not to be as helpful as  
21 we'd like. And again, we don't really have any of  
22 those tests for small fiber neuropathies, and

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1 probably more importantly, we don't have any tests  
2 for sodium channel dysfunction or nodal  
3 dysfunction.  
4 So the contactin antibodies, the neurofascin  
5 antibodies, we now know are affecting the nodes but  
6 not necessarily the myelin diffusely. And all the  
7 sodium channel defects that we see, we don't have a  
8 good way to test that clinically to know whether  
9 that's relevant as well.  
10 So how about biopsies? We like skin  
11 biopsies. I've got a lot of the skin biopsies, so  
12 we like that. Skin biopsies traditionally have  
13 been okay for allowing us to look for acquired  
14 neuropathies.  
15 Here are a couple of different studies that  
16 looked at doing patients that they were really sure  
17 had CIDP, and about 1 in 5 are normal. So it's  
18 about 80 percent, which is about as good as any of  
19 the different sets of nerve conduction study  
20 criteria that we have. But very often you also  
21 just see external degeneration, so that now means 2  
22 in 5 are going to be completely unhelpful in

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1 distinguishing immune neuropathy, even in cases,  
2 again, with our gold standard mixed fiber  
3 neuropathy of CIDP.  
4 Then what about all the immune neuropathies  
5 that are demyelinating, all the vasculitides that  
6 we see? So again, looking for demyelination as the  
7 gold standard of some type of acquired  
8 demyelinating or autoimmune disorder may miss a lot  
9 of potential patients.  
10 But when it comes to pathology in skin  
11 biopsies, this paper from I guess six years ago now  
12 began all of us thinking in a slightly different  
13 way. I like it. I don't think it's perfect. But  
14 what they basically did here was to say we're going  
15 to look at patients that have a length-dependent  
16 small fiber neuropathy by pathology, so worse  
17 distally, and compare those to patients that have a  
18 non-length-dependent small fiber neuropathy. And  
19 what they found was that if you have a  
20 non-length-dependent small fiber neuropathy, you're  
21 more likely to be female and you're more likely to  
22 have an autoimmune disorder.

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1 This began a lot of us thinking, well, we  
2 probably need to pay attention to this. Again,  
3 it's not perfect, but I do think it argues a little  
4 more strongly. But again, if you look at this, the  
5 immune-mediated neuropathies were only in  
6 14 percent of the non-length dependent. So think  
7 about that 15 to 20 percent number. That's  
8 probably about as good as we're going to do in  
9 terms of the overall neuropathies that we're  
10 talking about.  
11 This is two other studies now trying to look  
12 at autoantibodies. Antoine had a very nice paper  
13 where they took patients that had a sensory  
14 neuronopathy clinically, so a non-length-dependent  
15 clinical syndrome, and they found elevated levels  
16 of antibodies against fibroblast growth factor  
17 receptor 3 in 15 percent of their patients compared  
18 to 0.5 percent of the controls.  
19 Pestronk had another paper that he looked at  
20 TS-HDS antibodies, and he found that the majority  
21 of the patients who had positive antibodies to  
22 TS-HDS presented with upper-limb symptoms before

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1 lower-limb symptoms, again, both arguing for a  
2 non-length-dependent clinical and pathologic  
3 syndrome in patients that have these autoimmune  
4 diseases.  
5 This was another series from last year,  
6 again, small numbers of patients, but they found  
7 patients that had -- children, actually, that had  
8 small fiber neuropathy, and they found elevated  
9 levels of IgM antibodies against TS-HDS I think in  
10 4 of the 5 patients.  
11 What about looking at CSF? Well, CSF,  
12 unfortunately, even in CIDP is not great, so we use  
13 it if we're kind of confused. But some people have  
14 tried to use it to distinguish, say, a diabetic  
15 neuropathy from an immune neuropathy. And the  
16 problem is that doesn't really work. We've got  
17 cases where diabetic neuropathy can have CSF  
18 proteins as high as 400. And probably more  
19 mistakes are made because the lab values cut off 45  
20 as being high. You get some 60 year old with  
21 diabetes, they get a spinal tap to protein 60, and  
22 then they're labeled as CIDP.

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1 So we can look for this. I've done a fair  
2 number of LPs in the presumed autoimmune small  
3 fiber neuropathies, and I've not found them to be  
4 very helpful. There was one report that I liked  
5 actually that looked at IgG synthesis rate,  
6 actually, as being one of the most helpful if  
7 you're trying to follow an immune-mediated process.  
8 So at least in CIDP, as the IgG synthesis rate  
9 comes down, their disease seems to be less active.  
10 So it's one thing that you could look for if you  
11 wanted to.  
12 This was a relatively large study looking at  
13 Sjogren's patients. What they found first off was  
14 that about 60 percent of patients with Sjogren's  
15 syndrome had peripheral neuropathy. They then  
16 looked in the spinal fluid of those patients. They  
17 found that 9 percent had a few cells, but nothing  
18 really too impressive. About 20 percent had  
19 oligoclonal bands in the patients that had  
20 peripheral neuropathy. So again, the sensitivity  
21 here is just very, very low, and probably makes it  
22 not all that meaningful to look for if you want to.

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1 This was another paper, actually, by Lopate  
2 at Wash U again, where they found 45 percent of  
3 patients with Sjogren's syndrome had small fiber  
4 neuropathy, pure small fiber neuropathy.  
5 Other autoimmune diseases, so sarcoid,  
6 there's a company now developing a drug that  
7 targets the innate repair receptor. They've  
8 published some early phase 2 results specifically  
9 in sarcoid-mediated small fiber neuropathy, but it  
10 seems to be relatively common.  
11 So they looked at sarcoid-related small  
12 fiber neuropathy in 143 cases. Pain was the most  
13 common symptom, dysautonomia in almost half of the  
14 patients. Then they treated patients with IVIG.  
15 They saw 47 out of 62 patients improve with IVIG; 8  
16 of 12 patients that got anti-TNF therapies  
17 improved; and 10 of 14 patients that got both  
18 therapies improved.  
19 So they argue that the small fiber  
20 neuropathy in patients with sarcoid is likely to be  
21 immune mediated, again, largely on the basis of the  
22 fact that the patients' symptoms improved with

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1 therapy.  
2 For the most controversial subjects, Ann  
3 Louise published the first of these papers. They  
4 compared patients with fibromyalgia, the control  
5 subjects, and found 41 percent of patients with  
6 fibro had small fiber neuropathy compared to  
7 3 percent of the patients in the control group.  
8 Then importantly, a large percentage of the  
9 patients that had fibromyalgia had some form of  
10 immune dysregulation.  
11 We published a few years later with Ohio  
12 State. We found 50 percent of our fibro  
13 patients -- we did not have a control group, so we  
14 biopsied just fibro patients. But we found very  
15 similar numbers to what Anne Louise found, which  
16 was at 50 percent, and then we found 20 percent of  
17 those patients had some evidence for disordered  
18 immunity. The important little phrase there, which  
19 I added, is that these are patients that were seen  
20 by rheumatologists, so they had not done a lot of  
21 the tests that you would normally think to do as a  
22 neurologist. So these patients had not been

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1 diagnosed with these immune disorders before.  
2 Again, also from Anne Louise was this one  
3 that looked at small fiber neuropathy in children  
4 with widespread pain syndromes, they identified  
5 definite or probably small fiber neuropathy in  
6 about 70 percent of these patients. That third  
7 bullet point I think was really one of the most  
8 important points of the paper that talked about a  
9 lot of the dysautonomia, the chronic fatigue,  
10 chronic headache that seemed to follow these  
11 patients and I think really are part of the same  
12 syndrome. In their paper, they found problems in  
13 immune system diseases in almost 90 percent of the  
14 patients, and 12 of the 15 patients that were  
15 treated with either steroids or IVIG subjectively  
16 got better.  
17 Most of you are probably familiar with this  
18 data. I put this up here to highlight two  
19 important points. Our best example of a chronic  
20 autoimmune neuropathy is CIDP. Most of us feel  
21 IVIG works in CIDP, and the response rate is less  
22 than 50 percent in our best controlled trial ever.

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1 So if we're going to rely on response to therapy,  
2 and we know our best response is 47 percent, again,  
3 we're going to have a really hard time trying to do  
4 this, particularly if our outcome measures are  
5 subjective.

6 The other important point is even in this  
7 disease in which these patients absolutely, as best  
8 any clinician in an academic center could do, had  
9 CIDP and had weakness, 22 percent got better with  
10 placebo. So we can't forget that basically half as  
11 many people improved with placebo as they did with  
12 active therapy.

13 So what about IVIG in small fiber  
14 neuropathies? Again, this is just a bunch of  
15 random case series that I've tried to highlight  
16 here. This was another case series that looked at  
17 IVIG in sarcoid-mediated small fiber neuropathy,  
18 only 3 patients, but the patients symptomatically  
19 improved, again, arguing that sarcoid in small  
20 fiber neuropathy may have a shared immunopathology.

21 This was a case series of patients with  
22 celiac-mediated small fiber neuropathy. They also

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1 had cerebellar ataxia. These patients got better  
2 with IVIG, and then in 2 of the patients, the IVIG,  
3 and they got worse again; again, trying to argue,  
4 again, the limitations being we're looking at  
5 response to therapy as an outcome measure. These  
6 are patients that have the ganglionic antibody and  
7 small fiber neuropathy. So 6 patients that were  
8 treated here, I think they either got IVIG or  
9 steroids -- IVIG or plasmapheresis, and the  
10 patients seemed to benefit from therapy; again,  
11 small numbers.

12 I'll highlight some of my own work. This is  
13 a poster that we presented, Dave and I, a few years  
14 back. These looked at patients, again, that had  
15 some evidence of immune dysregulation that's  
16 pathologically proven small fiber neuropathy. They  
17 were given IVIG for 6 months. And the point I kind  
18 of want to make is that we did pre- and post-nerve  
19 biopsies, or skin biopsies. And this really  
20 provides, I think, some way to start to think about  
21 objective measures.

22 If you look at this patient, in a

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1 pre-biopsy, they had zero nerves at their calf, and  
2 then after the biopsy, they had 6 nerve per  
3 millimeter at their calf. There have been a few  
4 papers in the last couple of years that have looked  
5 at the natural history and the variability. That  
6 seems to be outside the spectrum of the normal  
7 variability.

8 This was a poster we presented from last  
9 year. Again, these were 3 patients that had small  
10 fiber neuropathy and those 2 autoantibodies. So  
11 TS-HDS and FGF are 3. They got IVIG for 6 months.  
12 And again, just to highlight the best ones, the  
13 patients that had 1.6 nerves per millimeter at  
14 their calf after 6 months was up to 8.4 against 3  
15 patients, but they had significant pain reduction.

16 So the question is, do these autoantibodies serve  
17 as a marker in some subsets of patients with small  
18 fiber neuropathy for an immune-mediated process?

19 This was just published again by Anne  
20 Louise's group, which was a great paper. They took  
21 a large number of patients that had small fiber  
22 neuropathy. What I really like about this

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1 paper -- and it's what everyone is going to not  
2 like about this paper. But what I really like  
3 about this paper is it goes back to my pornography  
4 analogy again. There is not one specific criteria  
5 that allows us to put people into a group and say,  
6 yes, this is autoimmune.

7 They found a quarter of the patients have  
8 systemic autoimmune disorders, some had  
9 organ-specific autoimmune illnesses, and some just  
10 had abnormal blood test markers as a sign of  
11 autoimmune or immune dysregulation. The idea is  
12 could we start to build a composite picture for  
13 what the people look like as opposed to just one  
14 test? Because we're very unlikely to get there  
15 with just one existing test.

16 So they looked at autonomic testing. They  
17 looked at pain scores. Both improved  
18 significantly. So 74 percent of the patients felt  
19 they were improved; 77 percent were rated as IVIG  
20 responders by the treating physicians; and  
21 16 percent had sustained remission once the IVIG  
22 was withdrawn. Again, the point being there is

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1 clearly a group of patients that have an  
2 immune-mediated small fiber neuropathy, and this is  
3 I think getting much closer to how we have to think  
4 about identifying those patients.  
5 This is my thought, which is, if we break  
6 patients into 5 different groups or 5 different  
7 categories for each patient, we can start to think  
8 a little bit more clearly about what makes us tick,  
9 what makes us think this patients has an  
10 immune-mediated process?  
11 The first will be clinical. Again, you get  
12 a vaccine, and 2 days later you're sick; yeah, we  
13 think that's the vaccine. You get an illness, and  
14 a week later you develop a horrible neuropathy.  
15 That tells us that there's an acute process. We  
16 like that. It sort of fits with what we know about  
17 other types of neuropathies.  
18 Clinically, are they non-length dependent?  
19 So we think very differently about a person with  
20 numb toes and feet than a patient whose face is  
21 burning. That's telling us something is very  
22 different about their neuropathy. And I would also

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1 add in there autonomic. So if there's a very  
2 pronounced autonomic component, it's telling us  
3 this is more of a widespread process.  
4 Pathology, I think we need to think about  
5 length-dependent versus non-length-dependent  
6 pathology separately the way we think about  
7 length-dependent and non-length-dependent clinical  
8 symptoms. I can tell you, in our series, there's  
9 not necessarily a strong correlation. I think  
10 those are two very different variables.  
11 Then can we start to find and be a little  
12 smarter? Can we look for some of these  
13 inflammatory markers in the skin? We've been doing  
14 this in our lab. I can't say we've found much  
15 exciting yet, but we're trying to see can you look  
16 at complement deposition and can you look at some  
17 of the inflammatory cells that might be in the skin  
18 as a way to really kind of look at this?  
19 The lab testing, obviously that's what we  
20 like. Again, maybe some growing evidence to TS-HDS  
21 and FGFR-3 are helpful. Other neural antibodies  
22 are important; non-specific antibodies, to me

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1 meaning SSA, SSB, and ANA, and those antibodies.  
2 If you want CSF, what if they have monoclonal  
3 gammopathies? All of those things are really  
4 pushing us to think this is immune mediated.  
5 Obviously, we talked about the associated  
6 disorders.  
7 Then the last category is really the tough  
8 one, which is do you include that as an outcome  
9 measure to think about what we're doing? Then if  
10 you were going to build this type of a table, would  
11 you include negative predictive factors? So what  
12 if you had a person who had Sjogren's and had  
13 diabetes? Is that going to make you think more or  
14 less likely that it's immune mediated? I think we  
15 have to think about those as well.  
16 This is what I would do. My thinking is  
17 that we take those variables, and I'll show you  
18 three cases, and I think it will start to make  
19 sense. If you took this patient that had an acute  
20 onset small fiber mediated pain and autonomic  
21 dysfunction; non-length-dependent pathology,  
22 elevated levels of FGFR-3 antibodies; positive SSA

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1 and SSB; inflammatory changes in their CSF; and a  
2 history of Sjogren's, you have a very hard time  
3 arguing that that is not immune mediated.  
4 So that's sort of the bullseye. And if you  
5 add up all the points from my previous table, that  
6 gives you 7 points, and says, yep, that's immune  
7 mediated. So that one is pretty easy.  
8 What about a patient with a 3-year history  
9 of distal burning, length-dependent pathology, a  
10 history of diabetes, and nothing else? Well,  
11 that's zero points. In fact, you could make it  
12 negative 1 point if you want to, if you take my  
13 negative scale. So they're not even on the target.  
14 What about the patient that's got a 6-month  
15 of history of burning that started in the hands,  
16 gradually spread to their chest and back, and  
17 they've got no autonomic features? Their pathology  
18 is length dependent, but they've got antibodies to  
19 TS-HDS? Well, it's getting hard, so I'd give that  
20 a couple of points. So on the board, but it's not  
21 really the bullseye that you'd want. So I think  
22 depending on how sensitive and specific we want to

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1 be, we can start to take these variables and really  
2 try to put together a picture that will allow us to  
3 identify these patients better.  
4 So the point is, again, all these are  
5 different. All these patients I think are truly  
6 different. The patient that's got just pain is  
7 different than the patient that's got pain and  
8 autonomic features, so we have to think about them  
9 a little bit differently. Then each of those  
10 really has a very different pre-test suspicion.  
11 When you go into treatment, we all come to our own  
12 conclusion in our head, is this patient likely to  
13 get better or not? If we're going to start to do  
14 trials in immune-mediated neuropathies, we would  
15 want to enrich that as much as we possibly can,  
16 obviously without hurting the enrollment.  
17 I think that's it.  
18 DR. FREEMAN: Thanks for a terrific talk and  
19 attempting to structure out thinking on small fiber  
20 neuropathy in a provocative way.  
21 Before we have questions, what I'd like to  
22 request is if the members of the audience can

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1 attempt mentally to dissociated immune-mediated  
2 small fiber neuropathy from pornography --  
3 (Laughter.)  
4 DR. FREEMAN: -- if it's at all possible.  
5 The question I had is, that paper by Liu et  
6 al., they had all these blood biomarkers, but did  
7 they actually look at the skin biopsy, and did they  
8 look at specific biomarkers of inflammation that  
9 were occurring in the skin? And do they correlate  
10 that with the intraepidermal nerve fiber changes or  
11 other changes in the skin fibers?  
12 DR. LEVINE: You mean the one from like 5 or  
13 6 years ago?  
14 DR. FREEMAN: Yes.  
15 DR. LEVINE: No, they didn't.  
16 DR. FREEMAN: Well, actually the 2018 paper,  
17 Liu at al., the one that's just been  
18 DR. LEVINE: Well, Anne Louise could  
19 probably -- I don't think so. So, yeah. Again,  
20 the difficulty -- the challenge is, the more you  
21 split these people into smaller groups, the smaller  
22 your numbers become. I recognize that that's sort

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1 of a dilemma. You'd like to have as homogeneous a  
2 population as possible, but then you end up with a  
3 very small population.  
4 So really, that paper, the idea was that  
5 this was suspected autoimmunity, and then suspicion  
6 that there was autoimmunity came from the variety  
7 of factors that they listed. But I don't think  
8 they broke it out by looking at biomarkers in the  
9 skin.  
10 DR. FREEMAN: Nurcan -- before she asks her  
11 question, I just want to emphasize, left out of  
12 your reference list was the terrific paper that  
13 Nurcan's group did on small fiber neuropathy in the  
14 setting of fibromyalgia. I don't know if your  
15 question is going to be related to that, but your  
16 interpretation was a little different to what we  
17 heard this morning. So if you could include that  
18 in your question as well.  
19 DR. UCEYLER: Well, thank you very much.  
20 Actually, my question was about another paper that  
21 we published on immune mediators or biomarkers in  
22 the skin of patients with small fiber neuropathy.

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1 That was Neurology 2010, where we looked at  
2 length-dependent and non-length-dependent patients  
3 with idiopathic small fiber neuropathy. And what  
4 we found is that we counted the T cells and  
5 macrophages in the dermis and saw no differences.  
6 And then we measured pro- and anti-inflammatory  
7 cytokines in the same skin biopsies of these  
8 patients using quantitative real-time PCR, and we  
9 saw an up regulation of asiatic proinflammatory  
10 cytokines in the length-dependent group.  
11 That was quite interesting, and in our  
12 hands, when we've seen our patients do the skin  
13 biopsy, we do not treat them with immunosuppressive  
14 drugs, only if we would see an increase, some kind  
15 of evidence in this prospective.  
16 Another aspect now going to this 2013 paper  
17 about fibromyalgia and small fiber pathology, we  
18 called it, the command I would have here is -- also  
19 looking at your slides -- we're talking about small  
20 fiber neuropathy for all of these conditions, what  
21 is now fibromyalgia, and sarcoid, and celiac  
22 disease, and diabetes, and whatever.



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1 I think we should think of making a  
2 distinction because the clinical presentation is  
3 obviously very different, so the fibromyalgia  
4 patient does not come with burning feet and burning  
5 mouth, but has an aching muscle pain. That's the  
6 reason why we called it small fiber pathology in  
7 our title in this first description. So this is  
8 maybe something to be discussed later also.  
9 DR. LEVINE: The second point, your last  
10 point, I think is a really important point. I  
11 agree. That's why I'm kind of trying to propose  
12 that we come up with a different terminology for it  
13 because the patient that has the fibro syndrome,  
14 that has abnormal epidermal density, does look very  
15 different than the patients that has burning toes  
16 or the patient that has burning mouth. And I think  
17 we have to think about them.  
18 DR. UCEYLER: And also doesn't have  
19 any -- at least in our hands, we also looked at the  
20 skin and looked for asiatic markers in the skin,  
21 again, looking for pro- and anti-inflammatory  
22 cytokines, nerve growth factors, and so on, and we

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1 didn't see this pattern that we found in the small  
2 fiber group. So I think there is really a  
3 distinction from the pathophysiology also.  
4 DR. FREEMAN: One of the issues that I think  
5 we should table for the moment, but will definitely  
6 come up -- that's why I wanted Nurcan to speak  
7 about their interpretation of their data, is the  
8 specificity of skin biopsy for small fiber  
9 neuropathy versus their interpretation. And that  
10 is small fiber pathology associated with  
11 fibromyalgia, which was their interpretation  
12 subsequently in a letter to the editor, I think,  
13 following a response to their paper.  
14 I think it was Giuseppe, then David, then  
15 Ahmet.  
16 DR. LAURIA: Thank you because it's a very  
17 sensitive area. I'm not arguing that the immune  
18 system is involved or may be involved. We've  
19 treated some kids, for instance, with very severe  
20 and acute, so it might happen.  
21 May I suggest -- following your idea to  
22 separate the neuropathy associated with a clear

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1 system disorder, just final, you have Sjogren  
2 disorder and you may have a neuropathy. That's it.  
3 The other point in which I would like to see  
4 whether there is an agreement is the concept that  
5 one data does not make a diagnosis. So if I have  
6 chest pain, probably I could have a myocardial  
7 infarction and a number of other things.  
8 If we agree on the principle, the fact is  
9 that the gammopathy, for instance, that you have  
10 listed is very common, and with increased age of  
11 the population, it becomes even more common. So  
12 the relationship between the evidence that one  
13 person has a neuropathy and one person has, at the  
14 same time, even one antibody, the antinuclear  
15 antibodies, it is very important because the  
16 relevance that it has in clinical practice is huge.  
17 There are patients requiring IVIG on the basis,  
18 from my perspective, of very little.  
19 DR. LEVINE: I agree completely. Again,  
20 that table I listed, in an ideal world, each of  
21 those would be a different point. The acute onset  
22 might be 3 points and ANA might be 1 point because

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1 we know the specificity of an ANA is very, very  
2 low. The problem is how do we get there and it has  
3 to be guesses to begin with. I think you're  
4 absolutely right, which is I would think about a  
5 known systemic autoimmune disease and a neuropathy  
6 differently than a patient who has a neuropathy and  
7 you find a blood test. Those are two very  
8 different things. Yeah, I agree.  
9 DR. FREEMAN: David Herrmann, Ahmet, and  
10 Anne Louise.  
11 DR. HERRMANN: Todd, on this question, as we  
12 think about diagnostic criteria for immune-mediated  
13 small fiber neuropathy and giving people points for  
14 different elements, to the point of treatment  
15 response, one of the concerns I have is I think we  
16 all need to be fairly stringent about what  
17 treatment response is.  
18 So IVIG's going to modify cytokines, and  
19 what I don't know is when a patient has response to  
20 IVIG with a small fiber presentation, and the  
21 endpoint is pain improved or symptoms got better, I  
22 don't know whether that's a symptomatic effect

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1 because I suspect that IVIG modulates pain pathways  
2 substantially as steroids would do. So I would  
3 argue that we probably need some objective  
4 evidence. When you give IVIG or plasma exchange to  
5 someone with CIDP, their strength gets better.  
6 So if we're going to include response to  
7 treatment, I think we have to have some criteria  
8 for what a response to treatment looks like, and I  
9 don't think it can only be improvement in pain.  
10 DR. LEVINE: I completely agree. Number  
11 one, even though they were small numbers, I  
12 followed up with a biopsy, and I probably now have  
13 20 or 30. You can do it in 3 or 6 months, and you  
14 see a change.  
15 Chris and I are designing a trial with  
16 Grifols, which will include outcomes of a biopsy.  
17 It's different than if you -- obviously, if you're  
18 using a sodium channel blocking drug and you're  
19 treating pain, then your outcome is pain. When we  
20 start to think about these drugs, even more  
21 cytotoxic drugs, you need something more than pain.  
22 I agree.

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1 DR. FREEMAN: So Ahmet, Gordon, and then the  
2 panel. [Inaudible - off mic].  
3 DR. HERRMANN: You've missed Anne Louise.  
4 DR. FREEMAN: Anne Louise, Gordon, and then  
5 the panel.  
6 DR. HOKE: I was going to also bring up the  
7 treatment issue because I think a large part of the  
8 acute onset non-length-dependent neuropathies, I  
9 would like the GBS equivalent. Those people  
10 improve on their own. They have a monophasic  
11 illness. Those people probably don't need  
12 treatment, but the ones who have a more slower  
13 onset, perhaps progressive type of neuropathy,  
14 deserve extra attention in investigations. But  
15 probably the majority of the ones that I see in my  
16 clinic, by the time they come to see me, 8,  
17 10 months later, they're already starting to see  
18 improvement in their pain levels. I biopsy these  
19 people a year or two years later. They all improve  
20 their epidermal nerve fiber density without any  
21 treatment.  
22 DR. LEVINE: Osvaldo Nascimento has a series

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1 in Brazil where they were post-Zika, very severe  
2 painful syndrome, and he doesn't treat them, and  
3 they get better.  
4 DR. FREEMAN: Anne Louise Oaklander?  
5 DR. OAKLANDER: So I hold open our 2013  
6 [inaudible - off mic] a week. We're actually  
7 pretty balanced, and we try to look at all  
8 available tools. I just want to mention the  
9 results of the other data we collected  
10 [inaudible - off mic]. We looked at symptoms. We  
11 looked at signs. We looked at pathology. We  
12 looked at physiology. I don't know what else to  
13 look for.  
14 DR. LEVINE: And you had a control group,  
15 which I will say our paper didn't. But that was in  
16 the 3 versus 40 percent.  
17 DR. OAKLANDER: We used the Michigan  
18 neuropathy screening instrument as a way to measure  
19 symptoms, and [inaudible - off mic] was 1.3, and  
20 the full group, 5.8. Fibromyalgia patients were  
21 [inaudible - off mic]. We used physiology. We  
22 used autonomic testing. That did not pick up any

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1 major difference, and the skin biopsy. So again,  
2 we are not proposing that skin biopsy -- in other  
3 words, it was more than just pathology in the  
4 study. It was symptoms and [inaudible].  
5 DR. LEVINE: Back to your point, we should  
6 really start to think about these terms that we're  
7 throwing around today because as Chris pointed out,  
8 Parkinson's patients have small fiber pathology.  
9 We're not saying they have small fiber neuropathy,  
10 to your point. So that's exactly right. I think  
11 that's a very important distinction.  
12 DR. OAKLANDER: Neuropathy has the word  
13 "pathology" in it, so I think we have to think  
14 about the words we use. For instance, I tend to  
15 use the word "small fiber polyneuropathy" because  
16 there are other types of neuropathy that are not  
17 polyneuropathy. So even at the most basic level,  
18 we're making assumptions that we may or may not  
19 want to make, but we should think about it.  
20 DR. FREEMAN: Gordon, last question for this  
21 talk, and then that will be it.  
22 DR. SMITH: Yes. I just have a couple of

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1 points. Just to go back to my first point, I think  
2 there's a real risk in conflating pain with small  
3 fiber neuropathy or pain with small fiber  
4 pathology. There are large fiber painful  
5 conditions, and pain can be generated out of large  
6 fiber entry. So I think that's really important in  
7 our concept of small fiber neuropathy. We see this  
8 from a clinical perspective. As you pointed out,  
9 patients with GBS can have pain. CIDP with  
10 contactin antibodies have very severe neuropathic  
11 pain with demyleinating features on nerve  
12 conductions studies.

13 I also want to go to the you know when you  
14 see it sort of thing. I'm not going to say what  
15 "it" is.

16 (Laughter.)

17 DR. SMITH: Al Gore has defined that for us.

18 (Laughter.)

19 DR. SMITH: In particular the vaccine,  
20 because I think the association between something  
21 that happens acutely with something else, one has  
22 to be very cautious. And I'm having flashbacks of

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1 the whole Gardasil vaccine ALS thing, for those of  
2 you in ALS and kind of the whole hubbub about that  
3 a number of years ago. And now I think most people  
4 accept that there isn't a risk relationship.

5 What I get concerned about I know it when I  
6 see it is we're layering on our own preconceived  
7 notions and looking for justification on the data  
8 we have. I think your construct is great, but we  
9 need to be really cautious, because I bet everyone  
10 in this room got a flu vaccine this year, and  
11 there's probably 15 or 12 percent of us who have  
12 low titer-positive ANA in the room. So in that  
13 target, right of the bat, if we had symptoms  
14 somewhere near our vaccine, we're going to be in  
15 one of these questionable categories. I think it's  
16 complicated.

17 Q & A and Panel Discussion

18 DR. FREEMAN: On that note, Chris Gibbons,  
19 as people begin to take their seats.

20 DR. GIBBONS: This is really meant for the  
21 whole group. But one of the things, in kind of  
22 listening to the talks that we've heard about,

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1 depending on what we're looking for as  
2 outcomes -- one of the questions that arise  
3 whenever we think of clinical trials or looking  
4 forward, is obviously response to treatment, as we  
5 just heard, particularly in the immune-mediated  
6 neuropathies, what gets better? Has pathology  
7 changed really significantly?

8 The reason I get to this question is because  
9 none of us have really looked at -- well, actually  
10 that's not true. Many of us have looked in detail  
11 of what the dynamic change is, even in the  
12 pathology. If we go back to Michael Polydefkis'  
13 original paper in the capsaicin model and the  
14 dynamic changes that occurred, there are dynamic  
15 changes that can occur even with pathology very  
16 quickly in short amounts of time. The Utah group  
17 has really looked at dynamic changes post-exercise  
18 in certain glucose dysmetabolism populations and  
19 seen improvement.

20 So we know there can be an effect of  
21 something on the small fibers, and they dynamically  
22 change. So I think we also need to be cautious

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1 about looking at our endpoints of improvement. As  
2 we just heard about the Zika virus and recovery,  
3 anything can change to some degree. And I wonder  
4 in some cases that looked at deeply depressed  
5 patients who are nearly bed bound, not really  
6 active, what is the nerve density? I would argue  
7 it's likely to be very low. And if they are  
8 treated with an SNRI, they would get better. Is  
9 that a small fiber neuropathy because they have the  
10 low density or is it because they've now moved,  
11 they've gotten better, they've gotten out of bed,  
12 they've gotten active? Where is the role for this?

13 I'm just throwing this out there for  
14 discussion.

15 DR. FREEMAN: Karin, you look like you want  
16 to respond.

17 DR. FABER: Well, of course this is  
18 something that has not one clear answer to. But I  
19 think if we look at other neuropathies, for  
20 example, the inflammatory neuropathies, we know  
21 that the voice of the patient really is important,  
22 and that the patient really is capable of telling

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1 us how he or she is doing. And we know that from  
2 the work that Ingemar Merckies has done on the  
3 [indiscernible], for example, and we also know that  
4 for other diseases, it works the same.  
5 So I would be in favor of also asking the  
6 patient how he or she is doing, and that also means  
7 including pain as an endpoint. It doesn't mean  
8 that you have to say that pain is the only  
9 endpoint, that's something else, but I think that  
10 for the patient, the main complaint and the main  
11 problem of small fiber neuropathy is the pain. So  
12 it should at least work on the pain, whatever you  
13 do.  
14 DR. SINGLETON: I was going to say that for  
15 me, those discussions make me think that we should  
16 cast a wide net for what we mean by small fiber  
17 neuropathy and that when we do clinical trials,  
18 it's crucial to have some sort of objective measure  
19 of nerve function. Whether that's pathological or  
20 quantitative sensory testing, I think we'll discuss  
21 that further, but that's the reason to have that,  
22 that it helps to defend against criticism that this

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1 is just a non-specific improvement in patients'  
2 perception. That's crucial to the FDA, but it's  
3 not the only aspect that should interest us or  
4 those who organize pharmaceutical trials.  
5 DR. FREEMAN: Anne Louise?  
6 DR. OAKLANDER: That's why we chose two  
7 primary outcomes in our IVIG study, one being  
8 improvement in pain because it's obviously central  
9 and not everybody has [inaudible - off mic]. But  
10 we also used an objective biomarker, so I don't  
11 think there's going to be any one metric. All of  
12 these clinical trials, we have to very strongly  
13 [inaudible - mic fades] primary outcomes.  
14 DR. BELL: Sorry. I just want to make one  
15 comment on that. I agree under the presumption  
16 that you have what you assume is a  
17 disease-modifying therapy, which for a lot of us in  
18 drug development when we're targeting pain -- we've  
19 had this discussion with Roy a number of  
20 times -- the value of having some of these more  
21 objective markers as primary endpoints is  
22 questioned because our primary outcome, for

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1 example, is pain because we are in the business of  
2 developing pain drugs that may or may not alter the  
3 actual course of the disease.  
4 So my question would be, how do you  
5 objectively -- I mean, how do you do that when you  
6 have a therapy that you don't suspect modifies your  
7 intraepidermal nerve fiber density? It doesn't  
8 change your QST phenotyping. All you're left with  
9 is how are you feeling and how is your pain.  
10 DR. FREEMAN: I want to maybe, just by way  
11 of clarification, the goal of the meeting was  
12 purposefully vague, and we do think of small fiber  
13 neuropathy, as with every neuropathy, as having a  
14 symptomatic component and also being the substrate  
15 for potential disease modification.  
16 The way I'm presenting it now, it is as if  
17 these are two discrete approaches to a disease. I  
18 think more and more we're beginning to  
19 recognize -- and I think the basic science slide  
20 that Karin showed us initially looking at the  
21 potential multifactorial approach to the etiology  
22 of a neuropathy suggests that there may be more of

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1 an overlap than we think, and that perhaps by  
2 disease modification, removing one factor of a  
3 polyfactorial or multifactorial disease, you may  
4 actually be modifying the actual history of the  
5 disease.  
6 So I think it's a really very important  
7 point that you are making that there will be  
8 strategies, target-directed therapies, that are  
9 symptomatic, and they may or may not also be  
10 disease modifying. But I think we need to  
11 recognize that these are at two ends of the  
12 spectrum, and that disease modification may in fact  
13 on some level make symptoms worse in some cases.  
14 Pain may get worse as you improve nerve function  
15 and nerve structure. So it is more complicated  
16 than perhaps meets the eye.  
17 Rayaz?  
18 DR. MALIK: I think it is important as a  
19 group for us to be clear that disease modification,  
20 we must have some improvement in function or  
21 structure. And I've talked to some pharma that  
22 there is danger almost of you wanting a quick

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1 target. So pain, you can do an 8 to 12-week study,  
2 and you can show a benefit, and go to the FDA and  
3 get an approval, but it's not necessarily disease  
4 modification. And as a group, we need to have  
5 clarity on that. I think if you have a disease  
6 modifier, you need to have I think an objective  
7 measure. You can't have both.  
8 DR. LEVINE: I think, too, all these points  
9 are kind of saying the same thing. But it comes  
10 back a little bit when you're trying to think  
11 about -- and we're going to talk later -- an  
12 inclusion/exclusion criteria. Number one, it  
13 depends on what kind of a drug you're doing. Is it  
14 a symptomatic treatment? Is it a disease-modifying  
15 treatment? Because that really reflects who you're  
16 going to choose. When you talk about outcomes,  
17 yes, I think you absolutely have to ask the  
18 patient, and it has to be pain, and it has to be  
19 function.  
20 I mean, all of us see a broad range of small  
21 fiber patients, those with a little bit of numbness  
22 or tingling. And clinically, you would never want

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1 to expose them to steroids or IVIG because they're  
2 fine. And then we see some patients that are  
3 horribly disabled that never get out of the bed,  
4 and the risk-benefit completely shifts in terms of  
5 how we think about how aggressive we want to be for  
6 those patients. So there we really want to improve  
7 function.  
8 So you can improve pathology all you want,  
9 and I'm an advocate for looking at the pathology,  
10 but if you don't make people better, what have you  
11 done?  
12 DR. FREEMAN: Let's go. I think Anne Louise  
13 was first, then Nurcan, and then Gordon.  
14 DR. OAKLANDER: I think it depends on the  
15 level of maturity of the field, and I actually  
16 followed the Alzheimer's field fairly closely as a  
17 good example. They're going into immunotherapy,  
18 and we understand -- we don't know everything, but  
19 people would argue there that even in patients who  
20 are not symptomatic, if you have strong evidence of  
21 ongoing and progressive neuronal degeneration, that  
22 treating neuronal degeneration alone may be a valid

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1 outcome even in the absence of major symptoms. And  
2 I think that's because it's much better defined.  
3 DR. LEVINE: But can I poll the room really  
4 fast? By a show of hands, if you treat small fiber  
5 neuropathy, do you think the majority of your  
6 patients stay the same over time or get worse over  
7 time? How many people think stay the same, the  
8 majority? I mean, some obviously do whatever.  
9 DR. OAKLANDER: Treat how?  
10 DR. LEVINE: You're just managing them  
11 clinically, so not treating with any  
12 immunomodulatory therapies, just a natural history  
13 of small fiber neuropathy, if you have a thousand  
14 patients, 500 patients. When I talk to my  
15 patients -- I have over a thousand small fiber  
16 neuropathy patients now -- I tell them 70 percent  
17 stay the same.  
18 DR. FREEMAN: Rather than a vote, there are  
19 people in the audience who actually have cohorts.  
20 It's a question that I wanted to ask Rob in his  
21 review, what is the natural history of this  
22 disease? What do we know?

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1 Giuseppe, what happened to your patients?  
2 Karin, what's happening to your patients?  
3 DR. FABER: Well, we didn't follow our  
4 patients for a very -- because we see them, we make  
5 the diagnosis, and they go back to their referring  
6 physician. So we are planning on doing a follow-up  
7 study. I think the best follow-up data are  
8 available from the study of DeVecheley [ph] and  
9 Giuseppe [ph], and that described that part of the  
10 patients, I think half of them stayed stable,  
11 30 percent had a decline, and very little -- I  
12 think 10 percent or something like  
13 that -- improved.  
14 DR. FREEMAN: They seemed dependent because  
15 there were multiple potential etiologies.  
16 DR. FABER: Yes.  
17 DR. FREEMAN: That was in your pure group  
18 that 10 percent improved.  
19 DR. LAURIA: This is something actually we  
20 don't know exactly, so we don't know at the long  
21 term what happens to these patients. Also we don't  
22 know what is the frequency of other systemic and

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1 non-conventionally associated disorders that might  
2 happen. So is this a fragile group of patients who  
3 eventually can suffer from other disorders? Does  
4 this maybe have a window for anything else? And in  
5 terms of the evolution of the neuropathy, we know  
6 that -- actually, we have started this long-term  
7 follow-up study recruiting patients we've started  
8 seeing 20 years ago. It will take a while  
9 actually. But yes, the person is generally more or  
10 less the same, but they come from a biased study.  
11 It's not a wide study, including all who came  
12 across our center.

13 DR. FREEMAN: Rob, is there any clue from  
14 the reading that you did as to what the natural  
15 history is?

16 DR. SINGLETON: The simple answer is no. I  
17 looked hard, relatively hard. I just don't think  
18 that there is a lot of information about the  
19 natural history in truly idiopathic neuropathy.  
20 There is obviously an abundance of natural history  
21 data in diabetic neuropathy. We know something  
22 about the rate of decline from work that Michael

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1 having several episodes of steroid responsive  
2 objectively documented with blood markers of  
3 crudescence. So I think just as with other types  
4 of neuropathy, there are different tempos probably  
5 due to different underlying causes.

6 DR. FREEMAN: David Herrmann?

7 DR. HERRMANN: I think there are some  
8 shorter term studies that look at chronic, small  
9 fiber, shall we say idiopathic neuropathies, I  
10 think David Wolk and others, over a 3 to 5-year  
11 window. And I think a sizeable proportion of  
12 individuals who start out with a pure small fiber  
13 clinical phenotype will develop some mild large  
14 fiber dysfunction over time. But I think that's  
15 slow, and we see this clinically. That slow change  
16 in signs over time may not necessarily be  
17 associated with clinical change over time.

18 So we're treating these patients, and many  
19 of these patients symptomatically or from a  
20 patient-reported standpoint do well or improve with  
21 the available treatments, at least symptomatically,  
22 but their signs may slowly evolve over time. At

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1 Polydefkis has done and that we've done both in  
2 terms of clinical measures and also nerve fiber  
3 density, but no equivalent work has been done in  
4 patients who have idiopathic neuropathy.

5 DR. FREEMAN: Where were we? I think Anne  
6 Louise, then David Herrmann, and then Nurcan.

7 DR. OAKLANDER: I can only speak to the  
8 apparently autoimmune. Obviously, the disease  
9 tempo is different in every disease, but in the  
10 patients with apparently autoimmune, we see, as was  
11 mentioned, an acute pattern where patients become  
12 abruptly ill, many are quite sick, and then they  
13 recover. Whether you treat them or you don't treat  
14 them, they get better.

15 A GBS-like pattern, if you will, we also see  
16 a CIDP-like pattern, if you will, where they're  
17 going to stay sick to a certain extent. No matter  
18 what you do to them, they may get better or worse.  
19 And we're going to publish a case of a very  
20 carefully followed medical professional with a  
21 relapsing, remitting form of being completely well,  
22 off all therapies for years at a time, and then

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1 least over 5 years, I would think the literature  
2 would largely point in that direction.

3 DR. SINGLETON: Thanks, Dave. I had  
4 forgotten to mention data that's out there, as  
5 you've just mentioned, that shows that many  
6 patients go from what seems to be predominantly or  
7 even pure small fiber neuropathy to a more mixed  
8 fiber neuropathy. I think that's important natural  
9 history certain for diseases that don't have a  
10 clear genetic background.

11 DR. FREEMAN: Okay. Where were we? Nurcan,  
12 then Deb, then somebody else in that area, a lot of  
13 people. Let's go. Nurcan?

14 DR. UCEYLER: Roy, just to comment on the  
15 natural history, we also did not follow these  
16 patients really systematically in a study, but from  
17 the clinical experience, I would also say the  
18 majority's really stable, and it is a small  
19 proportion of patients. I would say even if they  
20 developed large fiber signs, this is mild.

21 There is one new study from this year, a  
22 very, very small group. I think it's a German

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1 group, 16 patients that have been followed where  
2 the authors come to the conclusion that large fiber  
3 neuropathy will develop. And in the majority of  
4 cases, I would not really go with this in the  
5 majority of cases. It is actually marginal.  
6 Another point, the discussion has turned  
7 around now a little bit and coming back to one  
8 point that was asked. When we produce a new drug  
9 against pain, what is then our outcome measure? Do  
10 we have an objective measure, as far as I  
11 understood it. I think we have to distinguish here  
12 very carefully is it about idiopathic small fiber  
13 neuropathy. Do we treat a reason? Is there other  
14 etiology? Will we improve neuropathy, and do we  
15 have any correlation for pain in any of the tests  
16 we're doing? So far we do not have this.  
17 Actually, when we're treating pain, the  
18 patient will tell us, okay, pain has become better.  
19 But I think we cannot expect then, from fiber  
20 density, or from QST, or from any other  
21 investigation, an improvement because this does not  
22 correlate with pain. So I think we have to

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1 distinguish what are we trying to improve;  
2 neuropathy, okay. Fiber density might become  
3 better, then we can do a follow-up biopsy or we can  
4 do QST. But for pain, we will now have anything  
5 inherent at the moment.  
6 DR. FREEMAN: And Simon's sitting next to  
7 me.  
8 Go ahead.  
9 DR. FABER: I think I completely agree with  
10 you. That's a very important distinction we have  
11 to make because otherwise, we define a biomarker  
12 that should improve while in fact it will never  
13 improve, and then you have a negative trial while  
14 the patients may be improving. So that's really  
15 important.  
16 DR. OAKLANDER: How about using the term  
17 "domains," and we can talk about treating the  
18 different domains of small fiber neuropathy; the  
19 symptom domain, the pathology domain, the  
20 functional domain.  
21 DR. FREEMAN: There may not be concordance.  
22 To follow up on Nurcan's comments, Simon's sitting

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1 next to her and is doing I think an excellent  
2 systematic review just on that very question. I  
3 don't know if you want to comment now or save it  
4 for tomorrow.  
5 DR. HAROUTOUNIAN: We're just finishing the  
6 systematic review on looking at the associations  
7 between intraepidermal nerve fiber density and a  
8 variety of other domains, so QST symptom, signs,  
9 NCV, autonomic testing, and the slide at the end of  
10 my presentation, what are the associations between  
11 intraepidermal nerve fiber density and each of  
12 those. This is not in small fiber neuropathy per  
13 se. We did it over the spectrum of distal  
14 symmetric polyneuropathies. So with that carrot,  
15 I'll just present.  
16 DR. FREEMAN: The sodium channel people are  
17 going to speak in a second. I just want to set up  
18 and take my chairman's prerogative by asking a  
19 question to Ahmet and Karin.  
20 We heard two discordant views; at least to  
21 me, they sounded discordant. In Ahmet's talk, he  
22 said -- and I don't know if this represents his

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1 view -- that BMS, who sponsored the study that he  
2 presented, withdrew from the selective sodium  
3 channel antagonist field -- correct me if I'm  
4 wrong -- following the results of that study. And  
5 Karin in response to a question noted that if you  
6 have a good selective sodium channel antagonist,  
7 whether or not there are polymorphisms, she would  
8 be very supportive of its use in patients who have  
9 small fiber neuropathy.  
10 I suppose another question that has always  
11 been on my mind is actually what is the evidence  
12 that having a polymorphism makes you more  
13 responsive to a selective sodium channel antagonist  
14 in that disease or perhaps could you be less  
15 responsive?  
16 DR. SINGLETON: Before you answer, can I  
17 just add more questions?  
18 (Laughter.)  
19 DR. FABER: I can't remember, not  
20 everything.  
21 DR. SINGLETON: I know. We'll remind you  
22 again. My question, you touched on this, just not

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1 as much as I want you to, is what's the evidence  
2 for epigenetic effects on sodium channels in  
3 diseases like diabetic neuropathy? Can you speak  
4 to whether inflammatory conditions, in metabolic  
5 injury or derangement, how does that affect the  
6 function of these sodium channels?  
7 DR. FREEMAN: Do you want to add a fifth  
8 question, or can it --  
9 DR. STEINER: It's I think along a somewhat  
10 similar theme, but if you start from the  
11 perspective of somebody in development and the idea  
12 that you want to work towards the treatment  
13 symptomatic, in our case, for small fiber  
14 neuropathy, we've discussed it in so many levels of  
15 painful small fiber neuropathy, are we looking  
16 specifically at pure? Should we be looking at  
17 painful peripheral neuropathy?  
18 So to me, Todd, the taxonomy that you put up  
19 was really helpful. The way that we should be  
20 approaching it, should we be approaching it by  
21 targeting patients who we know have genetic  
22 mutations. Should we be targeting it at a broader

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1 level? I think that's one of the big challenges  
2 before you even get to what the outcome measure is  
3 and how important either the INFD count is, the  
4 QST, and maybe there are differences, which was  
5 already brought up earlier, about the results based  
6 on the ideology.  
7 DR. FREEMAN: Okay. You have five  
8 questions. You've got 30 minutes.  
9 (Laughter.)  
10 DR. FABER: First, I think that if you  
11 block, for example, Nav 1.7, and you would do it  
12 very good, then you would diminish pain, whether it  
13 comes from small fiber neuropathy or from any other  
14 disease, because Nav 1.7 is a central channel in  
15 the development of pain, so that's important.  
16 The other thing is how would you design a  
17 trial, and would you use only patients with pure  
18 small fiber neuropathy? Would you use other  
19 things? Well, it depends on what you want. But I  
20 think that if you want to do it properly, you  
21 should have a homogeneous group because if you mix  
22 diabetic neuropathy, idiopathic small fiber

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1 neuropathy, and immune-mediated neuropathy, and a  
2 drug does not work, then you will always say, well,  
3 what happens if. And if it works, then you have a  
4 proof of principle, and then you can go to other  
5 groups. That would be my best way to go I think.  
6 We did a small trial in patients with  
7 Nav 1.7 mutation with lacosamide. Lacosamide is  
8 also a sodium channel blocker, and it blocks  
9 especially Nav 1.3, 1.7, and 1.8. That trial was  
10 positive. It was an add-on medication, but it  
11 really had a good effect in those patients, and  
12 there was not a difference in patients that had a  
13 proven pathogenic mutation, so with  
14 electrophysiology, in patients that were suspected  
15 to be pathogenic mutations. So that was really  
16 helpful.  
17 The next step would be to go to a bigger  
18 group of course, but in the meantime, I think we  
19 have better Nav 1.7 and 1.8 blockers to test, and  
20 those probably tested in a bigger group of  
21 patients.  
22 DR. STEINER: No, I agree with you --

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1 DR. FABER: Then for the epigenetic  
2 things --  
3 (Crosstalk.)  
4 DR. STEINER: With a proof of concept, I  
5 completely agree you start with a homogeneous  
6 group. I guess I'm saying more what is the  
7 eventual goal? Is the thinking that there's pain?  
8 We know that Nav 1.7 is involved in pain, so  
9 something that targets that is going to work in any  
10 population. I'm saying is that the thinking?  
11 DR. FABER: I don't know. I think that's a  
12 reasonable hypothesis, but I don't know if that's  
13 true. It's not very useful to say, okay, we will  
14 treat any patient with pain because then your trial  
15 is going to be a mess.  
16 DR. STEINER: I know.  
17 DR. HOKE: But why do you think that's the  
18 case? If you think the Nav 1.7 is central to the  
19 pain sensation, why shouldn't it work for any pain,  
20 even osteoarthritis pain?  
21 DR. FABER: It probably will, but you have  
22 to --



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1 DR. HOKE: So why not test it?  
2 DR. FABER: I think your trial design will  
3 be different for osteoarthritis and for small fiber  
4 neuropathy, for example.  
5 DR. HOKE: If the primary outcome is going  
6 to be in response to pain because you assess  
7 symptomatic treatment -- we're not talking about  
8 disease modification.  
9 DR. FABER: No, no.  
10 DR. HOKE: If it's symptomatic, then you can  
11 theoretically test all pain patients.  
12 DR. FABER: Yes. But I think that's why  
13 pharma is interested in Nav 1.7 or auto blockers  
14 because pain is a huge problem, and it's not the  
15 small fiber neuropathy on its own that's very  
16 interesting; it's the entire population that is  
17 interesting. The question is how do you start? I  
18 think that's the big question.  
19 DR. HOKE: I mean, if it's really central to  
20 the pain sensation, and I think the preclinical  
21 data suggests it is, then where we have trouble  
22 defining the idiopathic neuropathy patients, there

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1 are other painful conditions like osteoarthritis  
2 pain, which is much easier to define and probably  
3 test. I would go to those doctors [indiscernible].  
4 But my question to the pharma would be, can  
5 you actually develop a selective Nav 1.7 inhibitor  
6 that won't have side effects, because it's such an  
7 integral part of many other functions of neurons  
8 and other cells, that it's going to be tough I  
9 think to develop something safe.  
10 DR. FREEMAN: I'm going to shelve that just  
11 for a second. I want to maybe ask Ahmet, if you  
12 were advising BMS, would you have advised them to  
13 stay in the field?  
14 DR. HOKE: I think it would because I think  
15 the data from the gain-of-function mutations is  
16 very strong, and also loss-of-function mutations,  
17 again, clearly plays a role in pain sensation. I  
18 think the challenge is going to be coming up with a  
19 drug that will be really safe, because if you're  
20 going to use it in this general population like  
21 ibuprofen, it has to be a very safe drug, and I  
22 think that's going to be the big challenge in my

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1 mind.  
2 I think their initial idea was that they  
3 wanted to, for a proof-of-concept trial, really  
4 define the small subset that had pure  
5 gain-of-function mutation that was enriched in the  
6 neuropathy population, and that's how they wanted  
7 to use their drug initially, and they didn't see  
8 that, at least in our cohort.  
9 DR. FREEMAN: Where were we? Amanda?  
10 DR. PELTIER: I have I guess two comments.  
11 One is about the whole, how you define small fiber  
12 neuropathy. I think you really have to put a time  
13 limit on it because I think we all know from  
14 clinical experience that almost every neuropathy  
15 that starts in one population will eventually  
16 involve another; HIV, amyloid, almost everything  
17 you look at. If you follow somebody long enough,  
18 it will eventually hit the other fibers conversely.  
19 CMT will then go back and affect those small fibers  
20 even with PMP22.  
21 I think you have to put a time limit on your  
22 diagnosis of patients that have symptoms for X

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1 amount of years and clinically still have  
2 involvement of only these fibers, because if you  
3 just say pure small fiber neuropathy, I don't think  
4 there is any such thing. So that's my first point.  
5 Then my second point is I think it goes back  
6 to the questions circulating around the sodium  
7 channel drugs because I think it's going to be an  
8 issue as far as what your target is because -- for  
9 example, all those medicines that were FDA approved  
10 for painful diabetic neuropathy, we use for  
11 everything else because we know it works for pain.  
12 So going back to Ahmet's point, pregabalin  
13 gabapentin,, duloxetine, we all use them for other  
14 conditions besides diabetic neuropathy, which is  
15 the cleanest most common painful neuropathy that  
16 was easy to test and easy to get patients for. So  
17 I think there is a rationale for including other  
18 populations for those pain trials, but I think one  
19 of the issues is going to be developing them for  
20 specifically channel mutations per se I think is  
21 going to be more challenging because -- I echo  
22 David Herrmann's experience that I've been testing

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1 sodium channel mutations for years in clinic, and I  
2 see a ton of small fiber neuropathy. I actually  
3 have only one patient that I found last week who a  
4 variant. I'm not saying it was pathogenic.  
5 So I think the experience in the U.S. for  
6 most of us is that it's a lot less common, and I  
7 think we still carefully phenotype these patients.  
8 So I don't think it's an issue of not phenotyping  
9 patients; I just think the mutation is just less  
10 common, where most of us --  
11 DR. FREEMAN: Genotype or phenotype?  
12 DR. PELTIER: Both.  
13 DR. FREEMAN: You said we all phenotype.  
14 DR. PELTIER: That's what I'm saying, is  
15 that my patients are phenotyped with a panel, not  
16 necessarily a whole exome sequencing. They're  
17 carefully phenotyped, and they still don't have the  
18 sodium channel mutations. And I see a lot of  
19 Pott's patients plus regular small fiber neuropathy  
20 patients. So I see the gamut of what you expect to  
21 see, those mutations, and we just don't find them.  
22 DR. FREEMAN: So let me maybe ask -- and

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1 this has always been a question that has plagued me  
2 since the BMS PNRR paper. At the end of the paper,  
3 the BMS writer wrote about a number of potential  
4 limitations, technical limitations, as to why there  
5 may be differences between the PNRR data and the  
6 data coming from Netherlands -- Waxman -- and  
7 Milan. I wondered to what extent what you, David,  
8 PNRR saw is actually technical. How complete was  
9 the sequencing done? Was it done in a similar way?  
10 Are we missing something for technical reasons?  
11 DR. FABER: Can I comment on that?  
12 DR. FREEMAN: Yeah. I'd love for you to.  
13 DR. FABER: I think that it sounds very  
14 easy. You do a genetic test, and you have a  
15 result. We had some very bad experiences with a  
16 commercial bureau, who really missed a lot of parts  
17 of the gene. If you don't check that -- we have a  
18 very good molecular biologist who really checks  
19 everything. If you don't check it, you will never  
20 find anything. So that's one thing  
21 So is the test really done very well? And  
22 also, if you use next-generation sequencing, how

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1 are your filter lines defined? Do you have a good  
2 bio plan? Do you have a good bioinformatician?  
3 Those are really crucial factors in defining  
4 whatever variant you are going to find.  
5 Another thing that was already mentioned is,  
6 of course, there may be differences in genetic  
7 background between the U.S. and Europe. We don't  
8 know that, but I think these technical factors may  
9 really play a big role. I would not rely on any  
10 commercial cheap test, for example. So that's one  
11 thing.  
12 Then you also asked about the timeline of  
13 the symptoms. Well, we see a lot of patients, and  
14 a lot of patients have symptoms for decades when  
15 they come to us, and they have a pure small fiber  
16 neuropathy. So in my opinion, the majority of the  
17 patients will stick to a small fiber neuropathy, or  
18 if they develop something, then it's really minor.  
19 So that's the majority of the patients.  
20 Giuseppe, I think you wanted to add  
21 something as well.  
22 (No response.)

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1 DR. FREEMAN: David Herrmann, Gordon Smith,  
2 Nurcan, and Chris. Try and remember.  
3 DR. HERRMANN: Two brief points. In terms  
4 of defining these disorders and then thinking about  
5 populations to test sodium channel blockers, while,  
6 Ahmet, you argued for lumping people together  
7 because you say targeting Nav 1.7 might be a  
8 universal target for pain disorders, I still think  
9 that as clinicians, I would rather argue to test in  
10 multiple models, a test that separate out the  
11 models because the mechanisms are complex. And we  
12 may see differential response rates depending on  
13 broad categories, be it osteoarthritis, small fiber  
14 neuropathy, distal small fiber neuropathy,  
15 et cetera.  
16 So it's still to argue for testing in  
17 multiple separate models rather than just a  
18 generalized pain indication. And I think we still  
19 want to know whether a treatment's highly effective  
20 in a large percentage of patients within a model or  
21 just only effective in 20 percent.  
22 DR. HOKE: I agree. Like if you're going

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1 to -- I would argue that there are probably easier  
2 clinical targets than small fiber neuropathy where  
3 we are debating how to even define the disease  
4 population. So if it is truly generalized pain  
5 mechanism, pick something, post-herpetic neuralgia.  
6 It's a very clear-cut patient population that you  
7 can test.  
8 DR. LEVINE: The other advantage to  
9 splitting the groups out is that we've got  
10 experience, both duloxetine and Lyrica, where doses  
11 are different in the different models. So the dose  
12 that works for diabetic neuropathy may be less than  
13 the dose that works for post-herpetic neuralgia.  
14 So if you do lump them together, they all just get  
15 the same dosing. You may miss that as well.  
16 DR. FREEMAN: Maybe to editorialize a  
17 little, I think there really are three issues. One  
18 is when you're doing a proof-of-concept trial, you  
19 want to remove as many confounders as possible, and  
20 one of the first steps in doing that is to have  
21 your populations and the study as specific as  
22 possible.

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1 The next point -- and I'll maybe only make  
2 two points -- is that even within a specific  
3 disease -- let's just say PHN or small fiber  
4 neuropathy -- a number of us have been focusing on  
5 different pain phenotypes as a way to address the  
6 underlying mechanism. And I think even in a  
7 disorder like PHN -- and I won't go into  
8 details -- as you say, a relatively pure disorder,  
9 the pain phenotype varies. And to me, there's no  
10 question that the response to an intervention is  
11 going to be different depending on the phenotype  
12 because that phenotype has to in some way reflect  
13 the underlying pain mechanism.  
14 Then finally, osteoarthritis, I imagine if  
15 we put a group of obsessive, compulsive  
16 neurologists on to osteoarthritis, we would spend  
17 hours discussing the different pain characteristics  
18 that exist in that population. I do think that  
19 it's not as simple as all that.  
20 Chris?  
21 DR. GIBBONS: I actually want to get back to  
22 Karin's point, which I thought was really critical,

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1 the issue you raise, which is genetic testing and  
2 quality control. I think that's actually something  
3 very simple that this group could accomplish in  
4 short order, which is you have very well  
5 characterized patients with mutations. They really  
6 should be tested across the different commercial  
7 labs. We need to know who is viable as a place to  
8 get our testing done, without which, clearly, we're  
9 going to be in a complete quandary.  
10 DR. HOKE: If I can comment, I work with  
11 GeneDX. If you use their whole exome sequencing to  
12 get at the Nav channel mutations, they say that  
13 their sensitivity is only about 90 percent. So if  
14 you're really interested in Nav channel mutations,  
15 you have to specifically ask for sequencing of  
16 those genes.  
17 DR. FABER: And you would need  
18 single sequencing, but even -- I had a bad  
19 experience where they said they do single  
20 sequencing, but still missed some parts of it, and  
21 they didn't correct for that.  
22 DR. FREEMAN: It was Nurcan, and then

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1 Giuseppe.  
2 DR. UCEYLER: First of all just another  
3 comment on the genetic aspect, as another European  
4 center with less patients but very well  
5 characterized also clinically, we do  
6 next-generation sequencing in all of our patients  
7 and still would have much lower, as I commented  
8 early in the morning, numbers, the published ones.  
9 I don't know what the reason can be  
10 One thing I wanted to ask here is, in your  
11 patient cohort -- so this was prospectively  
12 recruited patients -- you did not maybe also  
13 include -- for instance, after having one index  
14 patient, then the siblings, which would increase  
15 the number, of course, in the study population.  
16 DR. FABER: The number of families are  
17 extremely low, so, no, that's not included in the  
18 12 --  
19 DR. UCEYLER: So you did not further recruit  
20 them when you have an index patient, that you say,  
21 okay, do you have siblings --  
22 DR. FABER: Of course, we do family

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1 investigations. We do that, but that's something  
2 else; or the co-segregation, we do that. But these  
3 are single patients, and the number of family  
4 members are extremely low, so the percentage is  
5 really for probands.  
6 DR. UCEYLER: So the percentage is without  
7 including further siblings after having found one  
8 in those patients.  
9 DR. FABER: Yes.  
10 DR. FREEMAN: Giuseppe?  
11 DR. LAURIA: We've been analyzing the exome  
12 sequencing from around 15 families, in which we got  
13 3-years DNA sampling and so on. But I want to  
14 bring your attention to the fact that we should not  
15 follow the idea that this is a monogenic condition.  
16 I think it is quite important because this is a  
17 condition in which -- our understanding or our  
18 hypothesis actually -- let's put it in this  
19 way -- is that there is possibly -- and based on  
20 the data which are relatively different from those  
21 that Ahmet presented there is a susceptibility  
22 background, a genetic susceptibility, clustering a

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1 different subgroup of patients. We decided to  
2 divide into painless and painful. Of course,  
3 there's a lot of work to do in terms of subdividing  
4 the painful groups by phenotype and whatever.  
5 As to the analysis, the number of patients  
6 in which you would find one single pathogenic  
7 mutation, assuming the time that you need to define  
8 that mutation, that the variant that's pathogenic,  
9 which is a long time, is clearly low. So assuming  
10 that the quality of any commercial company will be  
11 fine, I don't know whether we are going toward the  
12 right direction with this discussion.  
13 DR. FREEMAN: Eva, and then I want to ask a  
14 question.  
15 DR. FELDMAN: Eva Feldman, University of  
16 Michigan. Maybe this will sound like heresy, but I  
17 think in 99 percent of the patients, this really  
18 isn't an issue, and I'm almost surprised we've  
19 spent this much time talking about genetic testing  
20 in that.  
21 I think that we all have the experience  
22 primarily that the variants are not affecting our

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1 clinical practice. I also think that we all agree  
2 that the sodium channel is a target. You can use  
3 an analogy of myasthenia gravis. We know the  
4 acetylcholine receptor is a target, and we target  
5 it. We don't see multiple genetic variance in that  
6 particular receptor. And maybe that's not the best  
7 analogy, but we understand scientifically and  
8 mechanistically that the sodium channel is a  
9 target. I think we probably have a consensus that  
10 whether or not there is a variant in that channel,  
11 we shall move forward with clear, well-defined  
12 populations and potential new clinical trials.  
13 So whether or not there is a variant or  
14 isn't a variant, I don't think should really drive  
15 further discussions necessarily at this meeting.  
16 DR. FREEMAN: I'm sure we will come back to  
17 this, and I think we have enough, how should I put  
18 it, foment for discussion. Let me come back to  
19 something for which I have less clarity, and I'd  
20 like to get a little bit more clarity. That is the  
21 immune factors in small fiber neuropathy.  
22 The way I see any intervention, and IVIG in

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1 particular given the expense associated with it.  
2 There two approaches. One is I would never ever  
3 give this therapy in the absence of a double-blind,  
4 randomized, placebo-controlled clinical trial for  
5 condition X, and here we're talking about small  
6 fiber neuropathy.  
7 At the other end of the spectrum is this is  
8 such a devastating condition, patients have such  
9 impaired quality of life, I am willing to try  
10 anything, even if there is a chance, however small,  
11 that this will improve patients' quality of life,  
12 sense of well-being, even if it's the 22 percent  
13 placebo response, which Todd showed in his slide.  
14 I would like to get a sense of where people  
15 stand on the spectrum. And having said that, then  
16 the subsequent step is if we stand somewhere in the  
17 middle, what are the criteria that you would use  
18 for deciding that this is reasonable to do? And  
19 I'm obviously most interested in a clinical trial,  
20 but I suppose as information to judge that, even in  
21 clinical practice. And we've got a couple of  
22 minutes left. I'd just like to raise that as a

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1 possibility for discussion.  
2 DR. FABER: Can I add one thing?  
3 DR. FREEMAN: Of course.  
4 DR. FABER: We are performing a  
5 double-blind, randomized trial now with IVIG. We  
6 never treat patients that are not in the trial  
7 because that's something that's not going to be  
8 reimbursed in the Netherlands without a good  
9 indication. But we are performing the trial, and  
10 it's supposed to be finished by the end of this  
11 year.  
12 DR. FREEMAN: So here we have we'd never do  
13 other than in a clinical trial.  
14 DR. LEVINE: In your trial, though, what is  
15 the patient population and how did you select that  
16 they might be immune, or did you just take  
17 all-comers of small fiber?  
18 DR. FABER: Because the definition of immune  
19 is very difficult, as you already said, we decided  
20 we would not go into that. So people with a clear  
21 immunological disease that should be treated with  
22 whatever the immunologist says it should be

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1 treated, those are not in the trial.  
2 DR. LEVINE: These are idiopathic small  
3 fiber?  
4 DR. FABER: Yes.  
5 DR. FREEMAN: Does anybody else on the panel  
6 want to address the question or in the audience?  
7 DR. HOKE: I think the big challenge is  
8 going to be how to define the immune-mediated small  
9 fiber neuropathy patients.  
10 DR. FREEMAN: So you would be more selective  
11 in a clinical trial than Karin?  
12 DR. HOKE: I think so. I think the patient  
13 population that I would think needs to be tested  
14 are people who have a progressive type of  
15 neuropathy symptoms, not the acute onset that's  
16 monophasic and then stable or improving, because I  
17 think those patient populations will probably  
18 improve on their own. At least in my experience,  
19 I've done probably skin biopsies in about 10 or 20  
20 of those, and they do improve over time. But the  
21 ones who are progressive, and especially if there  
22 is an autonomic neuropathy component, that's a big

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1 one. That group of patients probably had some  
2 autoantibodies that we don't recognize yet.  
3 So we're actually working with our Sjogren's  
4 clinic colleagues. Out of 300 or so Sjogren's  
5 patients with small fiber neuropathy patients, we  
6 have identified 2 novel autoantigens that bind to  
7 DRG in both human DRGs and rat DRGs. So we're  
8 writing those papers up right now. And the  
9 frequency of these autoantibodies are relatively  
10 low. One is about 7 percent; the other is  
11 14 percent. I suspect there is going to be a lot  
12 more, and these are often patients who are  
13 non-length-dependent small fiber neuropathy  
14 patients.  
15 DR. FREEMAN: I'm going to put people on the  
16 spot and ask for clarification because we're going  
17 to need it. Define progressive; symptomatic pain  
18 or something more objective?  
19 DR. HOKE: I think for a lot of those  
20 patients, it's either the intensity of the pain  
21 changes over time or the location. If it started  
22 in the hands, it may spread 2 or 3 months later

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1 down to the trunk or to the legs. To me, that's  
2 progressive.  
3 DR. FREEMAN: But pain, not small fiber  
4 sensory loss and not skin biopsy changes.  
5 DR. HOKE: I mean, if you had that type of  
6 data, that's even better. You can define it.  
7 DR. FREEMAN: But pain for you is  
8 sufficient. I apologize for putting you on the  
9 spot, but these are -- I don't apologize a lot.  
10 (Laughter.)  
11 DR. HOKE: So I would like to see skin  
12 biopsy changes. And in fact, I think one of the  
13 issues we need to define -- and I think I was  
14 talking with Nurcan earlier -- if we use this  
15 strict criteria of reduction in intraepidermal  
16 nerve fiber density, we probably are missing a lot  
17 of non-length-dependent small fiber neuropathy  
18 patients, where the only findings on the biopsy are  
19 sometimes axonal swellings and fiber fragmentation  
20 at all three sets. At Hopkins, we routinely do  
21 three-set biopsies, and if I see that in patients  
22 with systemic symptoms, I consider that as a

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1 painful, non-length-dependent small fiber  
2 neuropathy.  
3 DR. FREEMAN: Can I put a few other people  
4 on the spot? Maybe, Eva, you're sitting there  
5 quietly. What's your approach? You've thought  
6 about this. Are there patients with small fiber  
7 neuropathy that you treat with IVIG, and if so,  
8 who?  
9 DR. FELDMAN: No, I have never treated a  
10 patient with, quote, "inflammatory small fiber  
11 neuropathy," with IVIG that I did not know had a  
12 clear underlying other autoimmune disease, such as  
13 SLE, sarcoid, et cetera. And then in those  
14 patients, I actually did not use IVIG.  
15 I will tell you that I do see in my practice  
16 a large number of fairly obese individuals who turn  
17 out to be prediabetic who are being treated with  
18 IVIG for inflammatory small fiber neuropathy. And  
19 when the IVIG is discontinued, there's no change in  
20 the course of their disorder.  
21 DR. FREEMAN: So these are patients that are  
22 referred to you.

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1 DR. FELDMAN: Yes, for lack of response of  
2 their inflammatory small fiber neuropathy on IVIG.  
3 That's my most common encounter with IVIG in small  
4 fiber neuropathy.  
5 DR. FREEMAN: So you're at that end of the  
6 spectrum.  
7 DR. FELDMAN: I am way, way, way --  
8 DR. FREEMAN: I've got way, way, but off the  
9 spectrum.  
10 DR. FELDMAN: -- off the spectrum  
11 DR. HOKE: I don't treat anybody either  
12 unless they have evidence of Sjogren's, sarcoid.  
13 But maybe Michael can comment. I know he has some  
14 experience with the neuro GI group at Hopkins who  
15 has severe GI autonomic dysautonomia, and at  
16 Bayview, they have some patients who were treated  
17 with IVIG.  
18 DR. POLYDEFKIS: In general, I'm not a  
19 proponent of treating small fiber neuropathy with  
20 IVIG. I think it's quicksand. And just looking at  
21 the numbers that Rob put up, we could bankrupt the  
22 country with IVIG. But in response to Ahmet's

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1 comment, there was this population of patients with  
2 gastroparesis that was well documented, where  
3 essentially everything failed. And a little bit on  
4 a whim, we tried to treat them with IVIG, and its  
5 subset clearly did improve.  
6 All that said, it's become so difficult to  
7 get IVIG improved for those patients. I'm not sure  
8 it's going to continue.  
9 DR. LEVINE: I was going to make one quick  
10 point. Actually, I was going to make the point in  
11 my talk, and I forgot. When we talk about  
12 immunomodulatory therapy for small fiber  
13 neuropathy, I think we also have to be very careful  
14 because we know of many immune-mediated  
15 neuropathies that don't get better with IVIG, and  
16 they'll only respond steroids. The vasculitides  
17 don't get better with IVIG. We tend to conflate  
18 the idea of immune therapy with IVIG, in this  
19 country at least, because that's what everyone's  
20 out there doing. But it may be a big mistake  
21 because if we don't understand the pathology, we  
22 may actually be missing a population of patients

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1 that we could treat with steroids or other  
2 therapies.  
3 DR. FREEMAN: James?  
4 DR. RUSSELL: I think we need to get back to  
5 the science here. We're kind of out here playing  
6 Star Trek basically. What we really need to do is  
7 we need to understand the pathophysiology, and we  
8 need really good biomarkers that tell us this truly  
9 is an inflammatory process and this has to be  
10 rigorously done, and it has to be confirmed by  
11 several groups.  
12 Once we're at that point, then I think we  
13 can say, right, we can then do our clinical trial  
14 and we can use this as an endpoint target for  
15 future studies. But I think we have to take a step  
16 back at this point and really get to the  
17 pathophysiology and get some hardcore scientific  
18 endpoints.  
19 DR. FREEMAN: So can I maybe just elaborate  
20 on this just a little? And I know we're running  
21 really late. Maybe I should stop because this is  
22 going to be I think a period -- a topic that we

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1 will discuss, and I ask both of you and Nurcan.  
2 So the work coming from the Pestronk lab,  
3 would you regard those as hard biomarkers? Are  
4 those epi phenomena? What do you think of that?  
5 And the same question is going to be directed at  
6 Nurcan in the evidence of inflammation found in  
7 skin biopsy.  
8 Eva, stop smiling.  
9 (Laughter.)  
10 DR. RUSSELL: My view of this is that if you  
11 can really show it in the skin biopsies, and you  
12 can show that there is a change over time, which  
13 correlates with the patients' clinical outcomes,  
14 and that it really reverses with a treatment, then  
15 I think you can believe they are useful and  
16 reliable. Beyond that, you have a problem with  
17 interpretation.  
18 DR. FREEMAN: At this point in time, what do  
19 you suggest?  
20 DR. RUSSELL: I think we need to start  
21 looking at the skin biopsies. We need to start  
22 looking at some of the markers that Todd was

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1 mentioning, and perhaps some other markers as well,  
2 and see whether any of those things show change  
3 over time, show correlation with clinical outcomes,  
4 and then we can start looking to see if they are  
5 reversed with treatment.  
6 DR. FREEMAN: Eva, for smiling, I'm going to  
7 ask you what your thoughts are.  
8 DR. FELDMAN: Alan Pestronk is one of my  
9 closest friends, so I'm smiling in that I think  
10 that he's opened up a very interesting field. And  
11 I don't know how much of the data are really  
12 pathogenic. As James says, we really -- I don't  
13 think necessarily that's the core of this meeting,  
14 but we do need to get back to the basics, and we  
15 have really strayed from that in terms of  
16 mechanism.  
17 DR. FREEMAN: So it will be Nurcan and then  
18 I think to provide a little balance, last word from  
19 Anne Louise.  
20 DR. UCEYLER: The question was about the  
21 inflammatory markers and the skin, and what I would  
22 think about them. I think this is very, very

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1 important to follow. There can be, in the  
2 periphery, mediators that do affect the fibers and  
3 then maybe also increase pain, not only looking at  
4 the neuron with the mutation, but also in the  
5 periphery, this is what I think is a very important  
6 aspect. But we do need much, much more research on  
7 this.  
8 What we are currently doing is we are trying  
9 to follow up our data that I just mentioned, now  
10 looking at expression from skin cells, really. You  
11 can use biopsies for many different things. So  
12 what we are doing is we're looking at fibroblasts  
13 with keratinocytes. This is ongoing work in a  
14 large group, and let's see what comes out then.  
15 But these are single studies at the moment. We  
16 need much, much more experience here and more data  
17 before we can answer is this now really  
18 inflammatory or any other aspect that really feeds  
19 pain here.  
20 DR. FREEMAN: Giuseppe, and then Anne  
21 Louise.  
22 DR. LAURIA: Actually, we just don't know.

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1 We don't know whether there is any real change in  
2 the skin. I agree that something may happen, but  
3 we don't know the influence of a number of  
4 variables which can affect the level of the  
5 cytokines in the blood, considering the skin which  
6 is a much dirtier environment.  
7 Just to make an example, the levels of the  
8 interleukin-2, and 10, and TMF changes with the  
9 pressure and recovers, so we don't know -- if you  
10 are not balancing. To my knowledge, what we know  
11 is that in the clear immune-mediated neuropathy in  
12 the skin, you can find some changes which are  
13 related to the pathogenic mechanism of that  
14 neuropathy, in CIDP, for example the neurofascin.  
15 But in this field, which remains quite blurred, I'm  
16 not sure.  
17 DR. FREEMAN: Anne Louise, closure. Your  
18 comment is between everybody leaving for lunch.  
19 DR. OAKLANDER: Biomarkers are critical.  
20 They have to be time linked. Biomarkers are going  
21 to change during the course of the disease. If  
22 somebody's already lost 98 percent of their nerve

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1 endings, they may no longer have inflammation, for  
2 instance, in the skin. And immunotherapy, not  
3 monolithic -- any therapy with regards to the  
4 inclusion criteria, you have to look at the costs  
5 and the risks. And the more expensive and  
6 potentially dangerous the therapy, if somebody  
7 wants rituximab or bone marrow transplantation, you  
8 really have to have a very high threshold. And  
9 also I think you have to prescribe very short  
10 courses.  
11       So I'll say I'll consider a trial for you,  
12 and I try to follow the ICE for IVIG, and do not  
13 prescribe more than a 3-month trial, and I see that  
14 person back, and I'll evaluate, and I will not  
15 continue unless there's clear evidence.  
16       DR. FREEMAN: This was a terrific session.  
17 I'll leave you to ponder bone marrow transplant --  
18       (Laughter.)  
19       DR. FREEMAN: -- for small fiber neuropathy  
20 at lunch.  
21       (Whereupon, at 12:13 p.m., a lunch recess  
22 was taken.)

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1       AFTERNOON SESSION  
2       (12:13 p.m.)  
3       DR. DWORKIN: I think it's time to get  
4 started. Roy has asked me to serve as moderator  
5 for this afternoon session, so my objective for the  
6 next three hours or so is to do half as good a job,  
7 at least half as good a job as what Roy did this  
8 meeting. So I hope I succeed.  
9       Two quick things before we get started.  
10 This morning I mentioned, in talking about the  
11 history of ACTTION, the kind of absolutely pivotal,  
12 critical role of Bob Rappaport, who's now joined us  
13 for this meeting. So I just want to reiterate what  
14 I said this morning, Bob. Without your vision, we  
15 wouldn't be here, and we all appreciate it a great  
16 deal. Thank you.  
17       The second thing, for those of you who  
18 missed it, Francis Collins, the director of NIH,  
19 just this morning announced the HEAL Initiative.  
20 That acronym stands for -- let's see if I can  
21 remember this -- Helping to End Addiction Long  
22 Term. And as part of the announcement, he said

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1 that NIH's budget for fiscal year 2018 will be  
2 increased half a billion dollars from what it was  
3 in 2016. And that half a billion dollars will be  
4 devoted to two broad sets of questions addressing  
5 opioid use disorder, kind of the development and  
6 treatment of addiction and improving the treatment  
7 of pain so that fewer patients will need to try  
8 opioid analgesics.  
9       Improving the treatment of pain will involve  
10 prospective studies apparently of the transition  
11 from acute to chronic pain; setting up a clinical  
12 trial network dedicated to studying pain;  
13 et cetera, et cetera. It's all online, and I think  
14 it's hard to imagine how this isn't anything but  
15 good news for many of us in the room who are  
16 interested in understanding pain and its treatment.  
17       So without any further ado, it's my pleasure  
18 to introduce Dr. Simon Haroutounian. Simon is an  
19 assistant professor of anesthesiology at Washington  
20 University in St Louis, and he has done a  
21 comprehensive systematic review of the criteria  
22 that have been used in studies of small fiber

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1 neuropathy and is going to, for the next half hour,  
2 present what he's found in his systematic review to  
3 us.  
4       Presentation – Simon Haroutounian  
5       DR. HAROUTOUNIAN: So much for this  
6 introduction. I think before we start with the  
7 slides, I want to present one slide from another  
8 systematic review we just finished and going to  
9 submit probably sometime this week, where we looked  
10 at distal symmetric polyneuropathies and tried to  
11 look at the associations between intraepidermal  
12 nerve fiber density and other parameters such as  
13 neuropathy score symptoms and various QST  
14 parameters or some of the other more objective  
15 functional measures.  
16       Just quickly to go through this slide,  
17 again, this is distal symmetric polyneuropathies in  
18 general, not only small fiber neuropathy. I just  
19 hope this can contribute to the discussion. In  
20 general, this pie chart shows what percentage among  
21 the studies that have included studies of small  
22 fiber -- distal symmetric polyneuropathy have



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1 assessed those specific parameters.  
2 For example, among those studies, only  
3 11 percent have looked at objective neuropathy  
4 scores, 25 percent have looked at the association  
5 between pain symptoms and interpreting when they're  
6 fiber density' 14 percent between -- is this  
7 supposed to be warm detection threshold, and  
8 et cetera.  
9 The color coding is that the green  
10 association is there is a positive association  
11 between reduced interpretable fiber density and  
12 those parameters. So the greens are positive  
13 association or expected association; blue is that  
14 they found no association; yellow is mixed; and red  
15 is that the association was in the opposite  
16 direction.  
17 Just to briefly go through this in terms of  
18 pain symptoms, the association between epidermal  
19 fiber density and pain symptoms is very -- or could  
20 say probably nonexistent. Only about 40 percent of  
21 studies that have looked at the association have  
22 found positive correlation between the two. In most

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1 studies it was negative.  
2 The two that have the highest or the closest  
3 correlation are neuropathy scores on questionnaires  
4 like MNSI or it looks at neuropathy rather than  
5 just symptoms contact heat evoke potentials, laser  
6 evoke potentials, and NCVs that find pretty  
7 reasonable association with skin biopsy findings.  
8 Among the QST measures is probably the warm  
9 detection threshold that is most closely related to  
10 interpreter or more fiber density and not so much  
11 the others, so just to answer some of the questions  
12 that were raised in the beginning.  
13 I'll present -- I think I'll skip this  
14 slide. Most of the things were already discussed.  
15 We did a systematic literature review to try to  
16 look at idiopathic small fiber neuropathy, either  
17 clinical trials or mechanistic studies that have  
18 characterized the patient populations with the  
19 objective of assessing the diagnostic criteria for  
20 idiopathic small fiber neuropathy, and then  
21 potentially to bring this data and show it here to  
22 help our discussion on kind of refining the

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1 criteria for idiopathic small fiber neuropathy.  
2 So we did a systematic literature search  
3 back in July of last year. We used those keywords  
4 to identify studies of small fiber neuropathy.  
5 When we ran all those keywords, we found about  
6 43,000 papers that somehow related to small fiber  
7 neuropathy or neuropathy or pain, and it's not an  
8 amount you can work with.  
9 So we limited it a little bit to primarily  
10 human studies and including reviews and  
11 meta-analysis, English language. This is just if  
12 you're facing a PubMed search, you will get what we  
13 received as a result of this search. And it ended  
14 up with about 6,000 abstracts that would be  
15 potentially relevant to this review.  
16 So the idea was to look through this  
17 abstract and obtain the full text of the papers, if  
18 these were either clinical studies, epidemiological  
19 observational or interventional, or if this were  
20 reviews or guidelines on small fiber neuropathy.  
21 The point was to include patient population and who  
22 has SFN, which is either idiopathic or is of

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1 unclear or mix etiology. So we didn't want to  
2 focus on patients who have diabetes,  
3 polyneuropathy, or chemotherapy-induced peripheral  
4 neuropathy. Much rather, those groups, they're  
5 either idiopathic, or kind of mixed, or included.  
6 So we excluded animal studies, ex vivo and  
7 in vitro studies, or studies with kind of  
8 well-defined etiology.  
9 Two people independently screened all those  
10 6,000 abstracts, Mathias Leinders who's a postdoc  
11 in my lab, and Marta Campagnolo who works with Roy  
12 at Harvard. And basically they color coded those  
13 abstracts by either those who seemed to be relevant  
14 or maybe relevant, and then excluded to two  
15 different categories, either to the studies that  
16 have a well-defined etiology or studies that look  
17 to be kind of irrelevant. So we have this record.  
18 In terms of the results, it ended up having  
19 about 594 papers in these green and yellow category  
20 that look either relevant or may be relevant, and  
21 another 11 papers were identified from the  
22 references of the different papers.

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1 We built this database where we  
2 systematically applied certain criteria to see if  
3 we're extracting the full data from those papers or  
4 that we're putting them aside. And we're primarily  
5 excluding nonhuman studies. Again, sometimes  
6 papers state that this is idiopathic or small fiber  
7 neuropathy study, but all patients are diabetic, so  
8 those would be excluded in that case  
9 We also excluded studies with less than 10  
10 subjects, which would actually exclude some of the  
11 clinical trials that were done in small patient  
12 populations. But we ended up having 123 papers in  
13 this group for which we extracted the full data on  
14 patient characteristics, biopsy findings, QST  
15 findings, et cetera.  
16 Out of this group, there were 38 that was  
17 either reviews or guidelines. Only 11 studies met  
18 the characteristics that they were called  
19 idiopathic small fiber neuropathy, and actually it  
20 included patients for whom the etiology was  
21 unknown, so kind of completely idiopathic.  
22 The largest group was what's called mixed

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1 small fiber neuropathy, so these were small fiber  
2 neuropathy patients, but the study group included a  
3 variety of either mixed etiologists, and then I  
4 think maybe and Gordon's presentation that will  
5 follow afterward will help us kind of figure out  
6 who are the patients who we can call idiopathic or  
7 we can give other names.  
8 This is this a lot of data, so I will  
9 present only kind of semi quantitative analysis of  
10 those. The way I'll present it is basically a I'll  
11 present those 11 iSFN papers and those 74 mixed  
12 small fiber neuropathy papers. This is kind of  
13 mapping where we looked at the variety of  
14 parameters, the QST, a skin biopsy, symptom  
15 measures, sign measures, et cetera. And we map  
16 them or color code it in a way that green would be  
17 the expected association, no difference between  
18 controls or association. In the unexpected,  
19 opposite direction, all the results were unclear  
20 and mixed.  
21 You will see that some of the boxes have  
22 this kind of cross-line, which means that the study

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1 compared patients to healthy controls. And if it's  
2 coded in this way, it would be the comparison is  
3 either to some kind of historic group or just with  
4 inpatient -- if it's a patient with distal  
5 symmetric polyneuropathy findings in the painful  
6 side versus non-painful.  
7 I'll start with the guidelines. If we look  
8 at a variety of recommendations of what we should  
9 include in the diagnosis of small fiber neuropathy,  
10 there have been about 38 different guideline papers  
11 on this topic.  
12 We separated the data to sensory symptoms;  
13 do we need sensory symptoms in this length  
14 dependent distribution; things like burning pain;  
15 paresthesia for the diagnosis of small fiber  
16 neuropathy; abnormal pin prick in length-dependent  
17 fashion; abnormal QSART; autonomic testing results'  
18 abnormal thermal perception; autonomic symptoms;  
19 abnormal skin biopsy that is with reduced  
20 intraepidermal nerve fiber density; and normal  
21 nerve conduction study to confirm this is small  
22 fiber neuropathy; or a battery of autonomic tests;

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1 and variety of laboratory tests to exclude other  
2 causes of neuropathy.  
3 So the findings are, in general, in the  
4 different guidelines for SFN, you can see that  
5 about 87 percent of guidelines recommend that we  
6 should include sensory symptoms in the appropriate  
7 distribution as a part of our diagnosis.  
8 Seventy-one percent of guidelines recommend  
9 that we include normal nerve conduction studies as  
10 a part of SFN workup. About 84 percent of  
11 guidelines recommend to use a skin biopsy to  
12 confirm small fiber neuropathy. And as you can see,  
13 there's a variety of other parameters, about  
14 40 percent recommend using a normal pin prick as a  
15 criteria; 24 percent recommend using a quantitative  
16 sudomotor axon reflex; 66 percent recommend using  
17 abnormal thermal perception like QST; and then  
18 about 40 percent using autonomic symptoms; and  
19 smaller percentages of guidelines recommend using  
20 either kind of a full battery of autonomic tests or  
21 exclude patients by doing laboratory diagnosis  
22 So this is just too small to figure out

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1 anything, but this is the way we mapped the  
2 studies, this set of the studies. It's 11 studies  
3 of idiopathic small fiber neuropathy. You can see  
4 that each study is here on the left side, and we  
5 looked at each of those parameters that were  
6 assessed in those patient populations: skin  
7 biopsy, distal proximal, or other CCM; corneal  
8 confocal microscopy; and then a variety of QST  
9 parameters; cold detection, warm detection;  
10 neurosensory alignment; et cetera; vibration,  
11 et cetera, et cetera; nerve conduction data;  
12 additional tests like laser Doppler; flare or  
13 synthetic skin response; skin wrinkling; contact  
14 heat evoked potentials; laser evoked potentials;  
15 and then a variety of autonomic tests.  
16 I think the striking part is there are a lot  
17 of white boxes, which means that those parameters  
18 were not assessed in those studies. So I think  
19 Nurcan is leading the way with the study that has  
20 assessed most of the parameter. But in any case,  
21 this is a representation of those findings; so,  
22 again, 11 studies that are called idiopathic small

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1 fiber neuropathy and have included patients in whom  
2 the etiology is really unknown.  
3 In terms of skin biopsy, 73 percent of the  
4 studies, 8 out of the 18, have looked at distal  
5 skin biopsy, and all of them are green, so confirm  
6 that those patients have reduced intraepidermal  
7 nerve fiber density. Only 3 of those 11 studies  
8 have looked at proximal biopsies, but again, all of  
9 the data was in the same direction.  
10 In terms of nerve conduction, EMG versus  
11 NCV, only two of the studies have looked at  
12 basically normal EMG. And then in terms of nerve  
13 conduction velocity, three of the studies have  
14 shown negative or normal NCV, and one has shown  
15 mixed results.  
16 In terms of QST, you can see that most of  
17 the parameters have been assessed in very few  
18 studies, so there's not much data we can draw from  
19 it. I think the three parameters that are probably  
20 worth discussing are the cold detection, warmth  
21 detection, and vibration detection thresholds.  
22 In terms of cold detection thresholds, there

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1 are eight studies that have looked at cold  
2 detection. In 5 out of 8, the patients have  
3 impaired cold detection, but you can see that in  
4 two studies, the results were mixed, and in one  
5 study, 2 patients did not have any difference from  
6 controls.  
7 In terms of warm detection, five studies  
8 have looked at it and four have found impaired warm  
9 detection in inpatients with idiopathic small fiber  
10 neuropathy, and one has resulted in mixed results.  
11 In terms of vibration detection, six studies have  
12 looked at it; four have found normal vibration  
13 detection thresholds in this population, and two  
14 have found abnormal. But the rest are  
15 really -- the interesting thing is studies that  
16 have looked at pinprick in the idiopathic small  
17 fiber neuropathy, all the results are mixed. So it  
18 doesn't seem that pinprick is really separating  
19 small fiber neuropathy from controls.  
20 In terms of additional tests, again, very  
21 few studies have actually looked at those things.  
22 I don't think it's even a point in focusing on

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1 those.  
2 (Laughter.)  
3 The second metrics -- again, I just  
4 presented it to look at the number of white  
5 empty cells. There's so much work to do to try to  
6 understand what are the different associations.  
7 You can see those columns that are filled  
8 primarily. These are the distal skin biopsies that  
9 most of the studies have performed. This is  
10 proximal skin biopsies. These are called detection  
11 and warmth detection, and these are the nerve  
12 conduction of muscle, and this is vibration.  
13 Again, to kind of summarize the data from  
14 this ugly metrics, we're looking at the same  
15 parameters in this group of -- again, these are all  
16 small fiber neuropathy, but the populations are  
17 mixed in a way.  
18 In terms of skin biopsy findings, you can  
19 see that 70 or 80 percent almost have distal skin  
20 biopsy, and in the vast majority, the skin biopsy  
21 was different from healthy controls, kind of to  
22 confirm small fiber neuropathy. A smaller amount

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1 of studies, about 40 percent, have looked at  
2 proximal biopsies. Only seven percent of all the  
3 studies have looked at a corneal confocal  
4 microscopy, but all of those five have shown  
5 differences from healthy volunteers and in  
6 production.  
7 In terms of nerve conduction, again, you can  
8 see in some, the results are mixed in terms of  
9 excluding patients. There are probably some  
10 subgroups of patients with large fiber involvement  
11 because in a proportion of those studies, the  
12 results are mixed.  
13 In terms of QST, there doesn't seem to be a  
14 very consistent pattern in those patients compared  
15 to controls. So even when we're looking at things  
16 they call detection warmth detection, we can see  
17 that only about half of the studies have shown  
18 clear differences between those small fiber  
19 neuropathy populations versus controls. And in the  
20 other half, the data or the endings have been  
21 mixed.  
22 The same with vibration detection, it's only

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1 about half of the studies where the vibration  
2 detection was normal in those patients compared to  
3 healthy controls, but in the half of the studies,  
4 there were differences or the results were not as  
5 straightforward.  
6 So I think just by looking at the data, we  
7 came to realize that it's even more complicated  
8 than we thought it is, but nevertheless, these are  
9 the findings.  
10 In terms of additional tests like autonomic,  
11 et cetera, you can see the picture is vastly mixed  
12 in terms LDI flare, which is just heating up the  
13 skin and laser Doppler response, sympathetic  
14 responses. Autonomic testing results, again, only  
15 a small proportion of studies have looked at QSART,  
16 11 percent, but about half have found consistent  
17 differences between SFN and healthy controls, and  
18 about half have found mixed findings, and autonomic  
19 testing has been also not very consistent.  
20 The thing is, though, you can see those  
21 three tests, like contact heat evoked potentials,  
22 laser evoked potentials, and histamine skin

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1 response, again, there have been testing in a very  
2 small proportion of studies, 5 percent, 4 percent.  
3 I don't know if there's a reporting bias or not,  
4 but those seem to be pretty consistently separating  
5 small fiber neuropathy versus healthy controls.  
6 I think one of the discussions maybe should  
7 be around those special tests, is there room for  
8 expanding those and maybe having more data in  
9 larger patient cohorts, or what might be the  
10 publication bias associated with those.  
11 As almost another search, we looked at  
12 clinical or therapeutic trials of small fiber  
13 neuropathy and looked just at the inclusion  
14 criteria, not the characterization of patients. We  
15 just looked what kind of criteria people use in  
16 clinical trials for enrolling patients with small  
17 fiber neuropathy. Most of them are therapeutic  
18 clinical trials. There are a few that are overview  
19 of studies. And those too have the same patient  
20 population in a way, but most of them are  
21 therapeutic clinical trials in small fiber  
22 neuropathy.

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1 Interestingly, about 90 percent have relied  
2 on relevance symptoms to enroll patients in the  
3 study and about 70 percent have used some kind of  
4 pain severity cutoff, most of them 4 or more on a  
5 0 to 10 numerical rating scale. And the interesting  
6 thing is that although most guidelines recommend to  
7 use keen biopsies for diagnosing small fiber  
8 neuropathy, if we look at SFN confirmation by skin  
9 biopsy, only 22 percent of the clinical trials have  
10 used skin biopsy to confirm small fiber neuropathy  
11 in these patients, and we had a discussion whether  
12 it's a useful or important tool for inclusion or  
13 not.  
14 About half of the studies use nerve  
15 conduction to exclude abnormal nerve conduction as  
16 criteria for inclusion, exclusion of other  
17 predisposing factors, and then about a third of the  
18 studies use QST, again, to confirm small fiber  
19 neuropathy to enroll patients in the study.  
20 This is kind of the overall high level,  
21 maybe semi-quantitative presentation of the  
22 findings from this systematic review, so I'll just

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1 try to summarize those. I know those histograms  
2 were pretty confusing.  
3 Clinical trials, there were 27 clinical  
4 trials in SFN, and in terms of inclusion criteria  
5 they used, so neuropathy symptoms, inappropriate  
6 distribution that were used by most of the studies,  
7 and then certain pain severity cutoff, and then SFN  
8 confirmed by normal nerve conduction. So these  
9 were the main criteria most studies used.  
10 DR. HOKE: Can I ask a question? How do  
11 they design a trial that excludes neuropathy? I  
12 mean, how did they include patients that didn't  
13 have the neuropathy symptoms? What was the  
14 definition of the -- like that 11 percent of the  
15 patients who --  
16 DR. HAROUTOUNIAN: Sometimes it's  
17 mainly -- the main criteria could be, for example,  
18 small fiber neuropathy by skin biopsy, normal nerve  
19 conduction, and pain. It didn't clearly say that  
20 the distribution of the symptoms should be --  
21 FEMALE VOICE: So more likely it was.  
22 DR. HAROUTOUNIAN: We're kind of just going

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1 through the inclusion criteria of the studies and  
2 extracting this kind of specific information. There  
3 was quite a mix in terms of how people define the  
4 inclusion. [Inaudible – mic off].  
5 So for guidelines and reviews, again, it's a  
6 separate group of papers, 38 papers. The key  
7 points are, in terms of what different guidelines  
8 recommend for diagnosing small fiber neuropathy,  
9 it's primarily looking at the appropriate  
10 distribution of sensory symptoms, skin biopsy  
11 findings in terms of reducing intraepidermal nerve  
12 fiber density, normal nerve conduction, and  
13 abnormal thermal perception. These are kind of the  
14 main recommendations from most of the guidelines.  
15 If we're looking at those clinical studies,  
16 it characterizes patients with small fiber  
17 neuropathy in this pure small fiber neuropathy,  
18 11 studies. I think the main take-home messages  
19 are that mostly it's the distal skin biopsies that  
20 were abnormal in those patients. And this is in  
21 73 percent of those studies. In terms of proximal  
22 skin biopsies, there are much fewer data.

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1 These are the percentages that use nerve  
2 conduction. About three-fourths, the results were  
3 as expected. In terms of cold detection and warm  
4 detection testing, you can see that more than half  
5 of the studies confirmed that there were  
6 differences between SFN and healthy controls, but  
7 it's not straightforward, clear-cut that you can  
8 find that there are warm detection or cold  
9 detection differences.  
10 DR. FREEMAN: Can you clarify something for  
11 me? And that is, these were the pure idiopathic  
12 small fiber neuropathy, and 3 out of 4 had nerve  
13 conduction abnormalities, so 25 percent didn't, and  
14 vibration detection, one-third did not.  
15 What I'm confused about is these are  
16 obviously launched fiber modalities, whether the  
17 result was unexpected. How did they use that  
18 information? Because some would say -- not all,  
19 but some would say that that is no longer pure.  
20 DR. HAROUTOUNIAN: So the inclusion -- these  
21 are studies that characterize those patients, so in  
22 terms of inclusion criteria, they say we're

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1 enrolling patients that have idiopathic small fiber  
2 neuropathy with certain criteria and no other known  
3 causes of neuropathy. But the extent to which they  
4 tested that this is indeed idiopathic and indeed  
5 small fiber, quite differs from the studies.  
6 So not all of them used vibration detection  
7 to exclude patients.  
8 DR. FREEMAN: I see. So it's not that they  
9 did that in a population they were then excluded,  
10 but these were included in that --  
11 DR. HAROUTOUNIAN: Were included as  
12 idiopathic small fiber neuropathy, but the  
13 findings --  
14 DR. FREEMAN: Were as they were.  
15 DR. HAROUTOUNIAN: -- was QST, et cetera.  
16 And you can see. Among the 11 studies, only 4 have  
17 done vibration detection, right? Only 5 had done  
18 warm detection, only 8 have done cold detection.  
19 I mean, we would love them to all those, but  
20 it's just some of the data are not there.  
21 DR. UCEYLER: Maybe just a comment on this  
22 question. So with the nerve conduction, velocity,

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1 I think it doesn't matter of definition, also how  
2 in these studies normal was defined. According to  
3 Lacoma [ph] and Stewart, I think marginally  
4 abnormal conduction studies will not exclude small  
5 fiber neuropathy.  
6 Another aspect -- I will present data on  
7 this tomorrow -- a very interesting finding, I  
8 think -- what we see also in others, large fiber  
9 neuropathy should be excluded. So we do the  
10 clinical examination. We do the nerve conduction  
11 studies. This is all normal.  
12 Interestingly, when we do QST, we do find  
13 mechanical detection threshold changes in these  
14 patients, which we do not understand. But we see  
15 this in several studies, and other people also do  
16 see this. So we have to think about that. As I  
17 said, I will show some data on this. Large fiber  
18 or what actually do these fibers sense, this is  
19 another question.  
20 DR. HAROUTOUNIAN: And I don't know about  
21 the association between NCV findings and mechanical  
22 detection threshold, how consistent they are and

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1 what's the kind of specificity.  
2 DR. HERRMANN: I think your review  
3 highlights one thing. All of these studies use  
4 somewhat different inclusion criteria for the  
5 patient of suspected small fiber neuropathy that's  
6 included. And then one of the problems with  
7 understanding what the diagnostic yield is of cold  
8 detection threshold or skin biopsy is this concept  
9 of incorporation bias.  
10 So many of the tests you're looking at are  
11 incorporated in your inclusion criteria for the  
12 study. So I think that's just the challenge that  
13 you have to face when you interpret data, at least  
14 diagnostic yield for any of these tests, is just to  
15 understand the limitations when the test is  
16 actually part of the inclusion criteria, like  
17 pinprick, well, some studies require it to be  
18 abnormal; some don't.  
19 DR. HAROUTOUNIAN: Those are the  
20 methodologies. Some use just a safety pin, but  
21 others use Von Frey filaments; others use the MRC  
22 German Neuropathic Pain Network weighted pins.

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1 Actually summarizing these findings was  
2 extremely hard because of the heterogeneity of the  
3 approaches and methods that people use. So even  
4 lumping them into as many categories might do some  
5 disservice to some high-quality studies versus  
6 highlight some of the findings of the lower-quote  
7 studies.  
8 DR. LAURIA: The problem is actually the  
9 lack of a gold standard. Right? So the point is  
10 that if you don't have one, you don't know --  
11 DR. HERRMANN: You have to used --  
12 DR. LAURIA: -- anyone to find the  
13 gains [indiscernible]. That's the reason why at  
14 the time, we decided that -- since there isn't  
15 anyone, we decided to combine some.  
16 That's in any case, a big issue because this  
17 creates an intrinsic limitation that cannot be  
18 overcome unless we define that something is the  
19 gold standard.  
20 DR. SMITH: The other issue is there's a  
21 Bayesian problem here too. It's one of my concerns  
22 about how nerve conduction studies are used. In a

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1 low population prevalence, they work very well.  
2 The negative predictive value is quite high. But  
3 if you look at a population prevalence where in  
4 diabetes, half of patients have neuropathy, the  
5 negative predictive value is terrible. And this is  
6 compounded by the fact that it's not clear what  
7 gold standard one would use to make those kinds of  
8 comparisons.  
9 DR. HAROUTOUNIAN: I think maybe the best  
10 example of the gold standard is the skin biopsies  
11 because before the EFNS guidelines on taking skin  
12 biopsies, if you look at the heterogeneity on how  
13 people have taken and analyzed biopsies,  
14 3 millimeter, versus 4 millimeter, versus doing  
15 30 micron cuts, versus 40, versus 50, versus 60,  
16 what to fixate in, what kind of anti -- there was a  
17 huge variability, but actually in the past seven or  
18 eight years, skin biopsy findings have been  
19 somewhat more consistent where people have followed  
20 the guidelines.  
21 So I think it is possible with data to  
22 convince users or researchers to use more universal

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1 or accepted techniques for assessing those things.  
2 Basically, the last part is the findings  
3 among those mixed small fiber neuropathy studies.  
4 And I think, again, there were some things that  
5 were expected, some that were not. But again,  
6 distal skin biopsy seemed to be the most consistent  
7 finding, separating SFN patients and healthy  
8 volunteers. And smaller percentages, CCM, but at  
9 least the studies were pretty consistent. Again, I  
10 don't know whether there's publication bias because  
11 there's only small amount, And EMG doesn't seem to  
12 be very convincing.  
13 In terms of nerve conduction velocity, most  
14 of the studies in this group at least work kind of  
15 as expected. A cold detection was not very  
16 specific. A warm detection was a little bit better  
17 maybe. But we can see that the pain parameters or  
18 psychophysical measures of pain, so heat pain and  
19 cold pain performed terribly in terms of separating  
20 healthy controls from small fiber neuropathy  
21 patients. Maybe it gives us a sense about the  
22 cognitive or cortical measures that are involved in

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1 the response or psychophysical response that  
2 includes pain rather than just objective  
3 neurophysiological measure.  
4 Pinprick performed pretty. And those two  
5 parameters, the contact heat evoke potentials,  
6 laser evoke potential, histamine flare, were all in  
7 the same direction but like CCM. I think there  
8 were just a small amount of studies, and we need to  
9 look a little bit more into those, but maybe they  
10 have an important value in separating patients with  
11 small fiber neuropathy controls.  
12 I want to thank my group, in particular  
13 Mathias Leinders, who did most of the work on this  
14 study. Although he's a Borussia Dortmund fan, I  
15 think he's still did a reasonable job on this. And  
16 thanks for your attention.  
17 (Applause.)  
18 DR. DWORKIN: Why don't we take just two  
19 questions, if there are two questions for Simon,  
20 and save the rest for the discussion.  
21 Are there two questions?  
22 DR. FREEMAN: While people are thinking of

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1 the two questions -- this is not a question. But  
2 anybody who has papers that you feel should have  
3 been included, you know the systematic reviews are  
4 like. One typo can ruin your study.  
5 So if there was anything that he presented  
6 that you thought a specific paper that belongs to  
7 you, your friends, your enemies, please let him  
8 know because that's quite critical to this.  
9 DR. HAROUTOUNIAN: Thank you for this  
10 comment, Roy.  
11 DR. DWORKIN: A couple of questions? We'll  
12 have lots more time later. Thanks, Simon.  
13 It's a great pleasure to introduce our next  
14 speaker, Gordon Smith, who just very recently  
15 became chair of neurology at Virginia Commonwealth  
16 University. Congratulations, Gordon.  
17 (Applause.)  
18 DR. DWORKIN: And Gordon will be talking  
19 about solutions and inclusion criteria  
20 [inaudible - off mic].  
21 Presentation – Gordon Smith  
22 DR. SMITH: And now that I'm a chair, I just

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1 want to be overt, and I'm going to try and take  
2 your money and recruit your colleagues.  
3 (Laughter.)  
4 DR. SMITH: This is downtown Richmond.  
5 I too am not sure whether I should thank Roy  
6 and curse him. I liked Rob's introduction. I  
7 think a bit of both.  
8 Everything I've said, and actually most of  
9 the slides I'm going to show you, you've already  
10 seen, which begs the question why I'm giving the  
11 talk. And I think what I hope to achieve in this  
12 is to look at the same data, much of which we  
13 examined this morning, but look at it from a  
14 different perspective.  
15 I actually have this perspective, where as  
16 many of you know, we're in the process of just  
17 getting off the ground the first large scale  
18 clinical trial for idiopathic neuropathy. And it's  
19 not focused purely on small fiber neuropathy, but a  
20 lot of the issues that we've been talking about  
21 here specific to small fiber neuropathy, we had to  
22 think about it in terms of enrollment criteria and

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1 clinical trial design.  
2       So as I go back through some of the data,  
3 and some of the slides are new, and my slides I  
4 have to say are much more colorful than some of my  
5 colleagues, just think of them from the perspective  
6 of an individual trying to design a clinical trial  
7 for idiopathic small fiber neuropathy. And these  
8 are my disclosures, none of which are really  
9 germane to this.  
10       First -- and it's a new slide -- I want to  
11 quibble a little bit with the term "idiopathic  
12 neuropathy." I had a patient once tell me you must  
13 be an idiot because you can't figure out my  
14 neuropathy, which I thought was sort of creative.  
15 But beyond that, I think it's a very vague term,  
16 and it leads us down -- I like the quicksand  
17 metaphor that someone used in terms of IVIG.  
18       There are lots of things that can be an  
19 idiopathic neuropathy, a patient who has  
20 unexplained distal lower motor neurons syndrome.  
21 Is that an idiopathic neuropathy?  
22 Non-length-dependent idiopathic neuropathy. So I

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1 think the terminology needs to be a little more  
2 precise. Anne Louise I think talked about this.  
3       These are the terms that are commonly used  
4 in the literature, which is idiopathic neuropathy,  
5 chronic idiopathic axonal neuropathy, Rick Barohn's  
6 term, CSPN, which is the term I actually have grown  
7 to like because it really describes the phenotype.  
8 And I'm going to use it I think fairly consistently  
9 in this talk.  
10       But I think it's something we ought to be  
11 thinking about. Do we really want to call  
12 idiopathic neuropathy idiopathic neuropathy, or  
13 should it be cryptogenic small fiber sensory  
14 neuropathy? And the other attraction of that is  
15 Bob Dworkin would like it because it can be CSPN  
16 with two S's.  
17       (Laughter.)  
18       DR. SMITH: And I think you need to give  
19 Francis a call and let him know he needs an  
20 additional letter to really juice up the acronym.  
21       So the initial publication about CSPN, I  
22 think almost 20 years ago. I don't know if, Todd,

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1 you're on here. But essentially, it examined a  
2 group of a hundred individuals who I think most of  
3 us would agree had cryptogenic or idiopathic  
4 neuropathy. They had three months of symptoms, and  
5 all of these various tests were normal.  
6       So this isn't going to be useful in terms of  
7 what tests are going to define idiopathic or  
8 non-idiopathic. I think it is useful in terms of  
9 thinking about the clinical phenotype. So what  
10 they found in this cohort was that 62 percent of  
11 individuals had sensory loss, numbness, or tingling  
12 with pain. Another 24 percent had numbness or  
13 tingling without pain; 10 percent pain alone. This  
14 is the primary presenting symptom. And there were  
15 a small number of people who presented with ataxia  
16 or tremor.  
17       This actually shows us a bit about the  
18 distribution of these various sensory modalities.  
19 For instance, vibration just on clinical  
20 examinations -- this wasn't vibration detection  
21 threshold necessarily. It was abnormal and  
22 something like 85 percent at the toes or feet, but

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1 was not abnormal in hardly anyone at the knee, and  
2 you can look across modalities.  
3       Here are the physiologic tests that were  
4 performed. Nerve conduction studies, for instance,  
5 sensory nerve conduction studies were abnormal in  
6 77 percent.  
7       So I'll let you look at that, and I think  
8 this highlights one point that has already come up  
9 today, which is that less than 5 percent, and then  
10 this cohort had what clinically and physiologically  
11 was an isolated small fiber neuropathy. And I  
12 suspect we're going to have vigorous discussion  
13 about the extent to which a small fiber neuropathy  
14 is a distinct disorder as opposed to part of a  
15 spectrum. But whatever it is, in this kind of a  
16 cross sectional study, it appears to be rather  
17 uncommon  
18       I did want to talk a little more but  
19 epidemiology, but from a different perspective from  
20 Rob's. I think the reason for this is that a  
21 neuropathy is common as I'll show you in a moment.  
22 And a lot of the diseases that caused neuropathy



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1 are common as I think Roy pointed out. So we need  
2 to understand this epidemiology so we can start to  
3 make judgments about which factors are causative,  
4 which factors are risk factors, and then how we  
5 tease this out.

6 So this was a fairly recent review of the  
7 literature, and I have to say I'm glad I didn't  
8 have to look at 4,000 articles to do this; I'm not  
9 a brave person. But this group viewed almost 4,000  
10 articles.

11 Actually the main point I want to make is  
12 not so much the age and sex distribution of  
13 cryptogenic neuropathy, but it's more just the  
14 number of publications. So these aren't just small  
15 fiber neuropathy papers; these are papers about  
16 idiopathic neuropathy. And you can see, for  
17 instance, 2011 to 2015, there were only seven  
18 papers.

19 So this just clearly and I think  
20 quantitatively demonstrates the need for better  
21 data on this. And it's striking for such a common  
22 disorder. We don't have good natural history data,

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1 and we really don't have good -- we're getting  
2 better in terms of epidemiology, but we really  
3 don't have a lot of evidence.

4 This is from the Dutch group and there are  
5 two papers I want to talk about here. This is  
6 another sort of analysis of the literature, and  
7 this shows the algorithm through which they went to  
8 examine about 30 studies of neuropathy to look at  
9 the epidemiology. Within the literature, the  
10 population prevalence, which is certainly an  
11 underestimate, was only 1 percent rising to  
12 7 percent in the elderly, more common in western  
13 countries, and a slight female predominance in  
14 this.

15 I think what's more useful is the  
16 prospective study from the same group, the  
17 Rotterdam study that looked at 1310 participants  
18 who had a peripheral neuropathy. I'll show you the  
19 prevalence in a moment. You can just read through  
20 this, but it's very striking with age.

21 Amongst this group -- and keep in mind these  
22 are just patients with all-comer neuropathy.

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1 Almost half had idiopathic neuropathy and about  
2 30 percent had diabetic neuropathy. But what's  
3 interesting is over half of the cases that they  
4 came across were newly reported, which would  
5 suggest that the actual prevalence is perhaps  
6 higher.

7 These individuals are screened for vitamin  
8 deficiencies, thyroid, gammopathy, et cetera,  
9 et cetera, and I'll show you the distribution of  
10 abnormalities. So this is looking at it  
11 differently than Rob did. Rob showed how many  
12 people with leprosy have neuropathy, and this will  
13 be turning it around the other way.

14 So this is a figure showing the prevalence  
15 of definite neuropathy, a probable or definite or  
16 possible probable or indefinite by decile. So for  
17 instance, by age 80, something like 12 percent of  
18 people have definite neuropathy, 30 percent have  
19 probable, indefinite, and so on. The  
20 categorization was really based on a panel review  
21 of individual cases, definite by-in-large required  
22 nerve conduction study abnormalities. They

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1 actually accepted a clinical diagnoses of definite  
2 neuropathy.

3 So I think the two points here are that  
4 neuropathy's common and it increases dramatically  
5 with age. And I think this is important in trying  
6 to tie individual laboratory abnormalities. Given  
7 the frequency with which people in the United  
8 States have diabetes and the frequency with which  
9 we have prediabetes and metabolic syndrome,  
10 particularly as we age, and the frequency with  
11 which we have neuropathy, really confounds our  
12 ability in an individual patient to determine  
13 whether or not these individual risk factors are  
14 disease causing or not, which has implications for  
15 how we define the boundaries of idiopathic  
16 neuropathy.

17 These are the laboratory testing data from  
18 the same group, and you'll see these are patients  
19 who had an existing diagnosis and new diagnosis and  
20 an aggregate. So for instance, chronic idiopathic  
21 axonal neuropathy, 46 percent.

22 I mean, this isn't saying for instance, that

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1 in the 7 percent who had thyroid dysfunction is  
2 causing neuropathy. But what it does show is that  
3 the prevalence of many of the things that we  
4 routinely test for in patients who we suspect have  
5 just a distal symmetric length-dependent axonal  
6 polyneuropathy are infrequent and likely not that  
7 much more frequent than in the general population.  
8       You can look through these. The big  
9 players, of course, are diabetes, vitamin  
10 deficiency, and individuals who have immune  
11 disorders, and I'll talk more about that and show  
12 some of the work that many of the people in the  
13 room have done.  
14       This is data that Rob was referring to that  
15 we published now almost 15 years ago. This is a  
16 group of about 140 individuals who are gathered  
17 prospectively, and for each test, this is the  
18 percent of individuals who had that test, and this  
19 is a busy academic neuromuscular clinic, and this  
20 is the frequency with which those tests were  
21 abnormal.  
22       For instance, 81 percent of people had a

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1 TSH, and out of 140 people there wasn't a single  
2 abnormality. What you'll notice is that measures  
3 of glucose metabolism are the most common  
4 abnormalities and everything else really is no more  
5 frequently abnormal than one would expect in the  
6 general population in this group. So 3 percent had  
7 an abnormal ANA. I think it's about 12 percent of  
8 blood donors have an abnormal ANA, so that's  
9 clearly less frequent than one would see there.  
10 The frequency of monoclonal gammopathy was quite  
11 low.  
12       So I think it's these kind of data, the  
13 perception of these kind of data, that lead to the  
14 consensus criteria that I'll show later in terms of  
15 diagnostic evaluation for patients with neuropathy.  
16       One vitamin that seems to get a lot of  
17 attention certainly in our clinical practice is a  
18 pyridoxine. I don't know what it's like in  
19 Virginia, but Utahans love vitamin supplements, so  
20 we're always on the hunt for people who are using  
21 too much vitamin B6, usually because they're taking  
22 multiple multivitamins. And we'll often test this

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1 and find someone whose level is high and go, aha,  
2 this may be important.  
3       This was actually a really nice paper where  
4 it was fairly significant numbers, 245 patients  
5 with neuropathy without ataxia, 33 with ataxia, a  
6 sensory motor neuropathy, 133 and 140 controls.  
7 And turns out there's no difference in pyridoxine  
8 levels across these populations. And there are a  
9 number of people, again, across these populations  
10 that have high B6 levels.  
11       So no one's really talked about B6, but I  
12 think it's a good example of the value of looking  
13 at good data in informing your thinking because  
14 without this, I think our biases to look at the  
15 person who has sensory motor neuropathy and an  
16 elevated B6 and think, okay, this may be  
17 meaningful; whereas in this data, I'm less clear  
18 whether it is.  
19       This isn't to say that someone who's taking  
20 megadoses and gets a non-length-dependent ataxic  
21 neuropathy doesn't have pyridoxine toxicity, but  
22 one needs to be cautious in interpreting these data

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1 in individuals with a distal symmetric  
2 polyneuropathy.  
3       There are a couple of papers, one of which  
4 has been referenced explicitly in another. I think  
5 Henry has referenced, circumferentially perhaps,  
6 about idiopathic small fiber neuropathy. So I just  
7 want to go through these because they're perhaps  
8 most directly germane to today's conversation.  
9       Anne Louise's study involved 213 patients  
10 who had small fiber neuropathy based on skin  
11 biopsy, autonomic testing, or nerve biopsy. What  
12 they did -- and this is a busy slide, but I can  
13 walk you through it -- they did a very  
14 comprehensive laboratory evaluation as you can see  
15 here, and then compared the frequency of  
16 abnormalities to publish a prevalence of  
17 abnormalities within that particular test. And  
18 then those who are I think green, there was a  
19 significant increase in risk in patients who had  
20 idiopathic small fiber neuropathy. So for  
21 instance, 4 percent had hyperthyroidism, whereas  
22 the population prevalence in NHANES was 0.5

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1 percent.

2       So you can peruse this. You'll see a few

3 surprising things, which is that diabetes didn't

4 float to the top. Now, a lot of these data are

5 obviously susceptible to referral biases and

6 whatnot, both in negative and positive ways. But

7 you'll see that there are a number of measures of

8 auto immunity that are overrepresented in this

9 population compared to the published population.

10 Now whether or not they are really more common than

11 they would be in another wise matched similarly

12 referral bias population, we don't know.

13       So for instance, complement levels were

14 abnormal in 11 percent, whereas only 3 percent in a

15 published a study. So take these data for what

16 they are, but they I think show some of the

17 complexity. And we can really cross-reference this

18 with Karin and Ingemar's study that was talked

19 about earlier and Rob showed.

20       This is a paper that was just published

21 involving 921 patients with pure small fiber

22 neuropathy. And I think for a study of this size,

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1 this was very, very carefully done. These

2 individuals had abnormal skin biopsy or thermal

3 testing with large fiber modalities being normal

4 and normal nerve conduction study. So you can get

5 into this with the normal skin biopsy, but you

6 couldn't have large fiber abnormalities, and you

7 had to have abnormal thermal testing.

8       These patients also all underwent a very

9 comprehensive evaluation, as you can see here,

10 including things that you already know aren't going

11 to be useful like alpha galactosidase activity.

12 We'll revisit briefly the sodium channel, but very

13 briefly because I don't want to get -- that's not

14 quicksand, that's a black hole of discussion, and

15 so forth.

16       This I think Rob already showed, the

17 histogram of abnormalities. The first point is

18 amongst this group of patients with a small fiber

19 neuropathy, 53 percent were truly idiopathic. So

20 there is a population that's sizable in this

21 neuropathy phenotype who do not have evidence of

22 any other abnormality. But keep in mind this

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1 population has some referral bias. We heard

2 earlier this morning they don't see a lot of

3 patients who have diabetes. And if you go to Eva's

4 clinic, we already heard that most of her patients

5 have metabolic syndrome and prediabetes.

6       The most common abnormalities are similar to

7 those from the other papers that we've talked

8 about, so B12 deficiency, diabetes, and

9 prediabetes, although less frequent than what we

10 might expect was common. Sodium channels, sequence

11 variants were common. And then auto immune

12 disorders, keeping in mind, though, this is an

13 aggregate of a whole bunch of different auto immune

14 disorders, so sarcoidosis, Sjogren's, celiac, and

15 other.

16       Sod does a 0.5 percent prevalence of celiac

17 disease really represent a higher number than the

18 normal population? I don't know. Those with a

19 known risk factor -- and this goes to I think

20 Todd's point about people having multiple different

21 risks leading to a common phenotype -- over a

22 quarter had more than one risk factor, so B12

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1 deficiency and alcohol use. So trying to identify

2 what's causing the neuropathy in any individual

3 patient can be quite challenging.

4       We've already talked about this and the

5 registry, so I'm just going to skip over that. I

6 did want to talk about this study, which is a

7 little bit far afield, but I think perhaps is a

8 call for common sense in terms of how we think

9 about genetic neuropathies.

10       This is a study that over about 100 patients

11 who were suspected to have a hereditary neuropathy

12 underwent an almost 200-gene next-generation panel.

13 The first point is there were 6 patients with

14 chronic idiopathic axonal polyneuropathy included,

15 which is intriguing to me why they did, but none of

16 these patients had any disease-causing mutations or

17 variants of unknown significance, so small number.

18       Well, what's interesting, even in people who

19 one is suspecting phenotypically have a hereditary

20 neuropathy, what's clear is if the age of onset was

21 over 40 and there was no family history, even with

22 the suggestive phenotype, the likelihood of finding

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1 something on genetic testing was 5 percent, whereas  
2 those less than 40 with family history, 33 percent.  
3 I think Karin commented on this earlier, is  
4 that one needs to think about the sodium channel,  
5 the narrative, and really the whole issue of  
6 genetics and small fiber neuropathy with clinical  
7 common sense and phenotype and family history.  
8 So just because Ahmet has access to  
9 \$100-exomes that insurance companies uniformly  
10 cover, it doesn't obviate the need for him to  
11 exercise a good clinical judgment, which I know he  
12 does on a daily basis. I'm just going to start  
13 saying in my referrals, I'm from Johns Hopkins, and  
14 I'm sure it'll get covered now.  
15 The next thing I want to delve into -- and I  
16 can go through this fairly quickly -- is thinking  
17 about the intersection between metabolic syndrome,  
18 obesity, prediabetes, and neuropathy. There are  
19 two reasons to do this. One is I'm kind of a  
20 one-trick pony, so if I were to show you my  
21 vacation slides, I'd still talk a little bit about  
22 this.

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1 Again, I want to cover it again fairly  
2 quickly because I just want to think about it and  
3 flip it around. And don't think about it as  
4 whether or not this is a meaningful cause for  
5 neuropathy, but how would you integrate this and  
6 your thinking about designing a clinical trial for  
7 idiopathic painful small fiber neuropathy.  
8 The first study I want to talk about is a  
9 very carefully done study by Richard Hughes that  
10 I'm sure most of you are familiar with where they  
11 recruited 50 patients and controls from the same  
12 region and did a thorough evaluation. And what  
13 they found is in a monovariant analysis, those who  
14 had painful neuropathy were more likely to have an  
15 abnormal glucose tolerance tests, more likely to  
16 have abnormal serum triglycerides in fasting  
17 insulin. But in the multivariate analysis, the  
18 only thing that percolated to the top was  
19 hypertriglyceridemia.  
20 There aren't very many studies that were  
21 this careful, and I'll quickly go through many of  
22 the same slides that Rob did that I think

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1 convincingly demonstrate a relationship between  
2 prediabetes, metabolic syndrome, obesity, and  
3 axonal neuropathy. I think one needs to be cautious  
4 about attributing, again, an individual patient  
5 causation with these, and these were probably maybe  
6 potent risk factors.  
7 I think the first point -- and this is an  
8 old slide -- there are over 90 million, probably  
9 100 million Americans now, with prediabetes. About  
10 1 in 3 adults has prediabetes. So again, if you're  
11 going to do a study of idiopathic small fiber  
12 sensory neuropathy and you're going to exclude all  
13 patients who have prediabetes, you have to ask  
14 yourself what that does to your enrollment and does  
15 that actually make any sense whatsoever?  
16 This is one of more colorful slides. This  
17 is the slide that Rob talked about. In the core  
18 study, Dan Ziegler's study, there's an increasing  
19 prevalence of neuropathy with increasing severity  
20 of glucose dysregulation and particular painful  
21 neuropathy.  
22 I think one thing to keep in mind, though,

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1 7.4 percent of the control population had  
2 neuropathy and 1.2 percent had painful neuropathy.  
3 So again, from a clinical trial perspective, keep  
4 that in mind.  
5 I'm going to skip over that. I'm going to  
6 skip over that. and I want to come to this slide,  
7 which Rob also showed a, which is the data  
8 comparing a prevalence of metabolic syndrome and  
9 chronic idiopathic axonal neuropathy, and painful  
10 chronic idiopathic axonal neuropathy compared to  
11 control, so a convincing increase in the prevalence  
12 of metabolic syndrome, yet it's still quite high in  
13 the control population.  
14 We'll skip over that as well  
15 This is data from our bariatric surgery  
16 cohort in Utah to emphasize the frequency with  
17 which morbidly obese individuals who are candidates  
18 for bariatric surgery have subtle abnormalities of  
19 neurological examination and also the presence of  
20 neurological or neuropathy symptoms.  
21 So this is the prevalence of an abnormal  
22 UENS and the bariatric candidates and controls and

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1 an MNSI greater than 2, which isn't really a cutoff  
2 threshold for neuropathy. But if you look at the  
3 distribution here, there are a fair number of  
4 people who have strikingly high UENS scores. And  
5 these are patients who just clinically didn't seem  
6 to have neuropathy. So we specifically did not use  
7 these scores to categorize patients, neuropathy or  
8 not.

9 This is another one of Rob's slides from  
10 Brian's study, the Health ABC study, showing normal  
11 glycemia, prediabetes, diabetes, prevalence of  
12 neuropathy relative to how many metabolic syndrome  
13 criteria are fulfilled. I think what I want to  
14 point out is while this is higher than this, and  
15 that's probably statistically significant, this is  
16 still a high number, and we need to factor that  
17 into our thinking and then designing clinical  
18 trials.

19 I'm going to skip through these slides just  
20 because I wanted to make the same point that Rob  
21 already made, that I think there's pretty good  
22 evidence now that strategies intended to address

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1 the metabolic abnormalities that I've been  
2 discussing seem to have benefit in terms of  
3 epidermal nerve fiber density and also symptoms of  
4 painful peripheral neuropathy, so we're going to  
5 skip over that.

6 This is the current guidelines for  
7 diagnostic evaluation of patients with peripheral  
8 neuropathy. This is quite old now, I think, nine  
9 years old. They felt that there was level A  
10 evidence for the utility of genetic testing and  
11 suspected hereditary neuropathy.

12 I think that the evidence probably remains  
13 the same, that there's insufficient evidence to  
14 determine usefulness in cryptogenic neuropathy.  
15 And as you're well aware, the recommendations are  
16 for vitamin B12 metabolite testing, paraprotein  
17 evaluation, and a workup for diabetes and  
18 prediabetes.

19 We don't have a revised set of a practice  
20 parameter from the ANN yet. This is just a nice  
21 continuum article, which is where I go for clinical  
22 common sense, and, Wow, this looks like a long

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1 list. It really captures in the literature review,  
2 the same theme that came out of John England's  
3 paper here, which is the need to look for  
4 vitamin B12 paraproteinemia, and diabetes.

5 So the question I was asked to address is  
6 what to exclude, and that's hard. But I would say  
7 that a lot of evaluation for peripheral neuropathy  
8 is really based on careful history and examination.  
9 This is something that can be challenging in the  
10 setting of a multicenter clinical trial and how you  
11 craft this in your enrollment criteria.

12 All patients with a suspected axonal  
13 neuropathy or axonal neuropathy suspected CSPN have  
14 to have these laboratory tests I talk about. And  
15 then depending on the individual's risk factors,  
16 the region in which you're practicing, and so  
17 forth, there may be other tests that one might need  
18 to do.

19 So I think to say that every patient who has  
20 a length-dependent axonal sensory motor neuropathy  
21 needs serological testing for hepatitis C is  
22 probably not true, but there certainly are areas

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1 and practices and referral bases where that's  
2 something that you do need to do.

3 I would posit that clinical trial enrollment  
4 may require more explicit evaluation than that  
5 which we use clinically, and we may want to tailor  
6 the enrollment criteria regarding definition of  
7 cryptogenic or idiopathic neuropathy based on the  
8 mechanism of the agent which we're using. And I'll  
9 show you how we did this in our trial in a moment.

10 I think at this point -- and this may be the  
11 most controversial thing I say -- is that routine  
12 genetic and immunologic testing and suspected CSPN  
13 is a low diagnostic yield, and one doesn't know  
14 what to make of subtle abnormalities. So a patient  
15 who doesn't have other evidence of an autoimmune  
16 disorder, unless there's a red flag -- and I think  
17 Todd captured this in his talk, and I kind of poked  
18 fun at the immunization thing.

19 But if there's something in the phenotype  
20 that suggests autoimmunity, then clearly a more  
21 careful evaluation is necessary. But in the  
22 absence of a family history or other phenotypic

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1 suggestions that the patient might have a sodium  
2 channel mutation, at this point, routine screening  
3 is probably not useful.  
4       There's a quote from an epidemiology article  
5 earlier that I really liked that I thought I'd put  
6 on a slide because I think it really captures the  
7 issue, and I'll actually read it.  
8       "Since polyneuropathy probably is a  
9 multifactorial disease, it's not entirely  
10 appropriate to attribute the development of  
11 polyneuropathy to only one factor. These factors  
12 should be considered as proponent causes and not as  
13 one sufficient cause." And I think several people  
14 have made that point today, and I think it's the  
15 challenge in determining what's idiopathic and  
16 what's not idiopathic.  
17       This is a trial. And I'll just tell you how  
18 we approach this. And this, again, is not a small  
19 fiber neuropathy trial, although patients with  
20 small fiber neuropathy can be included. This is a  
21 study of topiramate as a disease-modifying therapy  
22 for CSPN. And the idea behind this is that

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1 topiramate, as you know, causes weight loss and  
2 improves insulin sensitivity. It is a sodium  
3 channel blocker, which suggests another potential  
4 mechanism.  
5       There are a data suggesting that get to  
6 Rob's question about epigenetics, that at least in  
7 diabetes models, abnormal sodium channel function  
8 not only can contribute to neuropathy phenotype,  
9 but can then subsequently lead via effects in terms  
10 of calcium homeostasis and others to axonal  
11 degeneration; so another potential mechanism for  
12 this messy drug.  
13       So the way we handled this was because the  
14 intent was to impact metabolism in this population,  
15 we only included patients who had metabolic  
16 syndrome. And in fact, so we're only including  
17 patients who are overweight or obese. And the idea  
18 here is to try to narrow the population into those  
19 who have metabolic syndrome as a risk factor, a  
20 major risk factor, for their neuropathy, not  
21 arguing that it is positive and to weed out some of  
22 those patients who might have other causes, genetic

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1 causes and so forth.  
2       We obviously needed to exclude other causes  
3 of neuropathy, and we did this in two different  
4 ways. One was to try to capture clinical judgment,  
5 any identified alternative cause of peripheral  
6 neuropathy and not limited to -- and  
7 [indiscernible] examples. So we didn't require  
8 everyone to get hepatitis B or C, but we asked  
9 investigators to use their common sense and  
10 thinking about these things. This has already  
11 engendered a few calls with good questions that I'm  
12 happy to share with you; what do we do about this  
13 individual patient?  
14       We felt it important to do testing for the  
15 guideline -- mandated is too strong a word, but the  
16 tests that are suggested by John England's paper.  
17 So everyone gets a B12 SPEP immunofixation actually  
18 they're only getting an immunofixation. Actually,  
19 they're only getting immunofixation in the study  
20 and an oral glucose tolerance test, which is in  
21 part to exclude diabetes and in part is just an  
22 endpoint of the trial; no family history, no

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1 history of alcohol and drug abuse.  
2       We are biobanking, and I think that's  
3 something that we ought to be doing in these  
4 studies. It's low-hanging fruit. So here we're  
5 just gathering DNA and banking it with the idea  
6 that we'll be able to go back and then look at  
7 sodium channel sequence variance. If there's an  
8 effect, we can look at whether or not any of these  
9 sequence variants or polymorphisms seem to predict  
10 treatment response, which is somewhat a different  
11 question as to whether or not these are risk  
12 factors for neuropathy.  
13       So that's kind of how we dealt with it, but  
14 one can easily see Todd or Anne Louise doing a  
15 study of some sort of immune immunomodulatory  
16 therapy in patients with idiopathic small fiber  
17 neuropathy that they think have a greater  
18 likelihood of having autoimmune mechanisms and  
19 constraining the population based on serologic  
20 testing or other clinical features that would be  
21 fit with their concept.  
22       So that's it. I don't know if that's what

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1 you're looking for, Roy, but I think I saved a  
2 little bit of time, so that's good.  
3 DR. DWORKIN: Questions for Gordon.  
4 DR. OAKLANDER: Great talk, Gordon. With  
5 everything [inaudible – off mic].  
6 DR. SMITH: Can we stop there?  
7 (Laughter.)  
8 DR. OAKLANDER: Also factor into our  
9 recommendations diagnostic testing. And I think  
10 you already – [inaudible – off mic].testing kids  
11 and what you need to look for in kids is fairly  
12 different; not entirely different [inaudible]. And  
13 then number 3 is the cost of the test as well as  
14 the diagnostic yield.  
15 DR. SMITH: I agree with everything you  
16 said.  
17 (Laughter.)  
18 DR. LEVINE: Just to follow up on what Anne  
19 Louise said, if the goal is to try to define an  
20 idiopathic group, my thought and listening to you  
21 talk there was also limiting age, but in the other  
22 direction.

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1 So you see the curve really start to  
2 increase at 60. So if you're trying match the  
3 natural history of a disease, defining the age  
4 group as a younger population of patients -- I mean  
5 normally we cut off 75-80, but then we're talking  
6 about 20, 30 percent of the patients that will have  
7 it through whatever that disease course, just  
8 natural aging as opposed to taking 20 to  
9 60 year olds where the difference may be much  
10 easier to see.  
11 I was just wondering what your thoughts were  
12 on that. I know we don't usually set the cutoff  
13 that low, but it seemed like it might be a logical  
14 thing to think about.  
15 DR. SMITH: I'm just going to go. I think I  
16 mentioned -- and what other people think of that.  
17 I think it's a very sensible suggestion. We  
18 certainly see patients who have -- I'm just  
19 thinking of the diabetes world, and you'll now see  
20 patients who have obesity and type 2 diabetes in  
21 their late teens and early twenties who may have  
22 neuropathy. But I agree that if I see a

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1 25-year-old person who has a small fiber  
2 neuropathy, my antenna go up.  
3 I don't know that we've got good data on  
4 what that means, but I agree it's a sensible thing.  
5 DR. LEVINE: I agree with you exactly. See,  
6 there's the curve. It starts to go up at 60, but I  
7 think all of us feel differently when you see a  
8 25 year old with a neuropathy than when you see a  
9 75 year old with neuropathy.  
10 DR. SMITH: This curve starts at 50.  
11 DR. FREEMAN: Can I --  
12 MALE VOICE: Last question.  
13 DR. FREEMAN: Can I do that? Thank you.  
14 A couple of questions. That was, as always,  
15 a terrific talk. I want to focus the discussion a  
16 little on the major reason we're here, and that is  
17 the clinical trial. And obviously a clinical trial  
18 is a little difference to clinical practice. And  
19 you made a statement on one of your slides about  
20 clinical trials may be a little different or words  
21 to that effect. And I think clinical trials are  
22 very different.

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1 So two points. The one is that we are  
2 beginning to, I think, develop the concept that  
3 small fiber neuropathy, axonal peripheral  
4 neuropathy has multiple potential factors that may  
5 work in conjunction and that many of the factors  
6 also have a very high prevalence in the population,  
7 and in a particular subject may or may not be the  
8 causative factor or even one of the component  
9 causes.  
10 So with that in mind -- and you have a  
11 clinical trial that's ongoing, and a number of  
12 people in the audience, including some from pharma,  
13 are beginning to develop clinical trials. We need  
14 to be fairly explicit about what is acceptable and  
15 what is not acceptable and what to look for and  
16 what not to look for. And this applies, one, to  
17 the screening tests for inclusion and exclusion;  
18 and also, as I'm becoming increasingly aware of,  
19 treated potential abnormalities like treated  
20 thyroid disease, or treated B12 deficiency, or  
21 elevated methylmalonic acid or homocysteine levels.  
22 So this is a very broad question, but we're

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1 going we need to be fairly explicit by the end of  
2 the day and certainly at the time of paper writing.  
3 Elaborate a little on what do you think is  
4 obligatory in a clinical trial, must be done at  
5 must be normal?  
6 DR. SMITH: This issue is one of the things  
7 that has come up, and I'll give you an example.  
8 There's a participant at one of our sites who had  
9 celiac disease, had been treated. Their antibodies  
10 were undetectable. Their neuropathy started some  
11 time after that celiac disease.  
12 I'm setting up a strawman, but we decided  
13 that patient was fine to screen because clinical  
14 common sense would dictate a neuropathy that  
15 started years after a successful treatment for  
16 celiac disease that was in remission essentially at  
17 this point was appropriate.  
18 On the other extreme, we aren't allowing  
19 people -- and I think it would be imprudent to  
20 allow people into a clinical trial obviously who  
21 have diabetes and neuropathy, or who have a new  
22 diagnosis of vitamin B12. The way we're dealing

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1 with this in another trial we have ongoing right  
2 now is patients with diabetic neuropathy trial.  
3 Patients who are B12 deficient, we're allowing  
4 treatment and rescreening, a bit of a messy  
5 solution, but this is a lifestyle based study. So  
6 I think part of it may depend on the particulars of  
7 the trial.  
8 That's sort of a really vague answer and an  
9 intentionally vague answer because I agree with  
10 what you're saying.  
11 DR. FREEMAN: So there's a lot of agreement  
12 all around. Maybe just a follow-up question. One  
13 of the critical questions with all of these trials,  
14 impaired glucose tolerance. A lot of people in the  
15 audience, pharma, are doing trials on small fiber  
16 neuropathy. Do they need to do an oral glucose  
17 tolerance test? You said 1 in 3 people in the  
18 United States has impaired glucose tolerance.  
19 How do we deal with that inflammation in a  
20 clinical trial?  
21 DR. SMITH: I think it depends on the idea  
22 behind the clinical trial, the agent's hypothesis.

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1 So in a trial where we are specifically targeting  
2 metabolism, we want to know what the glucose  
3 tolerance looks like as a marker of the underlying  
4 physiology which are addressing.  
5 I think I kind of think of this in the same  
6 way I think of blood pressure and stroke, and I  
7 think we may learn a lot from thinking about other  
8 multifactorial, complicated conditions with very  
9 clear, very potent risk factors. So I think of  
10 prediabetes in the same way, is poorly controlled  
11 blood pressure to stroke as it is to neuropathy. So  
12 if one's doing a stroke trial, you measure the  
13 blood pressure, but it doesn't necessarily mean  
14 you're going to do something different with it.  
15 So I think my advice would be for a  
16 idiopathic small fiber neuropathy study, I would  
17 not frankly look at oral glucose tolerance tests  
18 unless there was some very compelling reason to  
19 exclude patients who had very mild diabetes. I  
20 would probably do a standard diabetes screen and  
21 not look at it. I don't see the reason one would.  
22 On the other hand, I've already given the example,

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1 where we're doing something to intervene with  
2 prediabetes, we of course want to know if that's  
3 successful.  
4 But I think the idea that in many of the  
5 things that we're measuring now, and this is  
6 probably true for the autoimmune markers, to the  
7 extent that they're relevant, they're probably  
8 not -- and I think it's true in this population for  
9 many of the sodium channel variants. If they're  
10 relevant, they're probably relevant to the same  
11 sort of way prediabetes is, as a risk determinant  
12 rather than the primary cause. So that's my bias.  
13 DR. DWORKIN: So let's carry on so we can  
14 get coffee. Thanks, Gordon.  
15 Our next speaker is Dr. Chris Gibbons who is  
16 an associate professor of neurology at Harvard  
17 Medical School, and he's going to be talking about  
18 diagnostic instruments used [inaudible – off mic]  
19 of cryptogenic sensory polyneuropathy.  
20 Presentation – Christopher Gibbons  
21 DR. GIBBONS: So again, another dubious  
22 lecture that I'm slightly honored and slightly



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1 chagrined to present. I don't want to start with a  
2 number of disclosures. I think this is possibly the  
3 most boring topic on the item list, so that is a  
4 problem. I intentionally try to be a bit  
5 provocative, so I hope you don't mind if I take  
6 some liberties.

7 I don't in fact have a small fiber  
8 neuropathy instrument named after me; still trying  
9 but I haven't gotten there. But I'm actually not  
10 developing one either, so if anyone wants to give  
11 me one, that's also fantastic. But in terms of  
12 disclosures, I don't really have any relevant to  
13 the talk, but I do want to highlight that as I go  
14 through this, that, again, this is a challenging  
15 topic, and we sort of hit on a lot of details  
16 already.

17 So in terms of what I'm trying to  
18 accomplish, at least during the next 4 and a half  
19 hours you have with me, is the review of existing  
20 patient- and clinician-oriented questionnaires,  
21 data that exists at the moment, to really review  
22 some of the information. But one of the things,

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1 obviously, when you start to dig into the  
2 literature, you can cast a wide net and end up  
3 with, as Simon had noted, 60,000 articles of  
4 dubious relevance to your data set that clearly can  
5 come into the case once you start to branch out  
6 into pain or other kind of outcome measures.

7 So I'm trying to be pretty precise in terms  
8 of what I'm including, at least for this  
9 discussion. I want to talk about examination  
10 criteria, and then I'm going to compare and  
11 contrast some of these, and I'm going to liberally  
12 editorialize on this to hopefully make this a  
13 somewhat more interesting.

14 I'm just going to jump right in. Hopefully  
15 you can see a little bit, and I'll kind of  
16 highlight what we're talking about. But these are  
17 some questionnaires that have really specifically  
18 been studied in small fiber neuropathy. The survey  
19 of autonomic symptoms, the Maryland group has  
20 published on this. There's the small fiber  
21 neuropathy RODS and SIQ, which are two separate  
22 scales we'll talk through.

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1 Here we have small fiber peripheral  
2 neuropathy from the MGH group. there's the NTSS-6,  
3 which many of you are familiar with. It's older.  
4 It's not specific for small fiber neuropathy but  
5 has been studied specifically in this.

6 Then some of these were actually validating  
7 studies are questionnaires that many of these other  
8 have been validated against, so I thought I would  
9 just mention them a little bit in terms of what has  
10 been done and why we're interested in them. Across  
11 the top here, in very small print so that none of  
12 you can read this -- I will highlight what we're  
13 looking -- a question of what domain. I think this  
14 is actually the name Anne Louise had suggested  
15 earlier, and I threw this out as well in mine.

16 So what domain are we talking about? Is it  
17 a sensory domain? Isn't an autonomic domain? Maybe  
18 that's an important question we need to ask.

19 Were these questionnaires physician  
20 developed? Were they developed by patients? And  
21 then, what are the standard things we think about  
22 with validation? Internal consistency,

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1 test/retest, reliability content, validity, so  
2 these important discussions.

3 If you go through, this is a pretty hot  
4 topic and I think pretty critical to the overall  
5 discussion of where we're going. Some of these  
6 really are our autonomic, so the survey of  
7 autonomic symptoms, for example, pretty clear where  
8 that's leading. Some are a little bit more  
9 sensory, the NTSS-8, or example.

10 Some cover both. So I have some question  
11 marks here with a small fiber neuropathy RODS,  
12 which is a disability based scale on small fiber  
13 neuropathy. It's not really a symptom assessment  
14 as much as a disability assessment.

15 I think these are pretty critical issues.  
16 First of all, whether patients were involved in the  
17 process or not, I think that does change the  
18 perspective on what the questionnaire will ask and  
19 potentially with your answers will be. So it's an  
20 important thing to consider. It's neither right  
21 nor wrong, though the FDA does suggest that  
22 inclusion.

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1        Actually to go back, everybody's included  
2 the standard kind of reliability, construct  
3 validity testing almost in everything these days.  
4 So I think everybody hits those marks. So the  
5 differences really are in these categories  
6 primarily and what that means going forward.  
7        One of the ways we ask questions, any  
8 particular questionnaire, and highlight what we do  
9 is, first of all, what have you looked at? Who are  
10 you studying and why? So what are the control  
11 groups? What are the disease groups? How do you  
12 make the diagnosis of small fiber neuropathy? What  
13 are exclusion criteria? These are just sort of the  
14 basis for all the talks that we heard about  
15 earlier.  
16        Some include controls prominently; some do  
17 not. Some control a specific to disease, either  
18 impaired glucose tolerance or newly diagnosed  
19 diabetes, some mixed disease, some specific things  
20 like sarcoid, so very specific diagnoses that may  
21 in fact be very relevantly different across disease  
22 states when you're comparing these.

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1        Then looking at how we make a diagnosis,  
2 this is pretty critical and this is sort of the  
3 topic of discussion for this whole group, how do we  
4 decide somebody has a small fiber neuropathy and  
5 whether it's truly pure or is it mixed?  
6        Do we include a sign and symptom approach  
7 with one abnormal test? Do we say symptoms? Do we  
8 say multiple symptoms? Do we say either one test  
9 or another abnormal without symptoms? Again, these  
10 are pretty important topics that really make a big  
11 difference in terms of outcomes of these studies.  
12        So as you can see, there are differences.  
13 Some people include controls; some people don't.  
14 Some add controls on at later study time points.  
15 The disease will vary between these studies, so  
16 even though we could think of this as a small fiber  
17 neuropathy, it may be small fiber neuropathy in  
18 something as opposed to an idiopathic.  
19        Then finally, really, this question of how  
20 we make the diagnosis. This is pretty critical and  
21 I think one of the major topics for discussion as  
22 we go forward in this meeting. Then finally, as

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1 you just heard from Gordon, what do we exclude and  
2 why? And can we justify that going forward and  
3 comparing between these tests?  
4        I thought I'd highlight some of these  
5 surveys. For people who aren't familiar with them,  
6 I thought it would just be useful to discuss a  
7 little bit about the questionnaires and what we're  
8 looking at. This is the survey of autonomic  
9 symptoms. It's a 12-questionnaire with kind of two  
10 parts.  
11        The first is do you have the symptom?  
12 Either yes or no, during the last six months. And  
13 then the next question is, if you have it, how much  
14 does it bother you on a 5-point scale? So it's  
15 fairly clear, fairly easy to administer,  
16 12 questions, and you kind of get these answers.  
17 And because these are really, again as noted in the  
18 title, autonomic symptoms, you're really focused in  
19 on those components. Some are sweating, some are  
20 kind of temperature feet, pale or blue, persistent  
21 diarrhea, constipation, urinary difficulty,  
22 erectile dysfunction, often what we would think of

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1 as a standard battery of questions for somebody who  
2 might be presenting with an autonomic  
3 problem.  
4        Small fiber neuropathy ROD's questionnaire.  
5 This is, again, a Rasch-built disability scales,  
6 and this is looking at -- it's a 32-question scale,  
7 and as you look at the rating, it says 0 to 2  
8 rating. And as you can see, not possible to  
9 perform; possible but with some difficulty;  
10 possible without any difficulty. So fairly clear  
11 in terms of how people complete this, and then the  
12 tasks. And these range from brushing your teeth  
13 and making coffee or tea, turning a key in a lock,  
14 et cetera, going down.  
15        So these are the first 12, and I've included  
16 the next 15 to 32 here as well. Most of these are  
17 straightforward, and some increasingly more  
18 difficult. Again, this is a Rasch-built score, so  
19 it doesn't, unfortunately, have a standard  
20 numerical output, which is one of the challenges.  
21        There's this symptom inventory questionnaire  
22 here, which is another way to look at small fiber

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1 neuropathy. This is, again, a 13-item  
2 questionnaire with a 4-point scale ranging from  
3 never to always; here are the questions coming  
4 down. And this again hits different domains as we  
5 talk about kind of autonomic sensory. Some include  
6 sweating, diarrhea, constipation, dryness,  
7 urination, palpitations, flushed, and then burning  
8 sensation in my feet; cannot stand the sheets on my  
9 legs. My legs are restless during the night. So  
10 again, this one covers a different selection of  
11 particular question.  
12 This one is from the MGH group and their  
13 questionnaire. It's small Unfortunately, I'm not  
14 sure you can read this, but they also have domains  
15 focused here. And these are looking at changes in  
16 sweating pattern, or mental fatigue, physical  
17 fatigue, skin-burning pain; GI related things,  
18 public related discomfort, and again, ranging from  
19 never to always in terms of the scale.  
20 So this particular, again, questionnaire,  
21 you've seen many of these questions have the same  
22 distribution in terms of number of questions or

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1 options, and then the different domains will vary a  
2 little bit in terms of the focus.  
3 The NTSS-6, another one where this is a  
4 6-question scale, however, it's a little bit  
5 different in that it's graded by both frequency and  
6 intensity in a 4-by-4 block. So the frequency goes  
7 from never to continuous and the intensity goes  
8 from not present to severe. So again, it's a 4 by 4  
9 block, which is in fact a little bit more confusing  
10 if you're trying to administer this. It's not  
11 quite as simple checking across the criteria.  
12 So what are the strengths of these scales?  
13 Well, in all of them, a large number of subjects  
14 that have enrolled. Some actually have large  
15 numbers of controls as well. So again, for any of  
16 these validated scales, I think this is what we  
17 sort of establish as a simple basic limitation, and  
18 in all cases, these fit this criteria. They're  
19 very well done. There is excellent internal  
20 consistency across almost all of them, excellent  
21 test/retest reliability; content validity, using  
22 many of the previously studied scales again as

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1 well.  
2 So all of these hit these kinds of fairly  
3 high watermarks in terms of how well they've been  
4 evaluated. So again, a lot of strengths for each  
5 of these. So maybe now I'm going to get into some  
6 of the more provocative stuff.  
7 Weaknesses. Why do they have weaknesses and  
8 what are they, and should we discuss this further?  
9 It comes up to the question, how do we know they  
10 have a small fiber neuropathy? What is our gold  
11 standard? In this case, we have some disagreement  
12 between these scales as to what we define small  
13 fiber neuropathy going in.  
14 Is this defined by an abnormal test result,  
15 abnormal symptom, a sign, some combination of the  
16 above? I could really imagine very different  
17 results coming across depending on how you arranged  
18 your criteria for entry.  
19 Now, is small fiber neuropathy in a single  
20 disease the same thing as small fiber neuropathy in  
21 every disease, or idiopathic small fiber  
22 neuropathy, or hereditary small fiber neuropathy?

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1 I see a lot of diabetes. I see a lot of autonomic  
2 neuropathies. Is this the same thing as a diabetic  
3 autonomic neuropathy or if it's an idiopathic  
4 neuropathy?  
5 There are a lot of questions you can  
6 ruminant over in this process, and if you're  
7 studying a disease, perhaps such a sarcoid, is this  
8 actually relevant to any other small fiber  
9 neuropathy? So these are questions I think we do  
10 have to ask.  
11 Even a bigger question, small fiber sensory  
12 neuropathies and autonomic neuropathies. Are these  
13 the same disease? Yes, no, maybe. It's an  
14 interesting question, but I would say that a  
15 patient with a severe isolated autonomic neuropathy  
16 is not the same as the severe isolated small fiber  
17 sensory neuropathy. And maybe there are some  
18 similar mechanisms. Maybe there's some similar  
19 problem, but I would say from a phenotype there are  
20 very different and probably the underlying  
21 etiology, if we ultimately discover what it might  
22 be would be very different.

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1 It does kind of get to this question for our  
2 questionnaire, if it's an autonomic questionnaire,  
3 we are looking at the apple, or are we looking at  
4 the orange, or are we looking at fruit? Which test  
5 are we doing for this particular scenario. and is  
6 it appropriate to apply this more broadly?  
7 So do we need to be more specific in our  
8 definitions of a small fiber sensory questionnaire,  
9 is it a small fiber autonomic questionnaire, or is  
10 it a domain-specific questionnaire that we  
11 subdivide depending on how the result is put out?  
12 So these are important details that aren't really  
13 discussed.  
14 There are other challenges to  
15 questionnaires. Not all are publicly available.  
16 Some are actually being developed. And one of the  
17 issues, of course, with any particular scale that's  
18 in validation, validation is an ongoing process.  
19 So maybe the most up-to-date version of the scale  
20 isn't available. But if we're going to use this in  
21 clinical trials, how do we access this information?  
22 How is this available? Can we make it available in

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1 the public domain? Are there going to be a few  
2 hurdles to acquisition of this? This is a problem.  
3 Some questionnaires can't be analyzed  
4 simply. You may need a psychometric analysis to  
5 actually get into the detail. And if that's the  
6 case, is that a barrier to using this more broadly?  
7 So when we ask this question, I think it's  
8 an important one if we're thinking about how to  
9 make this information widely available for everyone  
10 to use and potentially be consistent.  
11 What about disease control subjects? Now  
12 this is a topic we sort of really haven't hit on,  
13 but people who are not well, who don't have  
14 neuropathy, do they have a particular bias, and do  
15 those underlying disorders, which may in fact crop  
16 up in our population, particularly as we just saw  
17 from Gordon slide, this aging population and  
18 multifactorial issues -- the questions that are  
19 being answered, are these the other diseases that  
20 are impacting us, or is this the neuropathy that  
21 these questions are being answered by?  
22 So this really comes into a big internal

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1 conflict bias question that I have, and I sort of  
2 ruminate over this probably far more than I should,  
3 but do these reflect the patients that I see? So  
4 in other words, if I'm using this questionnaire in  
5 my patient population, does it mean anything? And  
6 I'm going to pick on one questionnaire because I  
7 can, and I'm up here, and I've got the mic, so  
8 that's what we're going to do.  
9 This is the small fiber neuropathy RODS, so  
10 this is a disability score. And I find it  
11 fascinating because I look at the questionnaire,  
12 and I've kind of gone through the questions with my  
13 patients and I've wondered about this. So brushing  
14 your teeth, making coffee or tea, turning a key in  
15 a lock, picking up small objects, kind of going  
16 down through the whole list, I see a range of  
17 patients with small fiber neuropathy from very  
18 mild, a little burning discomfort in the toes, to  
19 the very severe, multiple amputations, really  
20 significant neuropathy to the point where, again,  
21 there are many complications that have been a  
22 result.

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1 I have yet to find anybody who's done  
2 anything saying they can do it all. There's nothing  
3 on this list they can't do. Maybe somebody will  
4 come up with one of these after an amputation and  
5 they haven't kind of regained mobility, but  
6 everybody signs this as a 2, which means they're  
7 normal.  
8 I have yet to find any of my own patients  
9 with any disability if I look at a scale like this.  
10 And is this because my patients that I see are very  
11 different than the group that sees this with their  
12 population? I would say probably. Many of my  
13 patients have predominantly small fiber neuropathy  
14 from diabetes or diabetes related complications.  
15 Maybe that's a different disease. But if I'm  
16 looking at this, and I'm seeing no disability,  
17 despite amputations, I sort of see a mismatch.  
18 So I struggle with this because it doesn't  
19 fit my own perceived bias of what small fiber  
20 neuropathy is. I suspect we all have these same  
21 perceived biases in what we're looking at, and this  
22 is something that maybe as a group we do need a

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1 better job in kind of discussing what it is we  
2 think we're seeing and how it fits to everybody  
3 else's practices and referral basis.  
4       So obviously if you're at a genetic center,  
5 you don't see diabetes. I don't see much in the  
6 way of genetic because I see a ton of diabetes. So  
7 maybe there's just, again, this difference, but  
8 it's important to bring this to the forefront  
9 because I would never use this particular  
10 disability score for my patients; it just wouldn't  
11 fit, so it's an ongoing question.  
12       So with that kind of discussion, I'm going  
13 to jump from diagnostic questionnaires to  
14 diagnostic examinations and kind of discuss that a  
15 little bit further.  
16       This is a very busy slide, and Jen Gewandter  
17 has done a phenomenal job of putting this together.  
18 This is coming from an upcoming paper, but this  
19 looks at individual examination scores here. This  
20 is neuropathy in general scores, not specific to  
21 small fiber neuropathy.  
22       This is looking at muscle strength, reflex

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1 testing, vibration touch, joint pinprick. And what  
2 you're seeing here is essentially the distribution  
3 of examination. Is it the full limb in the upper  
4 and lower, or just part of the limb, so just the  
5 distal toes?  
6       So it just sort of gives you an idea of how  
7 much any particular test is measuring. Are you  
8 measuring everything or are you measuring just a  
9 few things?  
10       Over in these columns here, you're seeing  
11 the percent of the max score as motor reflex, large  
12 fiber or small fiber. What you do immediately see  
13 is there, again, expected, depending on the type of  
14 score you're interested in, wide variability, up to  
15 90 percent motor or zero percent. So again, big  
16 range in distribution of where the focus of the  
17 score may be.  
18       Of course we're at a small fiber neuropathy  
19 meetings, so where are we here? Small fiber  
20 neuropathy, generally 20 to 40 percent or less for  
21 many of these. The only exception being the Utah  
22 Early Neuropathy score, which is at 60 percent, not

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1 surprisingly. And again, the distribution, widely  
2 variable, but what we're seeing in terms of small  
3 fiber focus, that's generally where we are. That  
4 would be the highest one, but there are a couple of  
5 others in here.  
6       So is that relevant to the discussion?  
7 Well, I think it is because obviously if we're  
8 doing detailed muscle strength testing, that's  
9 probably unnecessary in an isolated small fiber  
10 neuropathy. We don't really want to consider the  
11 ones that spent a lot of unnecessary time focusing  
12 in on irrelevant details.  
13       So kind of highlighting the UENS scale  
14 primarily because, first of all, it's publicly  
15 available, so it's easy to download. Everybody can  
16 get access to it. It is easy to understand. The  
17 instructions are simple. It's quite clear. How  
18 you rate with a pin kind of distribution on the  
19 legs. The motor examination is just great toe  
20 extension, pin sensation, allodynia, hyperesthesia,  
21 large fiber sensation. They do look at vibration  
22 and great toe joint position, and reflexes at the

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1 ankle.  
2       So it's fairly clear how to do this. This  
3 is something that is very helpful if you're  
4 thinking about studies, because obviously clarity  
5 counts. If you can make a, a study easily  
6 accessible to a large group in a multicenter trial,  
7 that is helpful. The more complicated an  
8 examination, the more likely you are to get that  
9 inherent variability, which makes things a little  
10 bit messier to move forward with.  
11       So here's what I'm going to pick on, the  
12 PNRR group, not necessarily in a bad way. But  
13 again, this is the peripheral neuropathy research  
14 registry. This is the examination involving this.  
15 It's a lot more detail. It's got a lot of data  
16 points here. This particular study is looking at  
17 more comprehensive neuropathy, so again, it's  
18 important to consider what is the goal of the  
19 study.  
20       This I would say probably isn't appropriate  
21 for a small fiber neuropathy study; again, a lot of  
22 detail in areas that are not relevant necessarily

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1 to what we imagine a traditional small fiber  
2 neuropathy to be. However, it is trying to be  
3 adaptive to multiple different types of neuropathy  
4 in the same trial, and this is where it is a  
5 strength. It is comprehensive. Even though it's  
6 complicated, it's comprehensive, and it is clear.  
7 It's not difficult to complete. Everybody I think  
8 will be fairly familiar with the approach once they  
9 kind of read through the details.  
10 So it's not a particularly challenging one.  
11 It is more complex in terms of the time and effort,  
12 but it's fairly clear on a standard neurologic exam  
13 what goes where when you review it. Unfortunately,  
14 it's not yet validated or publicly available in  
15 terms of study because it's -- isn't that correct,  
16 it's not yet publicly available?  
17 DR. HOKE: We haven't published it, but  
18 hopefully soon.  
19 DR. GIBBONS: So again, it's one of these  
20 that it's in an iterative process, so although  
21 widely used by many centers in this trial, it's not  
22 yet something that has widespread availability.

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1 So, again, one of the limitations.  
2 This was a study that the Maryland group did  
3 kind of looking at examination scores in early  
4 neuropathy, in this case due to impaired glucose  
5 tolerance, and really looking at some of the  
6 details of whether small fiber function or  
7 structure was in any way related valuably to an  
8 examination.  
9 So this is nerve fiber density at the distal  
10 leg, the distal thigh, QSART, cold detection  
11 thresholds. These numbers are probably hard to  
12 read. The p-values are all particularly  
13 nonsignificant mostly because the correlations were  
14 particularly bad.  
15 James, am I summarizing that appropriately?  
16 DR. RUSSELL: Sadly, that's true. I wish it  
17 weren't, but it is.  
18 DR. GIBBONS: And I think it's an important  
19 point to raise because why? Why would all of these  
20 correlations have been so bad? And this is looking  
21 at multiple different examinations scores,  
22 including the UENS, the NDS, NIS-LL, the modified

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1 Toronto, et cetera.  
2 So it's a lot of very good validated  
3 studies, which raises an important question, and I  
4 think we can kind of get into these details. All  
5 of the skills were terrible and correlating with  
6 tests of either structure or function. The  
7 modified Toronto correlated best with the diagnosis  
8 of neuropathy.  
9 Why? Why do we think it correlated best?  
10 Well, because of the inclusion criteria, of course,  
11 for this study. Everybody had to have symptoms for  
12 less than two years without requiring any science.  
13 The modified Toronto is the only scale that asked  
14 questions of symptoms. There were no signs  
15 required for this, which meant it was probably  
16 either extremely earlier, essentially, from a  
17 pathology or functional point, probably proceeded  
18 many of the abnormalities. So in a very mild  
19 neuropathy, all your examination scores will be  
20 normal.  
21 I would think we'd probably not be  
22 surprised. The only one that was correlating well

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1 was the modified Toronto because it had questions  
2 of neuropathy involved in the examination.  
3 So again, how we want to kind of look at  
4 this depends a bit on our outcomes. Again, if  
5 we're looking at a defined small fiber neuropathy  
6 population that's incredibly early, maybe a nerve  
7 density isn't adequate because it's not going to be  
8 abnormal yet. Maybe this is a challenge we have to  
9 think through; what are the other alternatives.  
10 So I think we have many steps ahead of us in  
11 this process, but I do think we need to come to  
12 some agreement by disease type or subtype. Are we  
13 going to be specific, in this case, for example,  
14 impaired glucose tolerance or other types of  
15 neuropathy? How do we define those disease states?  
16 I think that's really critical. Test questionnaire  
17 availability is important. If it's not available,  
18 we can't use it. It's as simple as that.  
19 Simplicity utility, so the NTSS is widely  
20 used. It is more complicated. I think you'd get  
21 more errors in its use because of the complexity of  
22 a 4-by-4 block. People get a little confused about

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1 how to fill it out. Clarity for this is important.  
2 These are my ruminating thoughts on  
3 questionnaires and examination, so questions?  
4 Noah?  
5 DR. KOLB: Noah Kolb. Chris, that was a  
6 really great talk. I'm interested in what you're  
7 saying about using the disability scores, like  
8 don't apply it to a lot of your clinic patients.  
9 And I guess the really important thing about using  
10 the right measure for the study that we're doing.  
11 I've noticed it in some of our chemotherapy  
12 induced neuropathy studies where although the  
13 NTSS-6 is clumsier, patients often say it's the  
14 thing that best describes their symptoms. And what  
15 I'm struck by is that in a world where a  
16 patient-reported outcome measures are increasingly  
17 important, that we don't have a lot of kind of  
18 quality-of-life metrics that are really specific to  
19 this, that really should be considered for outcome  
20 measures.  
21 DR. GIBBONS: Yeah, it's an important one.  
22 Gordon?

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1 DR. SMITH: Yeah, that was a great talk. We  
2 have data, and we're gathering more looking at the  
3 relationship between clinical scales, symptom  
4 scales, exam scales, quality of life, and  
5 biomarkers. And I can tell you in diabetes,  
6 including very mild diabetic neuropathy, what we're  
7 finding is very good correlations actually between  
8 sensory amplitude, nerve conduction studies, and  
9 skin biopsy, and these measures. And the measures  
10 correlate with one another.  
11 But I think what's also important is it  
12 doesn't really matter -- it matters somewhat  
13 whether or not skin biopsy correlates with an exam  
14 score, but I think what we're really interested  
15 in -- and this goes I think to Noah's point -- is  
16 the extent to which these scales, particularly  
17 examination scales in our biomarkers, correlate  
18 with meaningful experience.  
19 I think your criticism of the scale is that  
20 it's not meaningful. So we're actually looking at  
21 objective measures of function, so fitness timed up  
22 and go balance measures and whatnot. And we're

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1 seeing similar correlations with several of these.  
2 DR. GIBBONS: I think this highlights  
3 really, what our own data is, is that in certain  
4 diseases like diabetes, there's a very strong  
5 correlation between nerve conduction studies,  
6 examination, and biopsy data that's very clean.  
7 You can move this into other disease states, and it  
8 may not be as clear, and I completely agree.  
9 DR. DWORKIN: Karin, James, and Roy.  
10 DR. GIBBONS: Karin?  
11 DR. FABER: Yes. I think if you go into  
12 more detail in the RODS scale, for example, this  
13 scale is being built by the patients, by their  
14 answers. So the scale is targeted for at least our  
15 population of small fiber neuropathies. And there  
16 was not lots of ceiling and floor effects on that.  
17 So it really means that you have a different  
18 population than we do. That's for sure.  
19 DR. GIBBONS: Yeah, I agree, and that's the  
20 challenging part.  
21 DR. FABER: Also, I think what we know from  
22 other diseases, especially from the inflammatory

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1 neuropathies in which we did a lot of research and  
2 outcome measures, is that the RODS scale was far  
3 more able than any other measure to capture changes  
4 over time and also after treatment.  
5 So it is very important to look carefully  
6 and not only measure, for example, whatever we want  
7 to measure on the patient.  
8 DR. GIBBONS: Exactly. I think picking your  
9 population understanding it well is so critical.  
10 James?  
11 DR. RUSSELL: Yes, Chris, I actually thought  
12 I may be suffering from dementia when I was  
13 listening to you doing that, which may be true.  
14 But I actually looked back at the original paper  
15 Lindsay Zilliox was the first author on, and in  
16 fact it was signs and symptoms of neuropathy, and  
17 they had to have an abnormality of  
18 electrophysiology or the skin biopsy. So they do  
19 have signs of neuropathy and they do have those  
20 other changes as well.  
21 DR. GIBBONS: There were two papers. This  
22 was the second one, and we can talk offline later.

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1 I think this one had only symptoms for two years in  
2 this particular group.  
3 DR. RUSSELL: Okay. Anyway, the latest one  
4 was signs and symptoms. But the point I really  
5 wanted to make here is I think you're really  
6 looking at entirely different factors here. Trying  
7 to compare a clinical scale with an objective  
8 measure like the intraepidermal nerve fiber  
9 density, there is a correlation. In fact, there is  
10 a strong correlation with the SAS and the  
11 intraepidermal nerve fiber density, but generally  
12 speaking, that is not the case.  
13 I think you're really looking at measures  
14 that are impacted by factors that are very remote  
15 from the pathology that's occurring in the  
16 peripheral nerve. And when you get to  
17 patient-reported outcome scales, you're even more  
18 remote from the system.  
19 So you're really looking at measures that  
20 look at many other factors that are impacted by  
21 many different systems, and that you really have to  
22 realize and say, are you going to include those?

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1 Plus you're going to have a more objective measure  
2 that looks directly at the nerve or are you just  
3 going to use those clinical measures? I would say  
4 probably not.  
5 DR. GIBBONS: You're making critical points  
6 which are the questions don't necessarily equate to  
7 any of our exam or test findings, and it may not be  
8 necessary to. But still understanding what the  
9 population is that you're intentionally studying  
10 and why, so that you can in fact get a dynamic  
11 change, hopefully, in response to a treatment would  
12 be the goal.  
13 DR. RUSSELL: I would agree.  
14 DR. DWORKIN: Let's go to Roy before coffee.  
15 DR. FREEMAN: I want to bring us back to  
16 case definition, inclusion and exclusion criteria,  
17 which is something that we're going to have to be  
18 writing about. So a couple of questions related to  
19 that, something for you to think about, in fact,  
20 all of us so that by tomorrow our thinking is  
21 fairly honed down on that.  
22 So question one is, any of the

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1 questionnaires and structured examinations that you  
2 presented, have any of them being used as screening  
3 instruments, cutoffs, patients above or below this  
4 can or cannot be excluded in a small fiber  
5 peripheral neuropathy trial? So that's  
6 question one.  
7 Question two, if we look at what  
8 we see in a typical small fiber peripheral  
9 neuropathy trial, whether it be a symptomatic or  
10 perhaps even disease modifying, the two  
11 primary -- let's use the word "domains," but this  
12 is actually bigger than the way you and we have  
13 been using domains in the people that you spoke  
14 about.  
15 But the two primary areas of interest have  
16 been pain and autonomic. In pain, there are a  
17 couple of generic screening questionnaires, DN4,  
18 LANS, and Pain DETEC. How do you see those as  
19 fitting into a potential inclusion criteria, or at  
20 least two of them have been used with specific  
21 cutoffs for inclusion in a pain clinical trial,  
22 and in fact in some small fiber neuropathy clinical

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1 trials, and then less has been done on the  
2 autonomic side. But do you see or have you come  
3 across any screening tool on the autonomic side  
4 that might be suitable as an inclusion/exclusion  
5 criteria?  
6 DR. GIBBONS: So many loaded questions, but  
7 the answer is yes, yes, no, yes, and no.  
8 DR. FREEMAN: I understand we need to think  
9 about it, but we're going to need to do this  
10 tomorrow.  
11 DR. GIBBONS: But to go into a little bit of  
12 the response here, clearly in many of the  
13 neuropathy trials, there are inclusion/exclusion  
14 criteria often based on examination thresholds,  
15 maybe severity of S above the NIS-LL, or I think  
16 you guys have done UENS as well.  
17 If it's above a certain score, it may be  
18 excluded. Have you done an above --  
19 MALE VOICE: For severity, yes.  
20 DR. GIBBONS: Severity, yeah. So that's  
21 often an exclusionary criteria on the examination  
22 scale. I think that standard for many -- the



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1 assumption being once you're at a certain point,  
2 you cannot improve.  
3 Minimum scores I haven't seen too many of,  
4 but I think people have included, particularly for  
5 disease modification, a minimum requirement of  
6 neuropathy on an exam score as well. So some score  
7 above a threshold has been a definite definition.  
8 Questionnaires inclusion, I don't think I've  
9 seen that particularly as an exclusion/inclusion on  
10 the -- the NTSS-6 has been used in some of the  
11 diabetic neuropathy trials as a minimum inclusion  
12 point, so you have to have a value above a certain  
13 amount to be included, an exclusion point above,  
14 which I have not seen or I don't know off the top  
15 of my head.  
16 For the autonomic, again, we get into there  
17 are a number of autonomic scales, particularly if  
18 they're autonomic neuropathies. The COMPASS scores  
19 have been used. Some people use CAST scores, which  
20 we'll talk about -- or I guess David Herrmann will  
21 be talking about later in terms of autonomic  
22 testing.

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1 So these scores have been used and defined.  
2 I think getting back to your pain questionnaire, I  
3 tried to focus a bit more on the small fiber  
4 neuropathy specific as opposed to pain just because  
5 I thought it would grow into too complicated a  
6 topic. But clearly, those are, I think,  
7 multifaceted questions that, depending on the trial  
8 design and what your focus is on as a primary  
9 endpoint, could be a primary endpoint in  
10 inclusion/exclusion criteria. All of these could  
11 be the case. So yeah, it is dicey.  
12 DR. DWORKIN: Thanks very much, Chris.  
13 (Applause.)  
14 DR. DWORKIN: We will reconvene here at  
15 3:20.  
16 (Whereupon, at 3:05 p.m., a recess was  
17 taken.)  
18 Panel Discussion  
19 DR. DWORKIN: We'll go to about 4:15. I'd  
20 like to welcome to the panel, in addition to the  
21 three speakers, Roi Treister –  
22 (Pause.)

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1 DR. DWORKIN: -- Dr. Roi Treister, formally  
2 at the University of Haifa; and Dr James Russell,  
3 professor of neurology at University of Maryland;  
4 and Dr Michael Polydefkis, professor of neurology  
5 at Johns Hopkins. So welcome.  
6 I think the very best way to start a panel  
7 discussion like this, I think is to ask the three  
8 people who you haven't seen yet because they  
9 weren't asked to be speakers, Dr. Treister, and  
10 Dr. Russell, and Dr Polydefkis, whether they have  
11 any questions or comments or thoughts about the  
12 presentations this afternoon from Dr Gibbons, and  
13 Dr. Haroutounian, and Dr Smith.  
14 So starting with you, Roi, any questions?  
15 DR. TREISTER: Sure. Many, many great open  
16 questions were raised today. I think what I  
17 believe would be the right pathway would be to try  
18 to be pragmatic and focus on the drug target, on  
19 the condition, on the outcome measure, excluding  
20 criteria which are obvious, while trying to answer  
21 most of the open questions by using exploratory  
22 measures that will be used in the phase 2 studies

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1 that are coming. Hopefully in the phase 3, there  
2 will be some open questions answered.  
3 I have more specific comments  
4 regarding -- but I will wait to the right time for  
5 these.  
6 DR. DWORKIN: Thank you. Dr Russell?  
7 DR. RUSSELL: Perhaps I can say, you  
8 addressed where we are now. Where would you like  
9 to see us be on the future? You very  
10 systematically went through and you looked at all  
11 these measurements that are used and how they may  
12 be associated with various measures. But if you  
13 were to come up with an ideal measurement, what  
14 would you see as that including?  
15 DR. HAROUTOUNIAN: I presented  
16 [inaudible - off mic].  
17 MALE VOICE: I don't think you're on.  
18 DR. HAROUTOUNIAN: I think one of the  
19 challenges was the huge heterogeneity in taxonomy  
20 and terminology that people use and also the  
21 inclusion/exclusion criteria of course for the  
22 studies. In terms of where I would like to see us

<p style="text-align: right;">Page 289</p> <p>1 in a few years, probably the ideal scenario would 2 be can we come up with a set of criteria that have 3 the optimal sensitivity and specificity that we 4 could use for including and excluding patients in 5 clinical studies and probably a different set of 6 those that would be relevant to the clinical 7 setting for diagnosing and then treating small 8 fiber neuropathy.</p> <p>9 I think just a more thorough analysis, 10 quantitative analysis of what people have found in 11 different studies looking a bit more thoroughly 12 into what might be the key three or four parameters 13 that could help us with good enough sensitivity and 14 specificity to enroll patients to studies because 15 obviously, there are dozens of various domains that 16 are tested, and apparently most of the things 17 people have done or not necessarily applicable to 18 the setting of large studies or multicenter 19 studies.</p> <p>20 So the way I see is to have gold standards 21 of well defined three or four criteria that we'd 22 come to an agreement on the diagnosis of small</p>	<p style="text-align: right;">Page 291</p> <p>1 I've spent a lot of time thinking about it, is 2 treatment-induced neuropathy of diabetes, which is 3 a predominantly small fiber, acute neuropathy in a 4 situation where I found it particularly valuable as 5 a construct because there is a dynamic change at 6 the initiation of the problem followed by a period 7 of recovery in people with type 1 diabetes, which 8 means that I can conceptually validate some of 9 these questionnaires and what responds. At least I 10 see a dynamic range that changes, and I can see 11 what happens.</p> <p>12 I think there are a couple things that I do 13 see. Examination scores do change. The UENS 14 actually changes fairly dynamically; even the 15 NIS-LL does change as well to a smaller degree. It 16 doesn't have quite the same dynamic range, but what 17 it would allow me to do is pick up any motor 18 involvement.</p> <p>19 So at least on my own thinking about this, I 20 would include two examination criteria, one looking 21 at more motor as well as one as small fiber, one to 22 exclude or to define what was involved and one to</p>
<p style="text-align: right;">Page 290</p> <p>1 fiber.</p> <p>2 DR. DWORKIN: Anything else, James?</p> <p>3 DR. RUSSELL: Let me take this a little 4 further. You actually looked at all the diagnostic 5 instruments, and I kind of have some fairly strong 6 views about I think that they are a value in a 7 sense, but perhaps not in a clinical trial setting.</p> <p>8 So what would you say based on those 9 instruments that you reviewed? I do appreciate 10 mine are in there, so I won't feel hurt if you 11 deeply criticize those neuropathy endpoints. So 12 what do you think?</p> <p>13 DR. GIBBONS: You promise you won't hit me 14 if I say the wrong answer?</p> <p>15 (Laughter.)</p> <p>16 DR. RUSSELL: Chris, I'm very critical of my 17 own instruments, I have to tell you, so feel free.</p> <p>18 DR. GIBBONS: I do think actually the 19 instruments will be a critical part of any clinical 20 trial, and I think both examination and 21 questionnaires are of incredible value.</p> <p>22 The disease I like -- well mostly because</p>	<p style="text-align: right;">Page 292</p> <p>1 really focus in on the small fiber component. But 2 then on the questionnaire side, I think as you 3 highlighted, I would include a small fiber sensory 4 questionnaire specific and a small fiber autonomic 5 questionnaire specific because I do think they both 6 respond but also informed differently depending on 7 the distribution of symptoms. And I think you need 8 to know that going in from the get-go as to where 9 the population will go.</p> <p>10 In this particular population, the 11 treatment-induced neuropathy, almost all our 12 sensory and they have a big component to that. But 13 there is a large autonomic piece, and many of the 14 symptom scores, the autonomic symptoms scores, will 15 respond dynamically to these changes.</p> <p>16 So I think there's an incredible value in 17 this, particularly as we're thinking about clinical 18 trials with endpoints that would have 19 patient-oriented outcomes or patient-centered 20 outcomes. I think they need to be included; 21 particularly once the FDA starts to consider 22 clinical trial endpoints, I think it's a</p>

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1 requirement. So I think we need to have these, but  
2 I think we need to be cautious about mixing which  
3 for one. But I would actually advocate, depending  
4 on the particular disease, having more than one.  
5 DR. DWORKIN: I want to interrupt and assert  
6 a moderator's prerogative and push you hard, Chris.  
7 DR. GIBBONS: Okay.  
8 DR. DWORKIN: So I'm hearing that a  
9 distinction needs to be made between the  
10 questionnaire as an outcome measure, where we give  
11 a baseline and some endpoint and look at change  
12 group differences, and something administered at  
13 baseline to be inclusion criteria in a clinical  
14 trial, part of the diagnostic criteria.  
15 I don't know if this is what James was  
16 asking, but I didn't hear anything in your talk, or  
17 Simon's talk, or any of the other talks that  
18 convinced me that there's a questionnaire out there  
19 that needs to be included with some kind of  
20 threshold score as an inclusion criteria and if  
21 we're going to do either a symptomatic or disease  
22 modifying clinical trial.

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1 Is there any sort of questionnaire, or can  
2 we just set that aside and leave the discussion of  
3 questionnaires for the next meeting of this group,  
4 which could be on outcome measures? And then we  
5 would talk about which of these questionnaires are  
6 reasonable, primary, or perhaps secondary outcome  
7 measures. But in the diagnostic inclusion/  
8 exclusion criteria setting, is there anything?  
9 DR. GIBBONS: This was Roy's point earlier,  
10 as he was prodding me for the same response, which  
11 is, yes, there are absolutely questionnaires that  
12 have been used and I think using criteria for  
13 threshold. I think the most widely used, at least  
14 in the neuropathy, is the NTSS-6, which has had a  
15 minimum threshold for inclusion in some studies.  
16 You have to have symptoms and it has to hit the  
17 score, so that has been used.  
18 DR. DWORKIN: Would you recommend that if we  
19 were going to design a clinical trial tomorrow  
20 afternoon between 1 and 4, would you recommend that  
21 as inclusion criterion for our clinical trial?  
22 DR. GIBBONS: So it would entirely depend on

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1 whether this was diseased modifying or symptomatic  
2 relief. If it was disease modifying, I'm not  
3 convinced that I would see a dynamic change. Maybe  
4 I would include it as a threshold for symptoms to  
5 be involved, but I wouldn't use it as an endpoint  
6 perhaps for recovery.  
7 DR. DWORKIN: Use it for diagnosis.  
8 DR. GIBBONS: Diagnosis.  
9 DR. DWORKIN: In a disease-modifying trial?  
10 DR. GIBBONS: I would be hard pressed to say  
11 to come up with a good rationale to say they had to  
12 be included. I think you would want it for many  
13 reasons that may not be scientific.  
14 (Laughter.)  
15 DR. DWORKIN: I'm not letting Michael off  
16 the hook. I want Michael that he gets to go.  
17 DR. SMITH: I think for enrollment criteria,  
18 I would answer we're going to use whatever taxonomy  
19 we come up tomorrow. It seems to me unlikely we're  
20 going to tie our taxonomy to a specific instrument.  
21 We may include the domains, which is the flavor of  
22 the day that that instrument queries. But that's

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1 not something --  
2 DR. DWORKIN: So that was my point, but said  
3 much more succinctly, Gordon. Thank you.  
4 DR. SMITH: You're most welcome.  
5 DR. RUSSELL: I would like to comment on  
6 that before we go on to Michael, and that is we  
7 have to be very careful with the symptoms scores.  
8 schools.  
9 Symptom scores are quite sensitive, as Chris  
10 pointed on his lecture. The big problem with them  
11 is that there's a high variance, and the variance  
12 is the thing that kills you when you look at power  
13 analyses for an endpoint measure. So that's the  
14 thing that you really have to take into account if  
15 you're going to use symptoms scores as endpoint  
16 measures.  
17 DR. HAROUTOUNIAN: Maybe if I can add,  
18 there's another point. If it's a disease-modifying  
19 agent trial and we use some of the symptoms scores  
20 to potentially correlate with outcomes, the  
21 questionnaires like NPSI, DN4, LANS, they have very  
22 little correlation or association with

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1 morphological changes in small fibers.  
2 FEMALE VOICE: You said very little?  
3 DR. HAROUTOUNIAN: Very little. So  
4 questionnaires like the Utah or the Michigan, the  
5 ones that are neuropathy scores, they correlate  
6 much better with the intraepidermal nerve fiber  
7 density, but symptom questionnaires, NPSI and DN4,  
8 they are very poorly correlated with biopsy  
9 findings.  
10 So I think it's a caveat, and there's quite  
11 a bit of work to be done I think research-wise to  
12 understand the association between what is the  
13 difference between painful and painless neuropathy  
14 because morphology-wise, they're not much  
15 different, but symptom-wise, there's a huge  
16 difference between them, and what is it that  
17 mechanistically differentiates those two patient  
18 populations, and only then maybe we can use symptom  
19 measures in a meaningful way.  
20 DR. DWORKIN: So I want to make sure that  
21 Michael has a chance to comment or question the  
22 speakers.

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1 DR. POLYDEFKIS: Well, I guess I'm kind of  
2 struggling with the concept of a trial because I  
3 think there are many different types of trials.  
4 You have the pain trial one way, disease  
5 progression a different way, and disease  
6 modification a different way. And all of those can  
7 be small fiber neuropathy. That sort of tailors  
8 the measures in the inclusion criteria based on  
9 what the objective is.  
10 DR. DWORKIN: I want to ask what's probably  
11 a naive question because of course I'm not on  
12 neurologist. It seems to me when we design a  
13 clinical trial for some treatment, symptomatic  
14 treatment, in painful diabetic peripheral  
15 neuropathy, you have criteria first of course for  
16 diabetic peripheral neuropathy, and then we have  
17 some criteria for the pain part of it that allows  
18 us to select which patients with DPN have enough  
19 pain to go into our trial of whatever, gabapentin.  
20 So I guess what I'm not getting is why is it  
21 any different for CSPN iSFN? Why can't we have a  
22 set of diagnostic criteria for the condition that

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1 we've been talking about all day today? And if  
2 it's a trial of a symptomatic treatment for pain,  
3 then of course the patients with CSPN are going to  
4 have that pain. It would be silly that they don't.  
5 But why are the diagnostic criteria for CSPN  
6 in any way a function of whether it's a symptomatic  
7 trial of gabapentin, a disease-modifying trial of  
8 topiramate, a disease-reversal trial of some brand  
9 new aldose reductase inhibitor. It seems to me  
10 that the diagnostic criteria and inclusion/  
11 exclusion criteria should be pretty invariant  
12 across the clinical trial, though the point we all  
13 agree on is your outcome measures might be very  
14 different depending on the drug and the objective.  
15 So am I missing something?  
16 DR. GIBBONS: I can get more specific about  
17 painful diabetic neuropathy trials. There were  
18 many diabetic neuropathy trials that didn't have  
19 those painful endpoints.  
20 DR. DWORKIN: That's exactly my point.  
21 Shouldn't the criteria for DPN be the same in the  
22 gabapentin trial as in the aldose reductase

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1 inhibitor trial? Because the condition is DPN, and  
2 if you want to treat pain in DPN, they've got to  
3 have pain.  
4 (Crosstalk.)  
5 DR. GIBBONS: I think Eva's going to jump in  
6 with an excellent point.  
7 DR. DWORKIN: Hopefully someone tells me I'm  
8 naïve and I'm barking up the wrong tree.  
9 DR. FELDMAN: No, not naive, but maybe  
10 barking up the wrong tree. I think it all goes back  
11 to the function of the fibers, right? A great deal  
12 of diabetic neuropathy that we've entered in -- I  
13 don't even know how many trials we've done at this  
14 point -- is primarily large fiber diabetic  
15 neuropathy, and those patients frequently have an  
16 insensate foot, so they don't really complain of  
17 pain. I mean, that's the function of those fibers,  
18 you know, large fiber function. Yet, when you  
19 think about small fiber function, it's very  
20 unusual.  
21 I hope the panel will agree with me. I'm  
22 going to particularly look at James in terms of

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1 thinking of the biology of the small fibers. It  
2 would be unusual to have a small fiber insult,  
3 whatever it may be, without it being painful. So  
4 it's the difference in terms of the function of the  
5 fibers that I think calls this particular aspect  
6 into question.

7 I go back to what Anne Louise said, the idea  
8 of domains, though, which is maybe, again, what  
9 you're kind of seeking, is there a domain or an  
10 idea that you're just going to define just  
11 structurally a small fiber neuropathy, and then a  
12 second domain is small fiber neuropathy with  
13 symptoms.

14 But I personally don't think I have seen in  
15 a fairly large clinical practice for many years a  
16 small fiber neuropathy that does not have some  
17 aspect of pain, except for of course the complete  
18 insensate, genetic neuropathies.

19 DR. OAKLANDER: I think there's an even more  
20 basic question here. We're trying to make a case  
21 definition for a cell-based disease, small fiber  
22 polyneuropathy. What's a small fiber, dudes? I

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1 mean, we used to talk about somatic; we used to  
2 talk about autonomic. The pathology studies,  
3 though, modern immunohistochemistry studies have  
4 shown so clearly that functions that we would  
5 intrinsically think of as autonomic are in fact  
6 mediated by CGRP positive, quote/unquote, "somatic  
7 small fibers." These, for instance, are the fibers  
8 that innervate the bone and that mediate deposition  
9 that control the bone mass. They're CGRB positive.

10 So I think that's the elephant under the  
11 rug, is that these small fibers have such protean  
12 functions, they're evolutionarily so primitive,  
13 pain is just one of their functions, but their  
14 overarching goal really is defense of our body  
15 against threats, and they also mediate itch, and  
16 they control the vasculature.

17 So how can you decide what small fiber  
18 neuropathy and what symptoms should be required for  
19 inclusion until you figure out what are we talking  
20 about as the small fibers? Does it include  
21 autonomies or is that separate? I think some  
22 people think of them as separate; some people think

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1 of them as together.

2 DR. DWORKIN: First Todd, then David.

3 DR. LEVINE: I mean, you've got the right  
4 tree. It's just that they have a lot better tools.  
5 They have a disease, diabetes. We're talking about  
6 dozens if not many, many dozens of diseases, so you  
7 have to branch off of that tree many, many times.  
8 And in those studies, they generally use nerve  
9 conduction studies, and they just said this is  
10 abnormal.

11 They could've picked many other things.  
12 We're in the same position. We're just a hundred  
13 years behind them. So we are just going to have to  
14 pick one thing and say this is what defines small  
15 fiber neuropathy the same way they defined what  
16 diabetic neuropathy was, and then go with it. The  
17 hard part is separating out -- I think Anne Louise  
18 is right -- is that you just have to decide what  
19 you're going to try to treat because there are -- I  
20 was actually going to raise the question also for  
21 the panel, one of the things that we haven't talked  
22 about in thinking about trials is other somatic

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1 symptoms, which in your paper is an enormous issue  
2 and I think in practice is a huge issue of fatigue  
3 and sleep and cognition, which, again, there are  
4 many reasons. It could be the drugs, it could be  
5 the pain, it could be sleep, but those are enormous  
6 issues for patients that we need to improve on as  
7 well, again, further complicating the issue.

8 So I think the only way forward is just to  
9 make a decision and move forward with it. This is  
10 the definition. These are the diseases we allow in  
11 or don't, idiopathic or these others, and then just  
12 go because it is very complex.

13 DR. DWORKIN: David and then Roy.

14 DR. HERRMANN: So maybe this is just stating  
15 the same thing slightly differently to the  
16 discussion between Chris and James, and then your  
17 question what am I missing. I would say you're not  
18 missing much, Bob, because I think operationally  
19 for any trial, you're going to have diagnostic  
20 criteria.

21 As we define those for small fiber  
22 neuropathy, I think we're going to have to be clear

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1 is this distal small fiber neuropathy, chronic with  
2 a certain time course, probably a very different  
3 entity or group of entities from an acute small,  
4 non-length-dependent small fiber neuropathy or from  
5 a autonomic predominant small fiber neuropathy.  
6 So we at least phenotypically going to have  
7 to define the entity and have a set of diagnostic  
8 criteria that could be applied across different  
9 trials, but then we're not going to enroll people  
10 who have no disability or no patient-reported  
11 impact in trials.  
12 So while it may not be a diagnostic  
13 criteria, some measure of disability or some  
14 measure of patient-reported impact and degree of  
15 impact is going to have to be there as part of  
16 inclusion. So when you do pain studies, you'd take  
17 a numerical rating scale of 4 or greater. Well,  
18 depending on what you're studying, there's going to  
19 be some not diagnostic criteria, but patient impact  
20 or disability inclusion threshold. And that could  
21 be different depending on what, as Michael said,  
22 you're starting

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1 DR. DWORKIN: Roy?  
2 DR. FREEMAN: So I actually rather like your  
3 approach to it, and I'm going to continue the  
4 analogy that you build up.  
5 The way I think of a painful peripheral  
6 neuropathy trial is you start off and you say,  
7 okay, does this patient -- a diabetic painful  
8 peripheral neuropathy trial -- does this patient  
9 have diabetes? And that's the first question. And  
10 the equivalent of that is does this patient not  
11 have. And how much do we need to do to define that  
12 the patient does not have, well, Gordon is going to  
13 tell us exactly how much we need to do, and it's  
14 going to be not quite as discrete as the diagnosis  
15 of diabetes. But even that, the diagnosis of  
16 diabetes as we know is not quite discreet either.  
17 The next step then is does the patient have  
18 neuropathy? And then we can talk about -- and David  
19 touched on that. But we can decide how we are  
20 going to define neuropathy. Will it be defined by  
21 a intraepidermal nerve fiber density? Will it be  
22 defined by symptoms? Will it be two out of three?

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1 Will it be proximal? Will it be distal? This is a  
2 discussion, but that's the point. Then the third  
3 and continuing the diabetic painful peripheral  
4 neuropathy trial, we will say does the patient in  
5 that case have pain, and is that pain neuropathic?  
6 So we've gone through diabetes, neuropathy,  
7 pain, neuropathic pain, because, as we all know,  
8 there are many causes of pain in diabetic patients  
9 that are not neuropathic. So I rather like the  
10 idea of saying, okay, does the patient not have  
11 diabetes and everything else, too? Does the  
12 patient have a neuropathy? And this is a  
13 discussion of distal sensory proximal  
14 ganglionopathy pattern can go on in that, and lots  
15 of spaces to fill in. And then the equivalent of  
16 pain is over here. We are dealing with the diverse  
17 manifestations of a small fiber neuropathy, which  
18 can be sensory, can be autonomic, can be both.  
19 Here is where I think the small fiber trial  
20 is unique. We're going to be talking about whether  
21 the drug is a drug directed against pain, or  
22 autonomic, or both, and whether the trial is

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1 symptomatic or disease modifying. So in brief, I  
2 like the tree.  
3 (Laughter.)  
4 DR. DWORKIN: How about Chris first, and  
5 then there were other people.  
6 DR. GIBBONS: So I just wanted to throw out  
7 sort of a conceptual kind of process to kind of  
8 work through some of the challenges that we are  
9 going to face going forward when we're trying to  
10 bring together a consensus on this. We talked  
11 about some of the hereditary neuropathies in terms  
12 of their genetic components and what the  
13 implications of that were. What we really didn't  
14 touch on at all were the hereditary sensory and  
15 autonomic neuropathies, where clearly you have a  
16 population of patients that has a profound loss of  
17 small nerve fibers from an early age on.  
18 I guess the question we can ask ourselves  
19 amongst those with really no sensory fibers  
20 whatsoever in their body, they are missing a set of  
21 symptoms that we widely attribute to maybe small  
22 fiber neuropathy. Is this in some way informing us

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1 about the relation of these symptoms to the disease  
2 or not? Can we infer something from those patients  
3 more broadly into the patients were asking you  
4 about? Do the dependent patients with hereditary  
5 sensory autonomic neuropathies, the Riley-Day  
6 syndrome, the classic ones, why don't they have  
7 fatigue? Some of our small fiber neuropathy  
8 patients, why don't they?  
9 They clearly have severe mutations or  
10 amputations, auto amputations, many issues related  
11 to lack of pain, but why don't they have some of  
12 these other symptoms that we presume must be  
13 mediated by? So is that in some way helping us  
14 think about this?  
15 So I'm just throwing that out there, again,  
16 as another point to examine.  
17 DR. DWORKIN: I think another systematic  
18 review, actually. Other comments, questions from  
19 the audience? Yes, Nurcan?  
20 DR. UCEYLER: Maybe one comment to what Roy  
21 just said with the tree. So when you look at what  
22 the patient does not have and then you go on

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1 looking for the neuropathy, and at the final stage  
2 actually ask for symptoms, the tree just to  
3 discuss, with this we would miss the patients I  
4 think who do have very typical small fiber  
5 neuropathy symptoms like burning pain in their feet  
6 and do not have any signs of neuropathy that we can  
7 get with the methods we have in hand at the moment.  
8 So there is a segment of subgroup of  
9 patients who have burning feet, very, very typical  
10 history, and you do the skin biopsy, and you do the  
11 QST, and the CCM, and the prep and whatever, and  
12 you do not find any sign for neuropathy. You will  
13 find some when you do microneurography. This is  
14 what we have experienced, a large group of patients  
15 going through all this with burning feet. But the  
16 sensitivity is not high enough for all these  
17 techniques, and in the end you do microneurography  
18 and do see spontaneous activity. I like very much  
19 the pragmatic way of looking at it with this tree,  
20 but just for discussion, there are patients who  
21 have, I would say, small fiber neuropathy, but  
22 where we do not see the neurography.

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1 DR. FREEMAN: Absolutely. And I absolutely  
2 agree with you, and I have thought about that, and  
3 I think my response to you would be you're  
4 absolutely right. But I think the likelihood of  
5 any clinical trial of introducing patients who do  
6 not have neuropathic pain is greater, and that I'm  
7 prepared to make that compromise to say that, sure,  
8 I may be admitting -- and I don't know -- an  
9 unknown number of patients who truly have  
10 neuropathic pain, but I would rather do that than  
11 risk including patients with metatarsalgia, plantar  
12 fasciitis, calcaneal spurs, and all of the other  
13 causes of non-neuropathic foot pain. But I take  
14 your point in its entirety.  
15 DR. UCEYLER: And maybe one has to  
16 distinguish here also, what we are trying to get a  
17 criteria for trials, and I think it is, again,  
18 something else. I'm thinking about criteria of  
19 small fiber neuropathy in general. So what are we  
20 using at the moment to make a diagnosis when we see  
21 these patients? So am I allowed to call the  
22 patient small fiber neuropathy patient if I do not

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1 find any science for neuropathy?  
2 But I think here we have to distinguish, and  
3 for a clinical trial, this is a very pragmatic and  
4 good way to go ahead I would say also. And the  
5 other question would be for another panel maybe to  
6 think about new criteria or reformation of the  
7 criteria.  
8 DR. DWORKIN: Rob, I think you had your hand  
9 up.  
10 DR. SINGLETON: I think Roy expressed my  
11 sentiment quite well. The only other thing, going  
12 back a couple of comments,  
13 there are a lot of potential criteria and different  
14 aspects of small fiber neuropathy, but I think I  
15 would advocate that we should be inclusive but  
16 honed to somatic sensory exam and complaints.  
17 I take your point there are any number of  
18 roles of small fibers, but kind of like Roy's  
19 point, there's a limit to how much we can take into  
20 account when we consider a practical set of  
21 eligibility criteria that will be useful for the  
22 majority of clinical trials.

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1 DR. OAKLANDER: Are we going to include  
2 clinical diagnostic criteria or only research?  
3 DR. DWORKIN: I'm going to get there.  
4 Gordon?  
5 DR. SMITH: Yes. I want to follow up on  
6 that because Anne Louise's comment is really  
7 resonating with me, and I'll just be honest. I  
8 have a lot of ambivalence about small fiber  
9 neuropathy as a distinct disease entity, and I'm  
10 trying to think of other disorders that we have,  
11 and personally I hope that we see, that are defined  
12 in that way. I can think of maybe motor neuron  
13 disease is a category of disorders, but when we  
14 think about the taxonomy of motor neuron disease,  
15 we talk about ALS or we talk about PLS. And it's  
16 not based on the structure; it's based on the  
17 clinical phenotype.  
18 I question whether there's anything  
19 fundamentally different about the patient who has a  
20 severe painful idiopathic neuropathy who has mild  
21 vibratory loss in their great toe and their next  
22 door neighbor who does not. And maybe this is a

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1 topic for later or tomorrow, but I think it's  
2 really important. I think Roy's description of  
3 climbing up the tree and your construct is  
4 absolutely the way we need to be thinking. I think  
5 we can factor in graded certainty, probable,  
6 possible, confirmed or whatnot to handle situations  
7 where there are individuals who have clear  
8 symptoms, signs, but not the pathology we're  
9 looking for. And in individual trials, a  
10 neuropathic pain trial, maybe you don't require the  
11 pathologic finding.  
12 But I think something that I'm really  
13 struggling with and I'd love to hear everyone else  
14 discuss is the concept of the validity of small  
15 fiber neuropathy as a diagnostic entity as opposed  
16 to idiopathic painful neuropathy with, I don't  
17 know, disproportionate small fiber injury, and I'm  
18 just throwing out words.  
19 DR. RUSSELL: Bob, I'd like to also follow  
20 up on Roy's comment. Roy actually slipped it in  
21 there, but it's a problematic branch of this tree,  
22 and that is disease modifying. For example, if a

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1 person gets an improvement to the NTSS-6 by 10  
2 percent, is that disease modifying or not?  
3 So we can agree that we can use certain  
4 scales to determine if there's been improvement in  
5 a measure of small fiber neuropathy, but the  
6 question is, is that improvement really disease  
7 modifying? And that's a branch which is going to  
8 be quite difficult to define.  
9 DR. DWORKIN: Giuseppe?  
10 DR. LAURIA: This part of the discussion, I  
11 want to share with you my opinion. I think doing a  
12 clinical trial means making a negotiation between  
13 real life, so real patients, the concept behind the  
14 trial and the feasibility of your outcome measures.  
15 So in this case, following what Roy just said, if  
16 you are dealing with a drug in which you want to  
17 see whether it has an effect on neuropathic pain,  
18 you will have to define a category of patients  
19 that -- I mean, I get your point, Nurcan, that  
20 probably not all the patients that you will recruit  
21 will present all the patient that enter your  
22 outpatient clinic, but you have to make a decision

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1 in terms of criteria to make the trial feasible.  
2 In this case, what you want to have is an  
3 homogeneous group of patients that can be assessed  
4 in order to have good specificity, so keeping away  
5 the patients who do not have the disease and trying  
6 to have a most true positive and deciding what is  
7 your outcome measure in terms -- James, your  
8 example, in my opinion, is symptomatic outcome, not  
9 a disease modifying because disease modifying has  
10 to be measured in terms of disability, at least.  
11 This is what happens to any motor neuron or  
12 whatever. But if you are talking about pain,  
13 you're talking about the symptom that is influenced  
14 by a number of variables that we are not taking  
15 into account because I haven't heard anyone talking  
16 about, for instance, mood, anxiety, depression.  
17 Should we stratify the patients based on that? It  
18 could be the case. I mean, we don't know whether  
19 the response to a drug, how much it is influenced  
20 by that. I'm very surprised by the fact that in  
21 the last 50 years, any drug that entered the market  
22 had the same performance,



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1 although the target is different.  
2 DR. DWORKIN: Roy?  
3 DR. FREEMAN: I have a very simplistic  
4 approach to disease modification. I think we in  
5 the neuropathy field and in the pain field actually  
6 have it relatively easy compared to say, for  
7 example, the Parkinson's field. I think if you  
8 stop the drug for a reasonable period of time and  
9 the effect of the drug endures compared to your  
10 placebo group, you have modified the disease.  
11 On Parkinson's disease, I think it's much  
12 more tricky because they are on symptomatic  
13 treatment, and you have to withdraw not only the  
14 drug but the symptomatic treatment and compare  
15 them. It's a real challenge, and I think that's  
16 one of the reasons why it's been so challenging to  
17 develop a drug to modify the natural history of  
18 Parkinson's disease. But I think we have it  
19 relatively easy. We can define how long you need  
20 to -- what kind of time window you need between  
21 stopping the drug and your assessment. But if it  
22 endures, I think that's modified the disease.

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1 DR. DWORKIN: Amanda?  
2 DR. PELTIER: Actually, I think that there's  
3 a couple issues, and actually the analogy of  
4 Parkinson's is actually probably better than you  
5 think it is because --  
6 DR. FREEMAN: I think it's good, by the way.  
7 (Laughter.)  
8 DR. PELTIER: But my point is a lot of  
9 movement disorder specialists will tell you that  
10 Parkinson's, if you see one Parkinson's patients,  
11 you've seen one Parkinson's patient. And I think  
12 that's one of the issues with small fiber  
13 neuropathy is that it's not due to a single  
14 disease; it's due to multiple different factors.  
15 It could be due to genetic factors, it could be due  
16 to toxicity, could be due to underlying metabolic  
17 factors, et cetera. And because those  
18 non-myelinated fibers have multiple  
19 functions -- you could have patient that has  
20 primarily autonomic, one patient has primarily  
21 burning.  
22 So it really goes back to what disease or

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1 drug that you're trying to specifically treat. If  
2 you're specifically trying to treat pain, you're  
3 going to be more broad than if you are trying to  
4 specifically treat a specific entity as is like  
5 small fiber neuropathy in sarcoidosis, because you  
6 can't be too broad in that case.  
7 It's just like saying, well, I'm going cure  
8 Charcot-Marie-Tooth disease. Well, am I going to  
9 cure Charcot-Marie-Tooth just from PMP22  
10 duplications, or am I going to delete all the  
11 300,000 other mutations that have been found? So  
12 that's I think the problem that we deal with is  
13 that it's not just one disease entity because it's  
14 not the one manifestation.  
15 DR. FREEMAN: Absolutely. I don't want  
16 to -- I said I have a sympathetic approach to it,  
17 but I think it's more complicated. You treat the  
18 pain, patient exercises more, is more mobile, and  
19 by being more mobile, maybe you're treating the  
20 underlying disease, sort of the Singleton-Smith  
21 approach to the treatment or disease modification  
22 in neuropathy. So it's not as simple as I made

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1 out, but I think it is not that complicated either.  
2 DR. DWORKIN: I think I saw another hand.  
3 Todd, yea?  
4 DR. LEVEIN: I just was going to say,  
5 Gordon, the analogy -- that's why I like that one  
6 slide I started with because causes for mixed fiber  
7 neuropathy is just put mixed fiber neuropathies on  
8 one side and small fiber neuropathies on the other.  
9 It's really the same pathway that we're following;  
10 we're just sort of behind it, right?  
11 So you just need a way to make a diagnosis,  
12 which we're going to have to agree what defines  
13 small fiber neuropathy.  
14 There are hundreds of different causes, and you can  
15 certainly blur them all together, but when it comes  
16 to doing clinical trials, most people  
17 prefer -- you're breaking the rule a little bit now  
18 with your current trial, but most people have  
19 preferred historically to take as homogeneous a  
20 group as possible. So we just define that as best  
21 we can.  
22 Again, I agree with Roy, which is it is

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1 hugely complicated, and we can either try to  
2 address all those complexities or just say this is  
3 the path that's been laid out with mixed fiber, and  
4 we're just going to try to follow that path as best  
5 we can.  
6 DR. SMITH: I just want to respond. I still  
7 am very skeptical of lumping patients with a  
8 particular phenotype into small mixed large. I  
9 just question why we aren't talking about painful  
10 neuropathy with small fiber pathology. There are a  
11 number of ways you can parse this, but I'll go back  
12 to is there fundamentally something different with  
13 patients who have very painful cryptogenic  
14 neuropathy, who have normal nerve conduction  
15 studies but have evidence of vibratory last on exam  
16 versus those who do not.  
17 I see more of those patients than not, and I  
18 just worry that we're overcomplicating our criteria  
19 for small fiber neuropathy by drawing these really  
20 bright lights. I get the idea that there may be  
21 scenarios and the genetic data create one. It may  
22 be something unique about these very carefully

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1 defined subsets of patients who have isolated small  
2 fiber neuropathy that are different, but is that  
3 the taxonomy we're looking for as opposed to a  
4 broader painful neuropathy umbrella?  
5 DR. DWORKIN: Simon?  
6 DR. HAROUTOUNIAN: Just kind of to follow,  
7 when looking through the studies, there seemed to  
8 be almost a rudimentary set of findings that are  
9 common to those hundreds of different etiologies  
10 and perhaps we should think about a very basic  
11 inclusion type, and then each study or each  
12 subgroup of small fiber neuropathy we could  
13 recommend to do different ancillary type of tests  
14 to gain more knowledge.  
15 It looks like the distribution of symptoms,  
16 potentially sensory symptoms, and skin biopsy, and  
17 perhaps warm detection threshold seem to be pretty  
18 consistent among all the trials; again, 80 percent,  
19 75 percent, 90 percent, and the other findings are  
20 pretty specific to etiology or patient subgroups,  
21 et cetera. So perhaps we should try to focus on  
22 this maybe basic rudimentary group of --

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1 DR. DWORKIN: We have 10 minutes left.  
2 Eva, go ahead.  
3 DR. FELDMAN: Could I just ask a question?  
4 It's kind of we're coming full circle. So would  
5 you -- and you have really done a very beautiful,  
6 careful review -- include symptoms or not in the  
7 definition? I mean, really, that's where you start  
8 it, right?  
9 DR. DWORKIN: I'm going to --  
10 DR. FELDMAN: I mean, I'm asking him, not  
11 you.  
12 (Laughter.)  
13 DR. DWORKIN: Okay, because I was going to  
14 say let's talk about exactly that for the next 10  
15 minutes. If I understood Roy's tree correctly,  
16 we're going to exclude patients with frank  
17 diabetes.  
18 (Crosstalk.)  
19 DR. FELDMAN: No, no --  
20 DR. DWORKIN: The way those of us have been  
21 involved in the development of this meeting is that  
22 primarily what we would like to do is come up with

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1 diagnostic criteria for this condition that also  
2 include inclusion/exclusion criteria for a clinical  
3 trial, and the model here is DSM-V, the ISP  
4 diagnostic criteria. So secondarily, perhaps  
5 clinical practice, but primarily we're designing a  
6 phase 3 trial for NINDS, or a pharmaceutical  
7 company is designing a phase 3 trial to go to EMA  
8 or FDA. So primarily, diagnostic criteria to be  
9 used in clinical trials.  
10 DR. OAKLANDER: Unfortunately, it ends up  
11 getting applied in clinical practice, which is  
12 what's happened to DSM. Given the absence of  
13 clinical diagnostic criteria, our criteria that we  
14 publish are going to end up becoming the de facto  
15 clinical criteria, and insurance companies are  
16 going to deny care reimbursement to patients  
17 because they don't fit into our action. I'm just  
18 saying at a practical --  
19 DR. DWORKIN: I don't know what we can do  
20 about that except put a sentence or two in an  
21 article that the primary intent of the diagnostic  
22 inclusion/exclusion criteria in this publication

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1 are for use in clinical trials. I mean, I don't  
2 see how we can prevent insurance companies from  
3 doing their reimbursement mischief. Unless someone  
4 has a better idea of how to prevent that, boy, does  
5 that seem above my pay grade.  
6 DR. HAROUTOUNIAN: Can I just take two  
7 minutes to address the symptom question?  
8 DR. DWORKIN: Sure.  
9 DR. HAROUTOUNIAN: If we're dealing with  
10 painful neuropathy, we have to address pain as  
11 symptoms. When we're looking at the specificity of  
12 things like burning pain or pins and needles or  
13 descriptors or DN4, NPS sites, none of the single  
14 symptom descriptors are specific or broadly  
15 applicable to different patient populations. So  
16 pain should be there, but it didn't seem that --  
17 DR. OAKLANDER: The symptoms should be  
18 there.  
19 DR. HAROUTOUNIAN: Pain.  
20 DR. OAKLANDER: Pain.  
21 DR. HAROUTOUNIAN: But I don't know if other  
22 symptomatic descriptors are kind of -- none of them

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1 was consistent enough amongst studies and none of  
2 them, both in terms of occurrence and severity,  
3 corresponded with the small fiber pathology.  
4 DR. SINGLETON: How about distribution? Did  
5 you look at whether these questions about pain  
6 were -- did that matter whether it was length  
7 dependent or not?  
8 DR. HAROUTOUNIAN: Could you repeat it?  
9 DR. SINGLETON: You just said it doesn't  
10 matter what the descriptor is. My question is the  
11 distribution, the anatomic distribution. Does it  
12 matter whether it's described as length dependent,  
13 and was that something that the questionnaires that  
14 you evaluated, the measures that you evaluated, was  
15 that one of the things that was approached by  
16 these?  
17 DR. HAROUTOUNIAN: So the distribution  
18 itself is not defined very well, but if you're  
19 looking at neuropathy questionnaire, like the Utah  
20 or the Michigan and the total score, they were  
21 pretty well associated, but not --  
22 DR. SINGLETON: The exam skills had a

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1 questionnaire, right?  
2 DR. HAROUTOUNIAN: No, we didn't look at the  
3 symptoms versus the exam skills.  
4 DR. GIBBONS: So I know this is going to  
5 come full circle to your clearly leading question  
6 from the very get-go, but I think you did highlight  
7 kind of the nudge in that direction, which is we  
8 can define a small fiber neuropathy, and then we  
9 can define a symptomatic small fiber neuropathy,  
10 and it may simply be that we check the first box in  
11 order to move onto the second box. But I think  
12 defining a symptom as we sort of heard and I think  
13 many of us are familiar with, once you've defined a  
14 symptom, is it this symptom or that symptom? It  
15 can quickly move in a different direction, but I  
16 think the starting box has to be small fiber  
17 neuropathy.  
18 DR. DWORKIN: We only have 7 minutes left,  
19 so let me continue to bark up the wrong tree.  
20 Couldn't one imagine symptomatic criteria? I  
21 realize there are other inclusion and exclusion  
22 criteria, but something like patient needs to have

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1 self-reported 2 of the following 5 symptoms; and  
2 those sensory symptoms are pain; and/or pins and  
3 needles, tingling; and/or self-reported,  
4 patient-reported numbness; and/or itching; and/or,  
5 I don't know, something else.  
6 This is really the DSM-V model. So  
7 criterion one is two, it could be three, it could  
8 be one of the following five patient reported  
9 symptoms. So we don't have enough time to come up  
10 with that list now. This is why I left it to the  
11 end, but is that something that Roy does tomorrow  
12 afternoon starting at 1:00, that criterion one for  
13 our diagnosis of small fiber sensory or mixed  
14 peripheral neuropathy is a symptom list, and a  
15 certain number of those symptoms is required?  
16 Or as I thought I heard Eva 45 minutes ago,  
17 maybe pain is so prevalent in this condition that  
18 it could be something like patient must have pain  
19 in the following distribution, and one of the  
20 following other three parasthesia/dysesthesia type  
21 symptoms, is that a model that's a reasonable one  
22 for tomorrow afternoon's discussion? David?

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1 DR. HERRMANN: I think the answer from my  
2 perspective it's yes, but I think to some of the  
3 other discussions, to Ahmet's discussion, I think  
4 if you're going to define some sort of phenotype to  
5 include in a particular trial, you want to have  
6 acuity, so an acute onset versus a chronic  
7 neuropathy, I think very different. I'm not sure  
8 that I would include those from knowing their  
9 natural history in the same trial.

10 Then also distribution. I really do think if  
11 we're talking about -- when Gordon's talking about  
12 painful sensory neuropathy, I think for the most  
13 part we're thinking about the broadest issues, the  
14 distally dominant painful neuropathy, and I think  
15 that needs to be distinguished from these acute or  
16 subacute non-length-dependent painful small fiber  
17 neuropathies that need to go in a different bucket,  
18 and for which the etiologies may be a bit  
19 different, and for which probably the treatment  
20 strategies may or may not differ.

21 DR. DWORKIN: So those are the two D's.

22 DR. HERRMANN: Yes.

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1 DR. DWORKIN: And I completely agree with  
2 you, distribution and duration, six months for  
3 example --

4 DR. HERRMANN: Absolutely.

5 DR. DWORKIN: -- they can't have developed  
6 these symptoms a week ago. They should have had  
7 them relatively stable for six months up.  
8 Amanda, and then Chris.

9 DR. PELTIER: I think getting back to  
10 Gordon's comment about what's the difference  
11 between somebody with small fiber neuropathy versus  
12 somebody with a little bit of vibration, I think  
13 one of the things that you probably also want to be  
14 careful about is what negatives you include in your  
15 criteria.

16 So for example, they have to have an absence  
17 of weakness, I believe, if you're going to make it  
18 a small fiber because it really should be a  
19 sensory-only disorder or primarily sensory and  
20 autonomic. But if they have any weakness, that  
21 should take them completely out because then you've  
22 automatically I think included patients that --

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1 DR. SINGLETON: Like the absence of lower  
2 motor neuron.

3 DR. PELTIER: Well, right. But I think that  
4 you have to define how are you going to define  
5 weakness, but they shouldn't be clinically weak on  
6 exam.

7 DR. DWORKIN: Chris?

8 DR. GIBBONS: I think you can take the  
9 approach of the symptomatic criteria, but you need  
10 to absolutely have qualifiers in there in addition.

11 But I think the classic example that I see in  
12 practice is the bilateral plantar fasciitis. They  
13 have the exact same complaints walking in the door,  
14 but it is not a small fiber neuropathy and it's  
15 clearly not treated as such, so you have to have  
16 some criteria in there that either brings you in as  
17 a loss of functional modality or excluding  
18 something else.

19 DR. DWORKIN: Gordon? Maybe Gordon's going  
20 to get the last word.

21 DR. SMITH: Oh, that would be a fresh  
22 change. I want to answer Eva's question directly

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1 and just say, yes. I don't think that one can make  
2 a diagnosis of small fiber neuropathy or painful  
3 neuropathy in the absence of symptoms. I think  
4 your construct is a valid one, and it's all in the  
5 way it's applied. And I think it's really  
6 important. I can use diabetes as an example, that  
7 many patients who have diabetes who do not even  
8 have neuropathy have clear evidence of small fiber  
9 injury and structural loss. We see it in CCM data.  
10 We see it in INFD.

11 So if we have a patient with diabetes, let's  
12 say, who does have numbness and tingling but no  
13 pain, and the only abnormality on testing is a skin  
14 biopsy, that's not the patient population we're  
15 talking about. So I think it's important to use  
16 these other structural measures of small fiber  
17 neuropathy and our class taxonomy and diagnostic  
18 criteria, but it really has to be founded in the  
19 patient experience and their symptoms and  
20 supporting signs.

21 The last point I want to make is we have  
22 existing tools. We have the ISP definition of

1 neuropathic pain. That works pretty well, and I  
2 think that's part of Roy's tree. That's one of the  
3 limbs -- I don't know how the metaphor works, if  
4 we're climbing up the limbs or what, but we have  
5 that, too.

6 DR. DWORKIN: It's 4:15. The last comment  
7 from Anne Louise.

8 DR. OAKLANDER: Well, I think we don't have  
9 enough data to know what should or should not be in  
10 the diagnostic criteria. So I think we should look  
11 at the literature. It's very important to do that.  
12 What do the studies show about the symptoms of  
13 patients who do have small fiber neuropathy? And  
14 looking at our abstract, which I don't remember  
15 because we got it in at quarter of 12 last night,  
16 it's exam findings in patients with objectively  
17 validated small fiber; loss of pin, 70 percent;  
18 most common, appearance of the foot; but then  
19 touch, and half of them have some diminution and  
20 great toe vibration. So half of them have some  
21 diminution and great toe vibration on exam.  
22 Patients who have objectively confirmed small fiber

1 neuropathy, how could we exclude them? Fifteen  
2 percent had reduced great toe strength. I'm just  
3 saying, those were the data.

4 Adjournment

5 DR. DWORKIN: Thank you all very much. It's  
6 time for the email break before dinner. Dinner is  
7 here from 7 to 9, and we will see you all then and  
8 look forward to a very lively discussion tomorrow  
9 afternoon.

10 (Whereupon, at 4:17 p.m., the meeting was  
11 adjourned.)

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