# *ACTTION - CONCEPPT MEETING ON SMALL FIBER NEUROPATHY*

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*April 5, 2018*

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*A Matter of Record*
*(301) 890-4188*

ACTTION

CONCEPPT MEETING ON

SMALL FIBER NEUROPATHY

Thursday, April 5, 2018

8:05 a.m. to 4:17 p.m.

Westin Georgetown

Washington, DC



C O N T E N T S





C O N T E N T S (continued)





P R O C E E D I N G S

(8:05 a.m.)

Welcome

DR. FREEMAN: Good morning, everybody. It's an experience for me to be at a meeting and have the audience filled with so many good friends. So it really is wonderful to be here today. This is the CONCEPPT Meeting on Small Fiber Neuropathy, and to get the proceedings going, I would like to introduce Bob Dworkin, who is professor of neurology, professor of psychiatry, and professor of anesthesiology and perioperative medicine at the University of Rochester. He also is the director of ACTTION under whose auspices CONCEPPT falls.

Sometime ago, at a meeting like this, maybe less than a year ago, I introduced him as the president of ACTTION, and he got very testy about it.

(Laughter.)

DR. FREEMAN: For me, it was really surprising because I couldn't imagine why anybody at a meeting in Washington would not want to be

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

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

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

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

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

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

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

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

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

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

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

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

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

Finally, the present meeting, and Simon

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

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

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

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

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

Is idiopathic peripheral neuropathy

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compatible with impaired glucose tolerance or are these two different entities? As we've learned, we will talk about the various polymorphisms or even inherited disorders for Reye's disease that are associated with small fiber neuropathy.

Do we consider a patient with a sodium channel polymorphism as having idiopathic small fiber neuropathy or is this a new discrete entity and we should no longer consider this small fiber neuropathy? And what about a patient who had a potential cause of a small fiber neuropathy? For example, B12 deficiency. It was treated a number of years ago. Can a patient like this enter a clinical trial? Is this an idiopathic small fiber neuropathy or are patients like that excluded from clinical trials?

We have now entered the molecular era with small fiber neuropathy, and a question that must be asked is, is it obligatory now in this era to genotype every patient that enters a small fiber neuropathy trial? Do we need, in conducting a clinical trial, to balance or stratify

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randomization based on the genotype? What are the therapeutic implications? Are different drugs going to work or not work in patients who have different genotypes?

How do we tie the beautiful, elegant work that comes from the Netherlands, comes from Italy, with this study that was done from the PNRR? It's a different methodology. It's a registry study, but is discordant with the results that come from Italy, and I'm sure this will be an area of Italy and the Netherlands. I'm sure this will be an area of discussion.

All of us in the field have been challenged by patients who appear in our clinics either having been treated, or on treatment, or desirous of treatment with immunomodulating therapy, and we will be addressing the question is there an immune-mediated small fiber neuropathy. If so, what is the clinical phenotype? Are there biomarkers, diagnostic biomarkers, for this disorder? Are there predictives of treatment response for this disorder? And we have a number

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of experts in the audience who will be discussing this.

Finally, or almost finally, we have a number of questionnaires in various stages of development. Some of these may be screening questionnaires, some of these may be diagnostic questionnaires, some of these may be phenotype-defining questionnaires, and these will be discussed as well.

One of the important questions is do we in these clinical trials need disease-specific questionnaires or are the general sensory pain questionnaires, autonomic questionnaires, sufficient at this point in time? And in terms of thinking of the framework, this is a very important part of the framework.

The focus of the meeting is going to be on inclusion criteria, and one of the important questions with inclusion criteria is, is a skin biopsy actually necessary for inclusion enrollment in a clinical trial? Now, all of us in the field are totally aware that this is a benign procedure. Many in the audience have pockmark legs from

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repeated skin biopsies --

(Laughter.)

DR. FREEMAN: -- and are very aware that this is, as we say in the field, a benign procedure. However, there is the consensus out there that somewhere between a liver transplant and a heart transplant lies a skin biopsy --

(Laughter.)

DR. FREEMAN: -- and we have members of industry in the audience, and it is a barrier to clinical trial inclusion. And there's no doubt that those who are in the drug development business would love it if we could say, well, this is a very reasonable substitute for skin biopsy. And indeed, Giuseppe Lauria, who is sitting at the back very quietly, in his disease-defining criteria said two of the following three, and only one of those three was skin biopsy. So it is using those very widely used criteria to define small fiber neuropathy possible to exclude skin biopsy. But if we decide that skin biopsy is objective and it is obligatory, can it be done by everybody?

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Now, as I mentioned, there are many laboratories around the country, widespread availability of skin biopsies, to assess intraepidermal nerve fiber density. Is one laboratory the same as another? And what about the patient in a clinical trial who had intraepidermal nerve fiber density assessed 6 months ago, 1 year ago, 2 years ago? When is the cutoff? When has too much time elapsed since the last biopsy?

What about QST? Is QST in there, another one of the criteria that is used very frequently in clinical trials, or in cohort studies, intervention studies? Is QST necessary? Not everybody has the $30,000 computer-aided QST equipment. Can one just use a structured clinical examination for small fiber neuropathy or even just a structured clinical examination in general, or just a clinical examination?

What about bedside QST? My group and a number of the groups have attempted to come up with a simple, quantified sensory examination using very simple equipment that can, perhaps for those who do

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not have the $30,000 equipment, allow them to do that quantitative sensory testing.

Autonomic testing. David Herrmann has published two articles on autonomic testing or autonomic test results as criteria for small fiber neuropathy, and conclusions of this work are that this is the holy grail. It increases sensitivity without decreasing specificity. Is this something that we should be more insistent of including in the diagnostic criteria for small fiber neuropathy? And the new kid on the block, corneal confocal microscopy, where does this fit in? How do we use it as inclusion and exclusion criteria?

How about the exclusion criteria? And I'll touch on just two of them. Nerve conductions studies, again thinking of those people that are in the business of drug development. Does every patient who enters a small fiber neuropathy clinical trial need to have nerve conduction studies in order to exclude any large fiber dysfunction?

Again, referring to Giuseppe's criteria,

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they were quite fitting with his character, very hard-nosed, rigid, and in those criteria excluded all signs and all features of large fiber neuropathy, including the necessity of having nerve conduction studies being normal. Nerve conduction studies, for those who are not in the field, of course only assess large fibers. And what about on the clinical examination? Do we permit in a clinical trial any large fiber dysfunction?

Well, there's more than enough to talk about. As I present all of this, I'm not sure that we are going to have nearly enough time, but we will of course do the best we can.

Let me, before getting things underway, give some housekeeping rules. The usual, keep your cell phones quiet. Microphones are voice activating. Please speak directly in the microphone. State your name before speaking. This is kind of important. The meeting is going to be recorded, and there will be a transcription, which will help us write the paper or papers afterwards, so please, the people transcribing will not recognize voices,

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accents, so please state your name, and we will remind you as the meeting goes on.

Sign in if you haven't done so. Lunch is in the Dupont Room, the conference level. You see the internet access code. Restrooms are located outside of the meeting room to the left. And Valorie and team -- who have done a fantastic job, and just in case I don't thank them at the end of the meeting, I think we all recognize what a wonderful job they've done so far -- they are available for assistance at the registration desk.

Well, that's all I have to say at this point. One last thing to say. For those of you who have not been at meetings like this before, they are highly interactive. There is no firewall between the audience, the panel, and the speakers. Everybody is expected to -- it's part of the price of entry -- participate very actively no matter where you are sitting in the room.

So we expect a very exciting and interactive meeting, which then brings me to the first speaker of the day, which is going to be Rob Singleton, who

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

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

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

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

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

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

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

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

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

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

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

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

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

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combination of direct and indirect costs.

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

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

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

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shown with each feature of metabolic syndrome broken out, then comes the same thing that there is this increased risk.

A second line of evidence comes from looking at patients who actually have diabetes, examining the features of metabolic syndrome and seeing how those contribute to risk for neuropathy. In the neuro-diab studies of type 1 diabetics, this looked at patients who had type 1 diabetes, followed them for up to 7 years, and then by doing an analysis that took out age and glucose control looked at other features of metabolic syndrome in order to look at the relative risk for developing new neuropathy in those type 1 diabetes patients. You can see that each feature of metabolic syndrome add some increased risk to the development of neuropathy over this period of time for this carefully performed study.

We've done kind of the same thing in a much better characterized group of patients with diabetes. We've taken patients, about 225 patients, with diabetes and followed them, a third

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of whom had neuropathy at the beginning. We followed those patients for up to 8 years in order to see how features of metabolic syndrome influenced risk for development of neuropathy and progression of neuropathy. Here again, you can see that these features of metabolic syndrome are predictive of progression of neuropathy and the presence of neuropathy independent of glucose control.

I guess a last area of epidemiologic data comes from looking at treatment. So if you intervene in patients who have diabetes or pre-diabetes, does that make some difference to their neuropathy and to their neuropathy risk? The STENO 2 trial is one of the largest studies that took a comprehensive approach to control of metabolic syndrome risk factors in type 2 diabetic patients and found that there was a reduction in risk primarily for cardiovascular endpoints, but there is a little bit of microvascular data, including some autonomic testing that suggests an effect on peripheral nerves and on small fiber

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nerves.

I would be remiss if I didn't at least point out that we now have a really rich set of animal models that recapitulate the clinical features of small fiber neuropathy in the period of metabolic syndrome before diabetes, and these can be used both to characterize that neuropathy, to look at the biology of those small fibers, and to show that if you intervene by changing the biology, the metabolism in these mice, you can have an influence on the severity of neuropathy on the progression to neuropathy for these rodents. I think these models are good enough now that they have the opportunity to serve as a real translational entry way to human treatments and how we use them.

The most specific and the least convincing, I think, of thee epidemiologic mechanisms or epidemiologic studies for prediabetic metabolic syndrome is to look at patients who have these different aspects of glucose control and directly measure how many of them have small fiber neuropathy. Dan Ziegler has probably done this

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best in my mind. He looked at 200 controls in 200 patients with various levels of abnormal glucose control and found that there was an excess number of patients who had both neuropathy and also neuropathic pain as patients stepped from controls to diabetes.

A much larger study done by Brian Callaghan looked at 2400 patients in the Health ABC study and found that, basically, each additional factor of metabolic syndrome added about 1 percent to your risk for neuropathy.

I think Roy's CONCEPPT meeting in December really helped us to begin addressing how we should consider patients with prediabetes. As Roy mentioned, we came to the understanding that we should talk about this as an association. It's I think one of multiple risks for small fiber neuropathy that should be considered when considering the cause of neuropathy in these patients.

Moving on to type 1 diabetes, this is the much less common cause of neuropathy, but still

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probably 400,000 patients in the United States have a small fiber neuropathy associated with their type 1 diabetes.

I just want to put in a plug here for the rare but perhaps underrecognized treatment-induced neuropathy in diabetes that Chris Gibbons and Roy Freeman have helped us to recognize in patients who have diabetes and have too rapid a correction of their hyperglycemia.

Now I'm going to get into neuropathies that clearly are associated with small fiber injury, which have a different distribution across the world, which I think need to be recognized as important causes globally but challenging targets for treatment.

Neuropathy associated with HIV infection, the overall prevalence is about 0.8 percent across the world. Different studies found a widely disparate frequency of neuropathy associated with HIV from 9 to more than 60 percent of patients. Risk factors are ones very similar to diabetes and pre-diabetes in the sense that duration of HIV and

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older age predicts the development of small fiber neuropathy in these patients.

We're kind of working our way in order of prevalence, and this is quite a diverse list. But chemotherapy-induced polyneuropathy is a surprisingly common cause of painful small fiber neuropathy. It's very difficult, I think, to get at the true prevalence of this disease because it's complicated. The best estimates are that 485 out of every 100,000 patients will have new -- or people will have new cancer diagnosis in a given year; 171 of those patients in any given year. So there's some residual survivors who make up the prevalence, and that number varies widely. It might be as much as 5 percent of the population who are cancer survivors in this setting.

Roughly 20 percent of patients who have cancer have a cancer that's treated with chemotherapy that may be neurotoxic. So you take that number and then work partly from Noah Kolb that looks at the frequency of neuropathy in patients who received chemotherapy. That number is

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surprisingly high, 40 to 50 percent of patients. So that gets us to this overall burden of perhaps a million patients who are at risk for small fiber neuropathy associated with their chemotherapy over time.

Hepatitis -- this is B, but C as well -- has a significant burden of illness, about 230,000 patients in the United States. Leprosy, just to illustrate a disease that has a dramatic difference across the world as a risk, there was a time when we talked about leprosy as the most common cause of neuropathy in the world. Those days are gone.

Recognize -- it's kind of hard to read here -- the risk across countries is spectacularly different, according to your exposure. In the United States, that risk really is on the order of less than 10 cases per 100,000, and most of those are immigrants in the United States, rare cases of international travel, and then there is beginning to be an indigenous risk for leprosy that comes from armadillos, that I discovered as I read about this, so Texas, be cautious. Clearly, 90 percent

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of patients who have leprosy express a neuropathy. One of the challenges is knowing for any given illness how frequently neuropathy occurs in that illness.

The talk really after mine is about the genetics of small fiber neuropathy, so I'm going to touch very lightly on these topics. At least for hereditary sensory and autonomic neuropathies, these are super rare, but there has been increasing interest in sodium channelopathies. And we're going to hear a lot about this I think in the next couple hours, so I'm not going to talk much about it, except to just point out that this is an example of how difficult it is to get a true prevalence for these genetic disorders.

Nav 1.7 coded genetic defects are the cause for some extremely rare gain-of-function neuropathies, including the scarily named paroxysmal extreme pain disorder. If you want to pick something you don't want to have, this is probably it. And loss of function causes insensitivity to pain in some patients.

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

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

DR. FABER: That's okay.

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

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

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

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

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

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

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

DR. FABER: Temperature threshold testing.

DR. FELDMAN: Thermal threshold, so --

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

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

DR. SINGLETON: That's right.

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

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

DR. FELDMAN: Right.

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

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

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

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

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come in the door have that much more often. So I think we just have to be very cautious about how referral bias affects our evaluation of the epidemiology.

DR. FABER: Again, I add one thing, and that's we hardly find any diabetics because they are not referred to us, so that's very simple.

DR. SINGLETON: Exactly.

DR. FABER If they have a small fiber neuropathy, they're not going to send them to our center, so we cannot state anything about diabetic small fiber neuropathy in these patients.

DR. SINGLETON: Right. And I'm not in any way criticizing this. I think that that's beautiful work. But I think when we review the literature in order to think about the population prevalence or the epidemiology of these small fiber neuropathies, we can't rely too heavily on the data that comes from very careful evaluation in tertiary care centers because it gives us a false idea about those prevalences.

DR. FABER: I do think what you can say is

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which tests are useful. If you find a patient with a small fiber neuropathy, for example, you can steal that out of these data. So some tests are not useful or do not give any additional information, and then you can leave it out. For example, testing for Fabry's disease is useless if you don't have any other signs compatible with Fabry. You will never find it.

DR. SINGLETON: Dr. Smith and I have done that same sort of analysis, but just less beautifully than you, in examining the utility of different tests. And I think that should inform our decisions about inclusion criteria.

Yes, Dr. Oaklander?

DR. PELTIER: And it really depends on what the cause is. It's Amanda.

DR. SINGLETON: You have to raise your hand if you want to talk.

DR. PELTIER: But it really depends on the cause of neuropathy because, for example, sudomotor testing is very sensitive in diabetic and glycemic related tests and HIV, but not very good with

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idiopathic sensory predominant small fiber neuropathy. So it really depends on your etiology, what you're thinking of as to what tests you should include.

DR. SINGLETON: I agree. Thank you. That's an important concept. I think one goal we should have is to consider tests that have the opportunity to be sensitive across causes of small fiber neuropathy.

Dr. Oaklander?

DR. OAKLANDER: So in our paper on this topic, which I think was in 2016, we pulled in the cost data. And I think it was called -- what was it called? I forget. But the point is we're all scientists, and we're all excited by these obscure diseases, but it's naive not to include cost considerations. So we went and actually tracked down the reimbursement codes for these diagnostic tests. For instance, diabetes neuropathy alone, which we all agree is a huge thing, what's the relative value of 2-hour GGT versus fasting alone versus A1c versus random?

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So let's consider cost more in our discussion for value as well.

DR. SINGLETON: Yes, Gordon?

DR. SMITH: I just want to amplify that. Brian Callaghan has done I think really beautiful work looking at healthcare utilization surrounding neuropathy diagnosis. And it turns out that drivers and the large data sets are really things that we're not going to even talk about today, which are MRI scans, brain MRI scans for small fiber neuropathy, which I think we can agree we don't need. So maybe that's our first consensus.

I think when we start thinking about do we need normal nerve conduction studies, do we require skin biopsy and these sorts of things, I think it's really important to differentiate the need in a clinical trial setting versus common clinical practice because those things really do cumulatively drive healthcare testing costs for neuropathy evaluation.

DR. SINGLETON: Just to finish the things I had to say, this represents, for these diseases, my

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

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

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

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

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

We need prospective studies that follow patients with small fiber neuropathy and other common neuropathies to see whether there's a difference in fate or response to treatment if you have a painful or non-painful neuropathy. And then we need additional studies that look at patients with idiopathic neuropathy to discover the importance of sodium channelopathies and other genetic influences on neuropathy because almost certainly, a significant portion of patients who have idiopathic neuropathy now have a genetic influence that we just haven't recognized yet.

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

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

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

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

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

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

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

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Now the course is oversubscribed. We haven't resolved the issue of definition quite yet, but I think this is a critical point, and perhaps we need to begin to refine the way we talk about this, the way we write about it, and the way we think about this. And obviously, every clinical trial will need to do this, and I think it's an important focus. And hopefully by the end of the meeting, we will have come away with more discrete criteria for differentiating those different parts of the small fiber neuropathy spectrum.

DR. SINGLETON: Chris?

DR. GIBBONS: I think the point that Gordon raised is perfect, and I actually want to throw out another disease we don't even actually talk about, Parkinson's disease. We see this really small fiber neuropathy that's totally asymptomatic, quite frequently if you look for it, but we don't talk about it. So just kind of, again, keeping that theme going.

DR. SINGLETON: Again, reviewing this literature, there is fairly convincing evidence

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that patients with Lou Gehrig's disease have a decrease in their nerve fiber density. Should w consider that small fiber neuropathy? I think not, but the harder you look --

MALE VOICE: That's for diabetes --

DR. SINGLETON: -- the more people you include.

DR. OAKLANDER: It's up to us. The field needs guidelines, and we're the people.

DR. SINGLETON: That's right.

Yes, Dr. Herrmann?

DR. HERRMANN: I think another issue I would say is the issue of age. When people get 75, 80, 85, I think it gets harder and harder. We always sort of dance around the issue of neuropathy of aging versus just normal findings for age. And I think at a certain point, in terms of clinical trial design, I think at a certain point everyone's losing small fibers. So if you have a density of X at age 83, we call that maybe normal for age, but a person who's 20 years younger has neuropathy.

I think thinking about how to think about

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the older individual with small fiber signs and abnormal skin biopsies I think will be important because at some stage we may want to exclude people above a certain age because I'm not sure we can really define a small fiber neuropathy entity in those patients well and distinguish that from normal aging.

DR. SINGLETON: I agree. But one thing I would say is a crucial piece of our definition needs to be clinical impact; that is you need to have symptoms. You need to complain of those symptoms. You need to have some consequence for your function. If you don't have those things, then I don't think that's neuropathy.

Okay. Roy looks like he might want me to stop talking.

(Laughter.)

DR. SINGLETON: Thank you, Roy.

(Applause.)_

DR. SINGLETON: So a couple of things. There will be plenty of time for questions. There's a one-hour panel, so if you still have

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questions to ask Rob, and if Rob still wants to keep talking, he'll have another round.

It's a pleasure to introduce Karin Faber from Maastricht Netherlands, who, as you've heard several times already this morning, allowed the field to take a giant step forward by defining, together with the group from Milan and the group from Yale, the molecular biology that underpins some patients who previously we thought, or perhaps still have thought, of as having small fiber neuropathy; and specifically by defining gain-of-function mutations in Nav 1.7, and then later 8 and 9. And it's wonderful to have Karin here.

Presentation - Karin Faber

DR. FABER: Thank you very much, Roy. It's a big honor to be invited here and to talk here about the genetics of small fiber neuropathy. And as Roy already pointed out to me, the most important thing is whether we should include genetics or not. So if I would answer this, then I would be on very quickly, but I will talk a little

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bit more about a background as well. I don't have any conflict of interest, but we have some grants from the European Union and also from a national foundation on neuromuscular research, and I'm on an advisory board for Biogen, Vertex, and Chromocell.

A small fiber neuropathy, as you already heard, is a disorder in which the small nerve fibers, the A delta and the C fibers, are affected. And you can have a lot of debate, so far as clear from the discussion we had, whether this is pure small fiber neuropathy or whether you should have predominantly small fiber neuropathy. And this leads to often very severe pain in combination with autonomic symptoms.

There are a lot of conditions, as Rob already told, that can be associated with small fiber neuropathy, and associated does not necessarily mean it causes neuropathy; that might be something different. But indeed, the list is growing and growing like in our peripheral neuropathies. When we started working on small fiber neuropathy, we thought, well, how does it

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come that all these patients have the same symptoms and so many underlying conditions or causes could have been some kind of -- well, one pathophysiological pathway?

That's when we started looking into the sodium channels, and the sodium channels seemed a logical way to go. You know that the first description of a locus on chromosome 2 was in 2001 for primary erythromelalgia, and then in 2004, the gene SCN9A coding for the Nav 1.7 was discovered in primary erythromelalgia. And later in the same year, also the electrophysiological properties were described by the lab of Steve Waxman.

In 2006, also mutations in SCN9A were described in paroxysmal extreme pain syndrome, which is another painful disorder. That's when we thought, well, maybe this could also play a role in small fiber neuropathy, and we included patients with the typical clinical picture of small fiber neuropathy in combination with an abnormal temperature threshold testing, as well as an abnormal skin biopsy. So those were very strict

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criteria for patients with idiopathic small fiber neuropathy. And indeed, in a number of these patients, we found a mutation in SCN9A.

The electrophysiological properties in these mutations were described. And as you may know, but I'm not sure whether everybody knows, you can test electrophysiology using patch clamp analysis, and there are two ways of doing this. You can have a voltage clamp analyze this, and that's testing the channel function, so meaning you test depolarization, repolarization, and inactivation. And you can also use the current clamp analysis, and with this you test the excitability of the channel. So it means that the resting membrane potential can change, or the current threshold can change, or you can have an increased spontaneous firing or an increased firing frequency.

Indeed what we saw was that in these patients you saw abnormalities in electrophysiological properties, so there was an impaired slow inactivation. For example, in this mutation, you can see that in C, the current

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threshold was lowered and also the resting membrane potential was different, meaning the potential was more depolarized. And in F, you can see that the firing frequency is higher in the patient with the mutation, and also there's more spontaneous firing compared to the wild-type channel.

This is another family, and this family taught us a lot, and that's why I'm showing this. It's a family in which we saw the proband, and you see a picture of him here. And he showed complaints compatible with erythromelalgia, so red hands and feet, extremely painful, but he also had severe autonomic symptoms, which is not compatible with erythromelalgia but more with small fiber neuropathy. And he also had very small hands and feet and also legs and arms.

You can believe it or not, but these are also normative values for your hands and arms and whatever part of your body you can think of, and this was really abnormal. Then his father and other brother, also affected, had the same clinical phenotype, including the small hands and feet,

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while his unaffected brother and mother did not have any symptoms. We now know that he has two daughters that are now 5 and 7 years old. They have the same mutation, and they also have the same clinical phenotype, including pain.

This is the electrophysiology of this patient, and you can see there are marked differences with the wild-type channel. I'll come to this mutation later on to show you something else that is important.

SCN9A is also associated with a lot of function mutation, meaning that these patients have a congenital inability to experience pain. This may sound fantastic, but it leads to severe problems, I think even worse than the hyperexcitability.

The Nav 1.7 channel consists of alpha subunit and one or more beta subunits. It is preferentially expressed in dorsal root ganglia and sympathetic ganglia neurons and their actions. It is encoded by the SCN9A. Now compiling this, you can say, well, you have the wild-type channel

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that's on the right, and then you have the loss-of-function mutation that's a widespread mutation, and the channel function is absent.

In small fiber neuropathy, what we see is gain of function. These mutations are located in domain 1 and 2, and they show an impaired inactivation. If you have the patients of the family with the G856D, the small hands and feet, they have also an impaired inactivation but also an increased opening of the channel. In primary erythromelalgia, you can also see the mutations in domain 1 and 2, and they have an increased opening and an impaired deactivation and paroxysmal extreme pain disorder. There's also a gain of function, and these are mainly located in domains 3 and 4, and there's impaired fast inactivation.

This may seem very clear. You have distinct groups, but of course, unfortunately, it's not always like this. So what we see is that it is more or less like a spectrum. The paroxysmal extreme pain disorder is at one end of the spectrum, but especially for the small fiber

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neuropathy and the primary erythromelalgia, we see patients that have an overlapped syndrome between the two. The gain-of-function mutation is important in that these are missense mutations, and it is an autosomal dominance inheritance. And the loss-of-function mutations can be nonsense, a frame-shift or splice-site mutations, and these are autosomal recessive inherited.

Now that we know a lot about these mutations, we also realize that there's a lot that we don't know. For example, there is large phenotypic diversity. For example, the I228 mutation is a mutation in which patients within the same family have a very distinct phenotype. For example, one brother and one sister. The first started with pain in the face and the other with more distal pain, more like a picture that we know of the lengthy pain in neuropathy. And also another patient, there's pain on the scalp, and both had the same mutations.

We were able to find also hyperexcitability -- not we, but the lab of Steve

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Waxman -- in the trigeminal neurons. With that, you can explain it, but we don't know why one patient has one phenotype and the other has the other phenotype. So that's still not completely clear.

We also know that there is a variable expression of the mutation. Some patients have severe autonomic symptoms, while others have hardly any autonomic symptoms. This was nicely demonstrated also with electrophysiology, but we simply do not know why some mutations do cause autonomic symptoms and others do not.

Then these mutations are partly penetrant. There's a large variation in age of onset of symptoms, so some are very young but there are also patients that exhibit symptoms after they are 40, or 50, or 60, and some may even not have any symptoms at all. We don't know at this point. We simply don't know what is the cause of this.

Also, if you look, for example, the first mutation, that was one of the mutations that was described in the Annals paper, and you can see that

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the frequency in our SFN cohort is very low, and also for the other mutation, it is higher than in the general population. But we don't know exactly how this is working, and one can argue, well, are these disease-contributing variants or are these risk factors? And I will come to this later on in the presentation. What we know is that also in the lab of Steve, they did testing on neurite outgrowth, and what they saw is, especially in the I228M mutation, so the second one, there was a reduction in neurite outgrowth.

If you treat these cells with a sodium channel blocker carbamezapine, you can see that the neurite outgrowth turns back to normal. So this is reversible, and the same is true when you inhibit the sodium calcium exchange. What is very important is, for example, in this G856D -- this is also published -- if you have these cells in culture for 18 days, you don't see axonal degenerations. So that's figure A and B.

DR. FELDMAN: I was going to say what cells? I was asking --

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DR. FABER: It's A and B. So A is the wild type and on B is the mutated channel.

If you then depolarize these cells for 4 days, that's C and D, you don't see anything happening. So there's no axonal degeneration. If you cause metabolic stress by impairing glycolysis, that's E and F, you don't see anything also for 4 days. If you combine it, then you can see that in the patients with the G856D mutation, or in the channels, you see marked axonal degeneration.

So it means that the mutation in itself does not cause in this experiment axonal degeneration, but it is pathogenic. It contributes to axonal degeneration given certain circumstances. So it may be that you call it a risk factor. It may be that you call it a multi-hit model or whatever, but there is something going on.

What is really important is that we realize that not every variant we see is contributing to the disease. You have to be very careful by stating that every variant is pathogenic because it's not, and that requires a very thorough workup,

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including the functional analysis, in silico testing. But in silico testing on its own is not enough I think, so you have to have a good family history, if possible; the functional testing, good clinical phenotyping. All these things are really important.

To make things even more complicated, there are also polymorphisms that are quite frequent, some of them, that also have an influence on the channel function, and these probably influence pain perception; so not being pathogenic, but it can also have an influence.

We also described gain-of-function mutations in Nav 1.8 and Nav 1.9 that also contribute to small fiber neuropathy. Of course there may be other genes. I thought this may be important because there was already discussion on the frequency of mutations, et cetera. In our own group of over 1500 patients, we have 1140 patients with a pure small fiber neuropathy, and we found patients with potential pathogenic mutation in SCN9A, 10A and 11A between 10 and 15 percent, and

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that's quite constant over the years now. The first publication was a very small group, but this is quite constant.

We also studied the PROPANE study of which Giuseppe Lauria is the coordinator, looking at the role of sodium channels in painful small fiber neuropathy but also in diabetic neuropathy. I think important here is that you can see that these percentages are more or less the same a s in our own population, which is much larger, but you can also see that there's a difference between the painful diabetic neuropathy and the idiopathic small fiber neuropathy. And this means that you cannot simply say that these are the same. I think these are distinct groups and that you need to look at them separately.

This is also underlined by this paper that was already discussed in which 278 idiopathic neuropathy, of which partly was painful, and diabetic neuropathy also 77 percent painful, and the number of gain-of-function mutations was extremely low, and there were no differences

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between painful and non-painful groups in the previously reported gain-of-function mutation. This means that painful neuropathy is not the same as painful diabetic neuropathy, and it's also not the same as idiopathic small fiber neuropathy, the genetic meaning anyway.

From the same PROPANE study, this is a work in progress. If we go to the group that we have now analyzed, the German painful diabetic neuropathy population, you can see that we found 51 variants that were unique for the painful phenotype. This needs to be further analyzed, but there are differences between the painful and the non-painful group.

Of course this leads to a lot of questions that remain unanswered. For example, the penetrant is caused by a difference in genetic background; what are really causes and what are contributors or risk factors, and what is the role of mutations in other genes or the genetic background? Is there a role for sodium channels in other painful neuropathies? We simply do not know at this point,

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or maybe if other genes and also of course therapeutic options. We do know that sodium channels play a role in small fiber neuropathy, and that it is important to make the diagnosis based on an integrated approach and that other genes or the genetic background might play an important role, and this may also be key to targeted treatment.

My main assignment was, well, what do we do with this in terms of trial design? At this point, I think there are too many questions open to say, well, you have to analyze only patients with this mutation or that mutation. Should you include gene mutations in the trial design, it really depends on the kind of trial you are aiming for.

For example, if you want to do a sodium channel blocker in a trial, it makes sense to do a secondary subgroup analysis on patients with mutations and patients without a mutation. For other trials, it doesn't make any sense at this point I think to do that, and there is so much more that we need to know before we can do any really strong suggestions regarding this.

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DR. FREEMAN: Thanks. Thank you very much.

(Applause.)

DR. FREEMAN: Any questions for Karin right now? Just know that there will be time [inaudible - off mic].

DR. UCEYLER: Karin, thanks for this very nice talk. Just to come back to the numbers you gave about the prevalence of mutations in your large group of patients with small fiber neuropathy, one that you showed with 1,000 and more patients, did I get it right? It is around 10 to 15 percent you would say that are positive.

These are sodium channel mutations?

DR. FABER: Yes.

DR. UCEYLER: All of them, and not other --

DR. FABER: No. These are only the sodium channel mutations.

DR. UCEYLER: Okay. That's very interesting. We also are looking at the genetics in our patients in the last years. For instance, in a group of around 60 patients, I would have maybe 4 to 5 with a mutation. One of those would

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be sodium channel and 3 to 4 really other genes, which is also important not only to focus on the sodium channels. But this is really all sodium channel, right.

DR. FABER: The analysis for the other genes that we are testing is following.

DR. UCEYLER: If I may add another short comment, coming back to your paper you presented in 2012, the Annals paper, very beautiful, where you had a higher number and where you had selected the patients. So these were those who had reduced further density and pathological QST, right, and had all sodium channel mutations.

This is very interesting. In our hands, interestingly, those with the channel mutations are mostly those who have normal fiber density and also normal QST when we use the DFNS criteria, which I always find very logical because you have the mutation. In the neuron, the exaggerability changes. Why should fiber density change, and why should thermal perception change? But very interesting, and I think something to be discussed

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

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

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

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

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

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

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

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

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450 subjects that was distributed across all three sodium channels. The idea was to look at rare mutations. Most of these coding variants resulted in amino acid changes in all three groups. And one of the things that came out of this study was that these rare mutations, some of the patients actually had multiple mutations; that they're not just unique to one patient that only has mutation Nav 1.7 but not the others. We had one patient that had rare mutation in all three of them, actually disease-causing mutations. They looked carefully at these variants, and basically they were distributed across the whole protein domains. And again, these are all considered the rare mutations that are less than 5 percent in the general population.

Let me go back. Four of these rare mutations were actually reported as the gain-of-function mutation that Karin also mentioned, [indiscernible] change in others.

When you look at these, quote/unquote, "know gain-of-function" mutations across the whole

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population, it was present only in about 3 percent of the cohort that we had. These were primarily in Nav .7, partly because that's where most of the publications have been. Even though I mentioned that there are some patients who had complex mutations with multiple -- most of the patients in the cohort had single, rare variants in the Nav .7 They then compared these non-synonymous, low-frequency variants to reference populations, and they were very similar, and again, similar results with the other sodium channel mutations. I think this is where perhaps the data from this cohort differs from Karin's and maybe Giuseppe's data set. These mutations were similar to the general population. The only one that was different was that in the Nav .17 [ph] mutations, the frequency was slightly higher than the reference populations.

Then they looked at the enrichment of these rare Nav mutations in painful versus non-painful categories. And again, this was basically patient-reported classification, so in the patient

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history questionnaire, the patients are asked about their pain status, and if they said no pain, then they're considered non-painful neuropathy. There was no enrichment across all three Nav channels.

Within the idiopathic neuropathy patient population, looking to see if there was any enrichment, again, there was no enrichment in this cohort of idiopathic peripheral neuropathy patients. Again, looking at the rare and missense mutations in the idiopathic small fiber neuropathy patient -- this is a subpopulation of the idiopathic peripheral neuropathy patients, and again, there is no enrichment.

Then they looked at the haplotype groups across all three genes, and again, they didn't see any enrichment in painful versus non-painful neuropathy, and there was no difference in comparison to the reference population. And again, there was no enrichment in the idiopathic subgroup.

In summary, this data set didn't really show any enrichment in the U.S. population of these rare gain-of-function mutations or even other rare

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mutations in either idiopathic neuropathy patients or in idiopathic painful neuropathy patients. So based on this, I know BMS basically stopped their Nav channel inhibitor program perhaps partly based on these results.

It's going to be interesting how this plays out, whether these are really druggable targets or not. The data from families is very convincing, but whether it's in the general population and are there other modifiers that make these more disease relevant will need to be seen. I'll stop. I think this is my last slide.

Amanda?

DR. PELTIER: As part of your study, did you have a chance to collect DNA from any of the family members of the patients to figure out whether or not those variants were -- I mean --

DR. HOKE: That's a very good question. As part of the --

DR. PELTIER: You've been hanging out with Jim [indiscernible] for too long.

DR. HOKE: -- we're not collecting blood

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from the family members. As I was listening to Karin's talk, I was thinking actually if we could go back to the patients that have been identified in this cohort with the gain-of-function mutations and look at the family members -- obviously, I need to write a separate [indiscernible] before that.

(Laughter.)

DR. FREEMAN: Can I ask something? This is just [inaudible - off mic] -- carefully done study as Karin and others have done and a registry study.

MALE VOICE: Roy, mic.

DR. FREEMAN: Okay. What I was saying is there's an enormous difference between a registry study and a very carefully study done by academic centers who are devoted to a study. But even so, looking at the data you showed -- and I think it was four slides back, how many subjects of the 440 or so do you think came very close to replicating the kind of patients that they have reported? And it looked to me like there were only 10 on the slide that you showed.

So what I'm asking is patients who had a

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pure small fiber neuropathy, normal nerve conduction studies, no large fiber modality dysfunction, abnormal skin biopsy, and some other measure or some other criterion for small fiber neuropathy.

DR. HOKE: Can you put the slides back? I just want to go back to the --

DR. FREEMAN: It's about three slides back, the slide that prompted the question.

DR. HOKE: Within the idiopathic -- yes. The pure small fiber neuropathy patients in this cohort is probably smaller than the reports of -- like Karin's large study with just a pure thousand patients with small fiber neuropathy.

DR. FREEMAN: There are many reasons why there might be differences. I wondered whether one of them might be a type 2 error.

DR. HOKE: Possible. We're looking at all-comers of idiopathic neuropathy patients and all-comers of diabetic neuropathy patients. That was BMS' interest, do you want to treat the tiniest population versus is this really applicable to the

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large patient population of painful neuropathies across different etiologies. That was the main reasons for this study.

DR. FREEMAN: David?

DR. HERRMANN: I do think, though, this probably speaks to differences in genetic background because I know at our center, we have, over the last maybe 5, 6, 7 years -- since next-generation sequencing has been available, we've taken every patient who's been younger with an early onset neuropathy, pure small fiber, normal medial plantars, normal surals, and with a clinical syndrome with or without the abnormal fiber density, and I've not found one pathogenic mutation in the sodium channels.

So clearly, these patients and families are there, but I think what you'd probably could do to supplement your numbers of pure small fiber neuropathies -- across several centers in the United States that have been doing similarly -- you could probably aggregate some of the data to get a larger number of patients who really match the

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European experience. And it may just be that there are different genetic backgrounds that are at play here.

DR. FREEMAN: Karin?

DR. FABER: I think that one issue that is not mentioned, and it's very important, is you really have to look at your filtering criteria because if you select variants with a frequency of less than 5 percent, that's not a rare variant. I mean, that's really a big issue I think because we select variants that are less than 1 percent or even less than 0.1 percent. So if you're looking for rare variants, then those are rare variants, but 5 percent or 4 percent, that's not a rare variant. That's a frequent variant.

DR. HOKE: They looked at both -- the analysis was done both looking at those variants that are less than 5 percent plus the reported gain-of-function mutations from your papers. And even if you look at just those patient populations, the numbers were much smaller obviously, and there was really no enrichment in those mutations in

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

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

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the reality that the insurance companies do not agree with that statement.
DR. HOKE: I haven't had a single patient's genetic testing rejected. Cost to the patient is only a hundred books for doing whole exome sequencing.
DR. FELDMAN: We should really talk about that because we have many more insurance issues in Michigan.
DR. FREEMAN: I'm speechless after that comment.
(Laughter.)
DR. OAKLANDER: So who here has insurance issues with ordering genetic testing for neuropathy patients?
(Show of hands.)
FEMALE VOICE: Huge.
DR. OAKLANDER: Who has no insurance issues?
(Laughter.)
DR. OAKLANDER: So my point is we want global recommendations and we want to be useful in other --

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

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which means if you were to do the math, some people are logging on more than once on more than one device.

So what we request is one device, one person, if you can manage that, which is a democratic principle.

(Laughter.)

DR. FREEMAN: And having set that in motion and talking about voting more than once, let me introduce Todd Levine, who will be discussing I think one of the more controversial aspects of the meeting, and that is immune factors in small fiber neuropathy. I think probably there was some subliminal, subconscious aspect over here wanting to avoid all controversy, that I decided to skip this talk.

Todd, please?

Presentation - Todd Levine

DR. LEVINE: Well, thank you guys for having me today. This is really going to be a lot of small anecdotal case series because, unfortunately, we don't have any good trials. But I think we'll

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sort of highlight the fact that many of us here from our patients treating small fiber neuropathies with immunomodulatory therapy is something that they want. I think for the clinicians in the room, we are looking for those patients that we can help, so this is a group of patients that we really try to identify.

I think the beginning and the end of this, we'll sort of make the point as some of the earlier talks did, but I think unless we get accurate and smaller definitions of these disorders, we'll never really going to be able to find anything that works for the groups as a whole.

A couple of disclosures, I work, by consultants and from the grant support, with some of the IVIG companies, so Shire, Grifols, and CSL, and also with Octapharma and with NuFACTOR home infusion company. And then I have a financial interest in Corinthian Reference Lab, which provides skin biopsy testing.

We don't have great case series for small fiber neuropathies, in part because it depends on

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how you define it. So is it abnormal skin biopsies? Is it clinical? Is it QSTs? This is a paper from a few years ago that looked at mixed-fiber neuropathies both in South America, which is the column on the right, and North America on the left, and really kind of highlights the point that at least in North and South America among mixed fiber neuropathy, about 20 percent are probably immune-mediated. I think if you wanted to throw a dart at a board and said what percentage of small fiber patients are probably immune-mediated, 20 percent would probably be a good starting point because, again, we don't have great data.

The cryptogenic here is listed as only about a quarter of the cases in both groups, and then the hereditary varies probably depending on how you actually define inherited neuropathies, polymorphisms versus pathogenic mutations, but the number I kind of wanted to highlight is the 20 percent number.

That really kind of brings us to a broader question, which is what the hell is an

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immune-mediated neuropathy? And this is where we have a problem from square one. So I was going to actually just use this case to demonstrate that we don't even know what a neuropathy is or what an etiology of a neuropathy is.

There's a 62-year-old female, 25-year history of diabetes, 3-year history of neuropathic symptoms. So is that diabetic neuropathy? Probably. Well, what if they had gotten chemotherapy five years ago because she had breast cancer? What if her family history's got 3 first-degree relatives? Is that inherited or is that diabetic?

What if she took Levaquin 10 days before the symptoms began? Is that a toxic neuropathy or a diabetic neuropathy? Or are a lot of our neuropathies actually caused by multiple causes, which is what actually I would believe, and that we don't really know the etiology of any of these neuropathies? And this is as good as it gets, right? Twenty-five-year history of diabetes, that's as good as we can do. Now we're going to

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try to talk about immune neuropathies, and we're not going to do as well.

How do we define a neuropathy as potentially immune mediated? These are my thoughts, and I'm sure we could probably add to it. The first is a clinical presentation. So that would be the pornography analogy, right? You know it when you see it.

(Laughter.)

DR. LEVINE: That's fair. I mean, we're clinicians. That's what we're supposed to do. What about acute onset? So somebody who's fine and 2 days later, they've got diffused neuropathic pain everywhere, that seems to suggest that, but why couldn't that be toxic? We don't know that either.

When it comes to the mixed fiber neuropathies, we've relied a lot on electrophysiology, and we'll talk about that a little bit. That can be helpful. It can also be very misleading. And then in the mixed fiber neuropathies, we used to rely on pathology. So some of the earliest descriptions of CIDP from

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Peter Dyck's group was based on actually doing vesicular nerve biopsies and seeing the inflammation in the nerve.

Again, in some of the neuropathies, you have to look at changes in the CSF, C-elevated protein, and those kinds of abnormalities. More and more, we'd like to rely on the presence of neural autoantibodies, but we don't know the sensitivity or the specificity of those antibodies.

What about associated autoimmune diseases? We'll talk a bit about that. If a person's got Sjogren's, does that mean their neuropathy is from Sjogren's or is it an idiopathic neuropathy and they just happen to have Sjogren's?

The last one is the really challenging one. What about response to therapy? Can you define a neuropathy as immune mediated because they get better with IVIG or prednisone? Well, maybe, but what about the placebo effect? And I'll kind of show you a bit of that as well.

This is a paper, actually after a lot of attempts, I just got published. And I'll throw it

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out there and you guys can attack it during the open session if we want. But my first point is that I don't think we can call this small fiber neuropathy anymore. We heard that a little bit this morning. I like the idea of small fiber predominant neuropathy because all neuropathies that cause pain, the pain's mediated by the small fibers; we know that, or pure small fiber neuropathy.

But even within that, if you see enough of these patients, they look very different. So I've tried to propose that we break it out into four different groups. One is the small fiber sodium channel patients, so they have clear genetic defects in their sodium channels. They look very different than our other patients. You can identify them. They often have the erythromelalgia. Then you've got the small fiber mediated painful neuropathy patients. That's most of the patients we're sort of talking about. But that now really overlaps -- and I'll show you some data -- in this kind of more widespread pain

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disorder, so fibromyalgia for example. We know a significant percentage of those patients have small fiber dysfunction.

Glenn Lopate's group at Wash U presented patients that only have muscle cramps and no neuropathic symptoms, that have small fiber neuropathy. So all of those sort of lump together and I think need to be split out because I think their clinical differences are probably telling us something. And then you have autonomic dysfunction on the other end. And then the problem is these overlap in a variety of different ways with different Venn diagrams. So obviously, some patients with painful neuropathy also have the autonomic symptoms and vice versa, but not always, and that may be telling us something different about their pathology.

Let's start a little bit with the mixed fiber neuropathies. The classic immune neuropathy is Guillaine-Barre. We all accept this is an immune-mediated neuropathy. But the patient comes in a day after their symptoms begin. Their nerve

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conduction studies may be normal. Their CSF may be normal. If a patient was exposed to campylobacter, it may be axonal, so demyelinating and autoimmune are not synonymous. That's not the same process.

Most of the patients with Guillaine-Barre don't have identifiable autoantibodies. They don't have to have a preceding illness. So we make the diagnosis of Guillaine-Barre clinically. Again, we know it when we see it, and we treat it. Everybody accepts that fact. Right? They don't say, oh no, your nerve conduction studies are normal on day 2; you can't give that person IVIG. Clinically we know it because we see it.

So it makes it very difficult now when we start to go to other syndromes when we don't have quite as good a clinical course. So let's talk about small fiber neuropathies. Again, these are small series, I understand, but we'll talk about really good data to not so good data.

So your classic Guillaine-Barre patient shows up. You know it when you see it. Here are two patients that were presented this year.

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Patients had acute onset preceded by an infection, diffused hyperreflexia, albuminocytologic association. They got IVIG. One got steroids. But most important, in the study, they took their sera, transferred it to a mouse model, and there were transient alterations in the thermal pain response.

It's very difficult to argue that this is not an immune-mediated small fiber neuropathy. Now, we're not going to have most of this data for most of our patients, but this argues it does exist. We just may not have all the things at our disposal, particularly the mouse model, every time that we see a patient.

So how about this case? This was a case that was published two years ago of a girl who got a vaccine, and beginning 9 days after the vaccine developed a diffused painful neuropathy. So skin biopsy was abnormal, everything else was normal, and they called this, again, a post-vaccination acute small fiber neuropathy. Probably, not as good a case as the one I just showed you before,

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but you go, "Yeah. I kind of buy it."

Then what about this series from 10 years ago where they took patients that had acute onset small fiber neuropathies? They had abnormal QSTs in skin biopsies, and they gave them steroids, and they got better, but it was all a length-dependent neuropathy. Are you convinced that that's immune mediated? Probably a little less so than the first two I showed you, but it could be, but we just don't know.

So when it comes to mixed fiber neuropathies, again, we've got the electrophysiology. We don't have the electrophysiology for small fiber studies. But the reason I've put this up here is in that first slide, you've got a long latency -- I think it's a median -- and the connection velocity is 31. Here you've got really impressive temporal dispersion. Here you've got conduction block.

So that's three different examples of different types of demyelination. We tend to lump them all together and say, yes, that's evidence of

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a demyelinating neuropathy. This is most likely acquired when you see these types of changes, and therefore, acquired demyelinating neuropathy means that this is an immune-mediated process.

The problem is we have -- actually I should say 20. We have 20 different sets of criteria for figuring out how much conduction block temporal dispersion with our prolongation latencies and velocities you need, and none of them are really all that good. Again, they help us, but they're not really that good.

Then even more importantly are a growing number of case reports of inherited neuropathies where you can have proximal weakness, conduction blocks, and patchy load conduction velocities; not the findings that you would expect to see in the inherited neuropathies, but they can occur. So even our nerve conduction studies, which we think of as the most helpful for small fiber neuropathies, turned out not to be as helpful as we'd like. And again, we don't really have any of those tests for small fiber neuropathies, and

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probably more importantly, we don't have any tests for sodium channel dysfunction or nodal dysfunction.

So the contactin antibodies, the neurofascin antibodies, we now know are affecting the nodes but not necessarily the myelin diffusely. And all the sodium channel defects that we see, we don't have a good way to test that clinically to know whether that's relevant as well.

So how about biopsies? We like skin biopsies. I've got a lot of the skin biopsies, so we like that. Skin biopsies traditionally have been okay for allowing us to look for acquired neuropathies.

Here are a couple of different studies that looked at doing patients that they were really sure had CIDP, and about 1 in 5 are normal. So it's about 80 percent, which is about as good as any of the different sets of nerve conduction study criteria that we have. But very often you also just see external degeneration, so that now means 2 in 5 are going to be completely unhelpful in

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distinguishing immune neuropathy, even in cases, again, with our gold standard mixed fiber neuropathy of CIDP.

Then what about all the immune neuropathies that are demyelinating, all the vasculitides that we see? So again, looking for demyelination as the gold standard of some type of acquired demyelinating or autoimmune disorder may miss a lot of potential patients.

But when it comes to pathology in skin biopsies, this paper from I guess six years ago now began all of us thinking in a slightly different way. I like it. I don't think it's perfect. But what they basically did here was to say we're going to look at patients that have a length-dependent small fiber neuropathy by pathology, so worse distally, and compare those to patients that have a non-length-dependent small fiber neuropathy. And what they found was that if you have a non-length-dependent small fiber neuropathy, you're more likely to be female and you're more likely to have an autoimmune disorder.

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This began a lot of us thinking, well, we probably need to pay attention to this. Again, it's not perfect, but I do think it argues a little more strongly. But again, if you look at this, the immune-mediated neuropathies were only in 14 percent of the non-length dependent. So think about that 15 to 20 percent number. That's probably about as good as we're going to do in terms of the overall neuropathies that we're talking about.

This is two other studies now trying to look at autoantibodies. Antoine had a very nice paper where they took patients that had a sensory neuronopathy clinically, so a non-length-dependent clinical syndrome, and they found elevated levels of antibodies against fibroblast growth factor receptor 3 in 15 percent of their patients compared to 0.5 percent of the controls.

Pestronk had another paper that he looked at TS-HDS antibodies, and he found that the majority of the patients who had positive antibodies to TS-HDS presented with upper-limb symptoms before

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lower-limb symptoms, again, both arguing for a non-length-dependent clinical and pathologic syndrome in patients that have these autoimmune diseases.

This was another series from last year, again, small numbers of patients, but they found patients that had -- children, actually, that had small fiber neuropathy, and they found elevated levels of IgM antibodies against TS-HDS I think in 4 of the 5 patients.

What about looking at CSF? Well, CSF, unfortunately, even in CIDP is not great, so we use it if we're kind of confused. But some people have tried to use it to distinguish, say, a diabetic neuropathy from an immune neuropathy. And the problem is that doesn't really work. We've got cases where diabetic neuropathy can have CSF proteins as high as 400. And probably more mistakes are made because the lab values cut off 45 as being high. You get some 60 year old with diabetes, they get a spinal tap to protein 60, and then they're labeled as CIDP.

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So we can look for this. I've done a fair number of LPs in the presumed autoimmune small fiber neuropathies, and I've not found them to be very helpful. There was one report that I liked actually that looked at IgG synthesis rate, actually, as being one of the most helpful if you're trying to follow an immune-mediated process. So at least in CIDP, as the IgG synthesis rate comes down, their disease seems to be less active. So it's one thing that you could look for if you wanted to.

This was a relatively large study looking at Sjogren's patients. What they found first off was that about 60 percent of patients with Sjogren's syndrome had peripheral neuropathy. They then looked in the spinal fluid of those patients. They found that 9 percent had a few cells, but nothing really too impressive. About 20 percent had oglioclonal bands in the patients that had peripheral neuropathy. So again, the sensitivity here is just very, very low, and probably makes it not all that meaningful to look for if you want to.

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This was another paper, actually, by Lopate at Wash U again, where they found 45 percent of patients with Sjogren's syndrome had small fiber neuropathy, pure small fiber neuropathy.

Other autoimmune diseases, so sarcoid, there's a company now developing a drug that targets the innate repair receptor. They've published some early phase 2 results specifically in sarcoid-mediated small fiber neuropathy, but it seems to be relatively common.

So they looked at sarcoid-related small fiber neuropathy in 143 cases. Pain was the most common symptom, dysautonomia in almost half of the patients. Then they treated patients with IVIG. They saw 47 out of 62 patients improve with IVIG; 8 of 12 patients that got anti-TNF therapies improved; and 10 of 14 patients that got both therapies improved.

So they argue that the small fiber neuropathy in patients with sarcoid is likely to be immune mediated, again, largely on the basis of the fact that the patients' symptoms improved with therapy.

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For the most controversial subjects, Ann Louise published the first of these papers. They compared patients with fibromyalgia, the control subjects, and found 41 percent of patients with fibro had small fiber neuropathy compared to 3 percent of the patients in the control group. Then importantly, a large percentage of the patients that had fibromyalgia had some form of immune dysregulation.

We published a few years later with Ohio State. We found 50 percent of our fibro patients -- we did not have a control group, so we biopsied just fibro patients. But we found very similar numbers to what Anne Louise found, which was at 50 percent, and then we found 20 percent of those patients had some evidence for disordered immunity. The important little phrase there, which I added, is that these are patients that were seen by rheumatologists, so they had not done a lot of the tests that you would normally think to do as a neurologist. So these patients had not been

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diagnosed with these immune disorders before.

Again, also from Anne Louise was this one that looked at small fiber neuropathy in children with widespread pain syndromes, they identified definite or probably small fiber neuropathy in about 70 percent of these patients. That third bullet point I think was really one of the most important points of the paper that talked about a lot of the dysautonomia, the chronic fatigue, chronic headache that seemed to follow these patients and I think really are part of the same syndrome. In their paper, they found problems in immune system diseases in almost 90 percent of the patients, and 12 of the 15 patients that were treated with either steroids or IVIG subjectively got better.

Most of you are probably familiar with this data. I put this up here to highlight two important points. Our best example of a chronic autoimmune neuropathy is CIDP. Most of us feel IVIG works in CIDP, and the response rate is less than 50 percent in our best controlled trial ever.

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

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

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

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

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

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

If you look at this patient, in a

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

This was a poster we presented from last year. Again, these were 3 patients that had small fiber neuropathy and those 2 autoantibodies. So TS-HDS and FGF are 3. They got IVIG for 6 months. And again, just to highlight the best ones, the patients that had 1.6 nerves per millimeter at their calf after 6 months was up to 8.4 against 3 patients, but they had significant pain reduction. So the question is, do these autoantibodies serve as a marker in some subsets of patients with small fiber neuropathy for an immune-mediated process?

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

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

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

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

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clearly a group of patients that have an immune-mediated small fiber neuropathy, and this is I think getting much closer to how we have to think about identifying those patients.

This is my thought, which is, if we break patients into 5 different groups or 5 different categories for each patient, we can start to think a little bit more clearly about what makes us tick, what makes us think this patients has an immune-mediated process?

The first will be clinical. Again, you get a vaccine, and 2 days later you're sick; yeah, we think that's the vaccine. You get an illness, and a week later you develop a horrible neuropathy. That tells us that there's an acute process. We like that. It sort of fits with what we know about other types of neuropathies.

Clinically, are they non-length dependent? So we think very differently about a person with numb toes and feet than a patient whose face is burning. That's telling us something is very different about their neuropathy. And I would also

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add in there autonomic. So if there's a very pronounced autonomic component, it's telling us this is more of a widespread process.

Pathology, I think we need to think about length-dependent versus non-length-dependent pathology separately the way we think about length-dependent and non-length-dependent clinical symptoms. I can tell you, in our series, there's not necessarily a strong correlation. I think those are two very different variables.

Then can we start to find and be a little smarter? Can we look for some of these inflammatory markers in the skin? We've been doing this in our lab. I can't say we've found much exciting yet, but we're trying to see can you look at complement deposition and can you look at some of the inflammatory cells that might be in the skin as a way to really kind of look at this?

The lab testing, obviously that's what we like. Again, maybe some growing evidence to TS-HDS and FGFR-3 are helpful. Other neural antibodies are important; non-specific antibodies, to me

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meaning SSA, SSB, and ANA, and those antibodies. If you want CSF, what if they have monoclonal gammopathies? All of those things are really pushing us to think this is immune mediated. Obviously, we talked about the associated disorders.

Then the last category is really the tough one, which is do you include that as an outcome measure to think about what we're doing? Then if you were going to build this type of a table, would you include negative predictive factors? So what if you had a person who had Sjogren's and had diabetes? Is that going to make you think more or less likely that it's immune mediated? I think we have to think about those as well.

This is what I would do. My thinking is that we take those variables, and I'll show you three cases, and I think it will start to make sense. If you took this patient that had an acute onset small fiber mediated pain and autonomic dysfunction; non-length-dependent pathology, elevated levels of FGFR-3 antibodies; positive SSA

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and SSB; inflammatory changes in their CSF; and a history of Sjogren's, you have a very hard time arguing that that is not immune mediated.

So that's sort of the bullseye. And if you add up all the points from my previous table, that gives you 7 points, and says, yep, that's immune mediated. So that one is pretty easy.

What about a patient with a 3-year history of distal burning, length-dependent pathology, a history of diabetes, and nothing else? Well, that's zero points. In fact, you could make it negative 1 point if you want to, if you take my negative scale. So they're not even on the target.

What about the patient that's got a 6-month of history of burning that started in the hands, gradually spread to their chest and back, and they've got no autonomic features? Their pathology is length dependent, but they've got antibodies to TS-HDS? Well, it's getting hard, so I'd give that a couple of points. So on the board, but it's not really the bullseye that you'd want. So I think depending on how sensitive and specific we want to

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be, we can start to take these variables and really try to put together a picture that will allow us to identify these patients better.

So the point is, again, all these are different. All these patients I think are truly different. The patient that's got just pain is different than the patient that's got pain and autonomic features, so we have to think about them a little bit differently. Then each of those really has a very different pre-test suspicion. When you go into treatment, we all come to our own conclusion in our head, is this patient likely to get better or not? If we're going to start to do trials in immune-mediated neuropathies, we would want to enrich that as much as we possibly can, obviously without hurting the enrollment.

I think that's it.

DR. FREEMAN: Thanks for a terrific talk and attempting to structure out thinking on small fiber neuropathy in a provocative way.

Before we have questions, what I'd like to request is if the members of the audience can

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attempt mentally to dissociated immune-mediated small fiber neuropathy from pornography --

(Laughter.)

DR. FREEMAN: -- if it's at all possible.

The question I had is, that paper by Liu et al., they had all these blood biomarkers, but did they actually look at the skin biopsy, and did they look at specific biomarkers of inflammation that were occurring in the skin? And do they correlate that with the intraepidermal nerve fiber changes or other changes in the skin fibers?

DR. LEVINE: You mean the one from like 5 or 6 years ago?

DR. FREEMAN: Yes.

DR. LEVINE: No, they didn't.

DR. FREEMAN: Well, actually the 2018 paper, Liu at al., the one that's just been

DR. LEVINE: Well, Anne Louise could probably -- I don't think so. So, yeah. Again, the difficulty -- the challenge is, the more you split these people into smaller groups, the smaller your numbers become. I recognize that that's sort

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of a dilemma. You'd like to have as homogeneous a population as possible, but then you end up with a very small population.

So really, that paper, the idea was that this was suspected autoimmunity, and then suspicion that there was autoimmunity came from the variety of factors that they listed. But I don't think they broke it out by looking at biomarkers in the skin.

DR. FREEMAN: Nurcan -- before she asks her question, I just want to emphasize, left out of your reference list was the terrific paper that Nurcan's group did on small fiber neuropathy in the setting of fibromyalgia. I don't know if your question is going to be related to that, but your interpretation was a little different to what we heard this morning. So if you could include that in your question as well.

DR. UCEYLER: Well, thank you very much. Actually, my question was about another paper that we published on immune mediators or biomarkers in the skin of patients with small fiber neuropathy.

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That was Neurology 2010, where we looked at length-dependent and non-length-dependent patients with idiopathic small fiber neuropathy. And what we found is that we counted the T cells and macrophages in the dermis and saw no differences. And then we measured pro- and anti-inflammatory cytokines in the same skin biopsies of these patients using quantitative real-time PCR, and we saw an up regulation of asiatic proinflammatory cytokines in the length-dependent group.

That was quite interesting, and in our hands, when we've seen our patients do the skin biopsy, we do not treat them with immunosuppressive drugs, only if we would see an increase, some kind of evidence in this prospective.

Another aspect now going to this 2013 paper about fibromyalgia and small fiber pathology, we called it, the command I would have here is -- also looking at your slides -- we're talking about small fiber neuropathy for all of these conditions, what is now fibromyalgia, and sarcoid, and celiac disease, and diabetes, and whatever.

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I think we should think of making a distinction because the clinical presentation is obviously very different, so the fibromyalgia patient does not come with burning feet and burning mouth, but has an aching muscle pain. That's the reason why we called it small fiber pathology in our title in this first description. So this is maybe something to be discussed later also.

DR. LEVINE: The second point, your last point, I think is a really important point. I agree. That's why I'm kind of trying to propose that we come up with a different terminology for it because the patient that has the fibro syndrome, that has abnormal epidermal density, does look very different than the patients that has burning toes or the patient that has burning mouth. And I think we have to think about them.

DR. UCEYLER: And also doesn't have any -- at least in our hands, we also looked at the skin and looked for asiatic markers in the skin, again, looking for pro- and anti-inflammatory cytokines, nerve growth factors, and so on, and we

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didn't see this pattern that we found in the small fiber group. So I think there is really a distinction from the pathophysiology also.

DR. FREEMAN: One of the issues that I think we should table for the moment, but will definitely come up -- that's why I wanted Nurcan to speak about their interpretation of their data, is the specificity of skin biopsy for small fiber neuropathy versus their interpretation. And that is small fiber pathology associated with fibromyalgia, which was their interpretation subsequently in a letter to the editor, I think, following a response to their paper.

I think it was Giuseppe, then David, then Ahmet.

DR. LAURIA: Thank you because it's a very sensitive area. I'm not arguing that the immune system is involved or may be involved. We've treated some kids, for instance, with very severe and acute, so it might happen.

May I suggest -- following your idea to separate the neuropathy associated with a clear

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system disorder, just final, you have Sjogren disorder and you may have a neuropathy. That's it. The other point in which I would like to see whether there is an agreement is the concept that one data does not make a diagnosis. So if I have chest pain, probably I could have a myocardial infarction and a number of other things.

If we agree on the principle, the fact is that the gammopathy, for instance, that you have listed is very common, and with increased age of the population, it becomes even more common. So the relationship between the evidence that one person has a neuropathy and one person has, at the same time, even one antibody, the antinuclear antibodies, it is very important because the relevance that it has in clinical practice is huge. There are patients requiring IVIG on the basis, from my perspective, of very little.

DR. LEVINE: I agree completely. Again, that table I listed, in an ideal world, each of those would be a different point. The acute onset might be 3 points and ANA might be 1 point because

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we know the specificity of an ANA is very, very low. The problem is how do we get there and it has to be guesses to begin with. I think you're absolutely right, which is I would think about a known systemic autoimmune disease and a neuropathy differently than a patient who has a neuropathy and you find a blood test. Those are two very different things. Yeah, I agree.

DR. FREEMAN: David Herrmann, Ahmet, and Anne Louise.

DR. HERRMANN: Todd, on this question, as we think about diagnostic criteria for immune-mediated small fiber neuropathy and giving people points for different elements, to the point of treatment response, one of the concerns I have is I think we all need to be fairly stringent about what treatment response is.

So IVIG's going to modify cytokines, and what I don't know is when a patient has response to IVIG with a small fiber presentation, and the endpoint is pain improved or symptoms got better, I don't know whether that's a symptomatic effect

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because I suspect that IVIG modulates pain pathways substantially as steroids would do. So I would argue that we probably need some objective evidence. When you give IVIG or plasma exchange to someone with CIDP, their strength gets better.

So if we're going to include response to treatment, I think we have to have some criteria for what a response to treatment looks like, and I don't think it can only be improvement in pain.

DR. LEVINE: I completely agree. Number one, even though they were small numbers, I followed up with a biopsy, and I probably now have 20 or 30. You can do it in 3 or 6 months, and you see a change.

Chris and I are designing a trial with Grifols, which will include outcomes of a biopsy. It's different than if you -- obviously, if you're using a sodium channel blocking drug and you're treating pain, then your outcome is pain. When we start to think about these drugs, even more cytotoxic drugs, you need something more than pain. I agree.

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DR. FREEMAN: So Ahmet, Gordon, and then the panel. [Inaudible - off mic].

DR. HERRMANN: You've missed Anne Louise.

DR. FREEMAN: Anne Louise, Gordon, and then the panel.

DR. HOKE: I was going to also bring up the treatment issue because I think a large part of the acute onset non-length-dependent neuropathies, I would like the GBS equivalent. Those people improve on their own. They have a monophasic illness. Those people probably don't need treatment, but the ones who have a more slower onset, perhaps progressive type of neuropathy, deserve extra attention in investigations. But probably the majority of the ones that I see in my clinic, by the time they come to see me, 8, 10 months later, they're already starting to see improvement in their pain levels. I biopsy these people a year or two years later. They all improve their epidermal nerve fiber density without any treatment.

DR. LEVINE: Osvaldo Nascimento has a series

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in Brazil where they were post-Zika, very severe painful syndrome, and he doesn't treat them, and they get better.

DR. FREEMAN: Anne Louise Oaklander?

DR. OAKLANDER: So I hold open our 2013 [inaudible - off mic] a week. We're actually pretty balanced, and we try to look at all available tools. I just want to mention the results of the other data we collected [inaudible - off mic]. We looked at symptoms. We looked at signs. We looked at pathology. We looked at physiology. I don't know what else to look for.

DR. LEVINE: And you had a control group, which I will say our paper didn't. But that was in the 3 versus 40 percent.

DR. OAKLANDER: We used the Michigan neuropathy screening instrument as a way to measure symptoms, and [inaudible - off mic] was 1.3, and the full group, 5.8. Fibromyalgia patients were [inaudible - off mic]. We used physiology. We used autonomic testing. That did not pick up any

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major difference, and the skin biopsy. So again, we are not proposing that skin biopsy -- in other words, it was more than just pathology in the study. It was symptoms and [inaudible].

DR. LEVINE: Back to your point, we should really start to think about these terms that we're throwing around today because as Chris pointed out, Parkinson's patients have small fiber pathology. We're not saying they have small fiber neuropathy, to your point. So that's exactly right. I think that's a very important distinction.

DR. OAKLANDER: Neuropathy has the word "pathology" in it, so I think we have to think about the words we use. For instance, I tend to use the word "small fiber polyneuropathy" because there are other types of neuropathy that are not polyneuropathy. So even at the most basic level, we're making assumptions that we may or may not want to make, but we should think about it.

DR. FREEMAN: Gordon, last question for this talk, and then that will be it.

DR. SMITH: Yes. I just have a couple of

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

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

(Laughter.)

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

(Laughter.)

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

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

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

Q & A and Panel Discussion

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

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

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

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

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

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

I'm just throwing this out there for discussion.

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

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

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us how he or she is doing. And we know that from the work that Ingemar Merkies has done on the [indiscernible], for example, and we also know that for other diseases, it works the same.

So I would be in favor of also asking the patient how he or she is doing, and that also means including pain as an endpoint. It doesn't mean that you have to say that pain is the only endpoint, that's something else, but I think that for the patient, the main complaint and the main problem of small fiber neuropathy is the pain. So it should at least work on the pain, whatever you do.

DR. SINGLETON: I was going to say that for me, those discussions make me think that we should cast a wide net for what we mean by small fiber neuropathy and that when we do clinical trials, it's crucial to have some sort of objective measure of nerve function. Whether that's pathological or quantitative sensory testing, I think we'll discuss that further, but that's the reason to have that, that it helps to defend against criticism that this

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is just a non-specific improvement in patients' perception. That's crucial to the FDA, but it's not the only aspect that should interest us or those who organize pharmaceutical trials.

DR. FREEMAN: Anne Louise?

DR. OAKLANDER: That's why we chose two primary outcomes in our IVIG study, one being improvement in pain because it's obviously central and not everybody has [inaudible - off mic]. But we also used an objective biomarker, so I don't think there's going to be any one metric. All of these clinical trials, we have to very strongly [inaudible - mic fades] primary outcomes.

DR. BELL: Sorry. I just want to make one comment on that. I agree under the presumption that you have what you assume is a disease-modifying therapy, which for a lot of us in drug development when we're targeting pain -- we've had this discussion with Roy a number of times -- the value of having some of these more objective markers as primary endpoints is questioned because our primary outcome, for

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example, is pain because we are in the business of developing pain drugs that may or may not alter the actual course of the disease.

So my question would be, how do you objectively -- I mean, how do you do that when you have a therapy that you don't suspect modifies your intraepidermal nerve fiber density? It doesn't change your QST phenotyping. All you're left with is how are you feeling and how is your pain.

DR. FREEMAN: I want to maybe, just by way of clarification, the goal of the meeting was purposefully vague, and we do think of small fiber neuropathy, as with every neuropathy, as having a symptomatic component and also being the substrate for potential disease modification.

The way I'm presenting it now, it is as if these are two discrete approaches to a disease. I think more and more we're beginning to recognize -- and I think the basic science slide that Karin showed us initially looking at the potential multifactorial approach to the etiology of a neuropathy suggests that there may be more of

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an overlap than we think, and that perhaps by disease modification, removing one factor of a polyfactorial or multifactorial disease, you may actually be modifying the actual history of the disease.

So I think it's a really very important point that you are making that there will be strategies, target-directed therapies, that are symptomatic, and they may or may not also be disease modifying. But I think we need to recognize that these are at two ends of the spectrum, and that disease modification may in fact on some level make symptoms worse in some cases. Pain may get worse as you improve nerve function and nerve structure. So it is more complicated than perhaps meets the eye.

Rayaz?

DR. MALIK: I think it is important as a group for us to be clear that disease modification, we must have some improvement in function or structure. And I've talked to some pharma that there is danger almost of you wanting a quick

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target. So pain, you can do an 8 to 12-week study, and you can show a benefit, and go to the FDA and get an approval, but it's not necessarily disease modification. And as a group, we need to have clarity on that. I think if you have a disease modifier, you need to have I think an objective measure. You can't have both.

DR. LEVINE: I think, too, all these points are kind of saying the same thing. But it comes back a little bit when you're trying to think about -- and we're going to talk later -- an inclusion/exclusion criteria. Number one, it depends on what kind of a drug you're doing. Is it a symptomatic treatment? Is it a disease-modifying treatment? Because that really reflects who you're going to choose. When you talk about outcomes, yes, I think you absolutely have to ask the patient, and it has to be pain, and it has to be function.

I mean, all of us see a broad range of small fiber patients, those with a little bit of numbness or tingling. And clinically, you would never want

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to expose them to steroids or IVIG because they're fine. And then we see some patients that are horribly disabled that never get out of the bed, and the risk-benefit completely shifts in terms of how we think about how aggressive we want to be for those patients. So there we really want to improve function.

So you can improve pathology all you want, and I'm an advocate for looking at the pathology, but if you don't make people better, what have you done?

DR. FREEMAN: Let's go. I think Anne Louise was first, then Nurcan, and then Gordon.

DR. OAKLANDER: I think it depends on the level of maturity of the field, and I actually followed the Alzheimer's field fairly closely as a good example. They're going into immunotherapy, and we understand -- we don't know everything, but people would argue there that even in patients who are not symptomatic, if you have strong evidence of ongoing and progressive neuronal degeneration, that treating neuronal degeneration alone may be a valid

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outcome even in the absence of major symptoms. And I think that's because it's much better defined.

DR. LEVINE: But can I poll the room really fast? By a show of hands, if you treat small fiber neuropathy, do you think the majority of your patients stay the same over time or get worse over time? How many people think stay the same, the majority? I mean, some obviously do whatever.

DR. OAKLANDER: Treat how?

DR. LEVINE: You're just managing them clinically, so not treating with any immunomodulatory therapies, just a natural history of small fiber neuropathy, if you have a thousand patients, 500 patients. When I talk to my patients -- I have over a thousand small fiber neuropathy patients now -- I tell them 70 percent stay the same.

DR. FREEMAN: Rather than a vote, there are people in the audience who actually have cohorts. It's a question that I wanted to ask Rob in his review, what is the natural history of this disease? What do we know?

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Giuseppe, what happened to your patients?

Karin, what's happening to your patients?

DR. FABER: Well, we didn't follow our patients for a very -- because we see them, we make the diagnosis, and they go back to their referring physician. So we are planning on doing a follow-up study. I think the best follow-up data are available from the study of DeVechely [ph] and Giuseppe [ph], and that described that part of the patients, I think half of them stayed stable, 30 percent had a decline, and very little -- I think 10 percent or something like that -- improved.

DR. FREEMAN: They seemed dependent because there were multiple potential etiologies.

DR. FABER: Yes.

DR. FREEMAN: That was in your pure group that 10 percent improved.

DR. LAURIA: This is something actually we don't know exactly, so we don't know at the long term what happens to these patients. Also we don't know what is the frequency of other systemic and

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

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

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

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

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

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

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

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

DR. FREEMAN: David Herrmann?

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

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

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

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

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

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

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

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group, 16 patients that have been followed where the authors come to the conclusion that large fiber neuropathy will develop. And in the majority of cases, I would not really go with this in the majority of cases. It is actually marginal.

Another point, the discussion has turned around now a little bit and coming back to one point that was asked. When we produce a new drug against pain, what is then our outcome measure? Do we have an objective measure, as far as I understood it. I think we have to distinguish here very carefully is it about idiopathic small fiber neuropathy. Do we treat a reason? Is there other etiology? Will we improve neuropathy, and do we have any correlation for pain in any of the tests we're doing? So far we do not have this.

Actually, when we're treating pain, the patient will tell us, okay, pain has become better. But I think we cannot expect then, from fiber density, or from QST, or from any other investigation, an improvement because this does not correlate with pain. So I think we have to

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distinguish what are we trying to improve; neuropathy, okay. Fiber density might become better, then we can do a follow-up biopsy or we can do QST. But for pain, we will now have anything inherent at the moment.

DR. FREEMAN: And Simon's sitting next to me.

Go ahead.

DR. FABER: I think I completely agree with you. That's a very important distinction we have to make because otherwise, we define a biomarker that should improve while in fact it will never improve, and then you have a negative trial while the patients may be improving. So that's really important.

DR. OAKLANDER: How about using the term "domains," and we can talk about treating the different domains of small fiber neuropathy; the symptom domain, the pathology domain, the functional domain.

DR. FREEMAN: There may not be concordance. To follow up on Nurcan's comments, Simon's sitting

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next to her and is doing I think an excellent systematic review just on that very question. I don't know if you want to comment now or save it for tomorrow.

DR. HAROUTOUNIAN: We're just finishing the systematic review on looking at the associations between intraepidermal nerve fiber density and a variety of other domains, so QST symptom, signs, NCV, autonomic testing, and the slide at the end of my presentation, what are the associations between intraepidermal nerve fiber density and each of those. This is not in small fiber neuropathy per se. We did it over the spectrum of distal symmetric polyneuropathies. So with that carrot, I'll just present.

DR. FREEMAN: The sodium channel people are going to speak in a second. I just want to set up and take my chairman's prerogative by asking a question to Ahmet and Karin.

We heard two discordant views; at least to me, they sounded discordant. In Ahmet's talk, he said -- and I don't know if this represents his

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view -- that BMS, who sponsored the study that he presented, withdrew from the selective sodium channel antagonist field -- correct me if I'm wrong -- following the results of that study. And Karin in response to a question noted that if you have a good selective sodium channel antagonist, whether or not there are polymorphisms, she would be very supportive of its use in patients who have small fiber neuropathy.

I suppose another question that has always been on my mind is actually what is the evidence that having a polymorphism makes you more responsive to a selective sodium channel antagonist in that disease or perhaps could you be less responsive?

DR. SINGLETON: Before you answer, can I just add more questions?

(Laughter.)

DR. FABER: I can't remember, not everything.

DR. SINGLETON: I know. We'll remind you again. My question, you touched on this, just not

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as much as I want you to, is what's the evidence for epigenetic effects on sodium channels in diseases like diabetic neuropathy? Can you speak to whether inflammatory conditions, in metabolic injury or derangement, how does that affect the function of these sodium channels?

DR. FREEMAN: Do you want to add a fifth question, or can it --

DR. STEINER: It's I think along a somewhat similar theme, but if you start from the perspective of somebody in development and the idea that you want to work towards the treatment symptomatic, in our case, for small fiber neuropathy, we've discussed it in so many levels of painful small fiber neuropathy, are we looking specifically at pure? Should we be looking at painful peripheral neuropathy?

So to me, Todd, the taxonomy that you put up was really helpful. The way that we should be approaching it, should we be approaching it by targeting patients who we know have genetic mutations. Should we be targeting it at a broader

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level? I think that's one of the big challenges before you even get to what the outcome measure is and how important either the INFD count is, the QST, and maybe there are differences, which was already brought up earlier, about the results based on the ideology.

DR. FREEMAN: Okay. You have five questions. You've got 30 minutes.

(Laughter.)

DR. FABER: First, I think that if you block, for example, Nav 1.7, and you would do it very good, then you would diminish pain, whether it comes from small fiber neuropathy or from any other disease, because Nav 1.7 is a central channel in the development of pain, so that's important.

The other thing is how would you design a trial, and would you use only patients with pure small fiber neuropathy? Would you use other things? Well, it depends on what you want. But I think that if you want to do it properly, you should have a homogeneous group because if you mix diabetic neuropathy, idiopathic small fiber

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neuropathy, and immune-mediated neuropathy, and a drug does not work, then you will always say, well, what happens if. And if it works, then you have a proof of principle, and then you can go to other groups. That would be my best way to go I think.

We did a small trial in patients with Nav 1.7 mutation with lacosamide. Lacosamide is also a sodium channel blocker, and it blocks especially Nav 1.3, 1.7, and 1.8. That trial was positive. It was an add-on medication, but it really had a good effect in those patients, and there was not a difference in patients that had a proven pathogenic mutation, so with electrophysiology, in patients that were suspected to be pathogenic mutations. So that was really helpful.

The next step would be to go to a bigger group of course, but in the meantime, I think we have better Nav 1.7 and 1.8 blockers to test, and those probably tested in a bigger group of patients.

DR. STEINER: No, I agree with you --

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DR. FABER: Then for the epigenetic things --

(Crosstalk.)

DR. STEINER: With a proof of concept, I completely agree you start with a homogeneous group. I guess I'm saying more what is the eventual goal? Is the thinking that there's pain? We know that Nav 1.7 is involved in pain, so something that targets that is going to work in any population. I'm saying is that the thinking?

DR. FABER: I don't know. I think that's a reasonable hypothesis, but I don't know if that's true. It's not very useful to say, okay, we will treat any patient with pain because then your trial is going to be a mess.

DR. STEINER: I know.

DR. HOKE: But why do you think that's the case? If you think the Nav 1.7 is central to the pain sensation, why shouldn't it work for any pain, even osteoarthritis pain?

DR. FABER: It probably will, but you have to --

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

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

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

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

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sodium channel mutations for years in clinic, and I see a ton of small fiber neuropathy. I actually have only one patient that I found last week who a variant. I'm not saying it was pathogenic.

So I think the experience in the U.S. for most of us is that it's a lot less common, and I think we still carefully phenotype these patients. So I don't think it's an issue of not phenotyping patients; I just think the mutation is just less common, where most of us --

DR. FREEMAN: Genotype or phenotype?

DR. PELTIER: Both.

DR. FREEMAN: You said we all phenotype.

DR. PELTIER: That's what I'm saying, is that my patients are phenotyped with a panel, not necessarily a whole exome sequencing. They're carefully phenotyped, and they still don't have the sodium channel mutations. And I see a lot of Pott's patients plus regular small fiber neuropathy patients. So I see the gamut of what you expect to see, those mutations, and we just don't find them.

DR. FREEMAN: So let me maybe ask -- and

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this has always been a question that has plagued me since the BMS PNRR paper. At the end of the paper, the BMS writer wrote about a number of potential limitations, technical limitations, as to why there may be differences between the PNRR data and the data coming from Netherlands -- Waxman -- and Milan. I wondered to what extent what you, David, PNRR saw is actually technical. How complete was the sequencing done? Was it done in a similar way? Are we missing something for technical reasons?

DR. FABER: Can I comment on that?

DR. FREEMAN: Yeah. I'd love for you to.

DR. FABER: I think that it sounds very easy. You do a genetic test, and you have a result. We had some very bad experiences with a commercial bureau, who really missed a lot of parts of the gene. If you don't check that -- we have a very good molecular biologist who really checks everything. If you don't check it, you will never find anything. So that's one thing

So is the test really done very well? And also, if you use next-generation sequencing, how

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are your filter lines defined? Do you have a good bio plan? Do you have a good bioinformatician? Those are really crucial factors in defining whatever variant you are going to find.

Another thing that was already mentioned is, of course, there may be differences in genetic background between the U.S. and Europe. We don't know that, but I think these technical factors may really play a big role. I would not rely on any commercial cheap test, for example. So that's one thing.

Then you also asked about the timeline of the symptoms. Well, we see a lot of patients, and a lot of patients have symptoms for decades when they come to us, and they have a pure small fiber neuropathy. So in my opinion, the majority of the patients will stick to a small fiber neuropathy, or if they develop something, then it's really minor. So that's the majority of the patients.

Giuseppe, I think you wanted to add something as well.

(No response.)

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DR. FREEMAN: David Herrmann, Gordon Smith, Nurcan, and Chris. Try and remember.

DR. HERRMANN: Two brief points. In terms of defining these disorders and then thinking about populations to test sodium channel blockers, while, Ahmet, you argued for lumping people together because you say targeting Nav 1.7 might be a universal target for pain disorders, I still think that as clinicians, I would rather argue to test in multiple models, a test that separate out the models because the mechanisms are complex. And we may see differential response rates depending on broad categories, be it osteoarthritis, small fiber neuropathy, distal small fiber neuropathy, et cetera.

So it's still to argue for testing in multiple separate models rather than just a generalized pain indication. And I think we still want to know whether a treatment's highly effective in a large percentage of patients within a model or just only effective in 20 percent.

DR. HOKE: I agree. Like if you're going

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to -- I would argue that there are probably easier clinical targets than small fiber neuropathy where we are debating how to even define the disease population. So if it is truly generalized pain mechanism, pick something, post-herpetic neuralgia. It's a very clear-cut patient population that you can test.

DR. LEVINE: The other advantage to splitting the groups out is that we've got experience, both duloxetine and Lyrica, where doses are different in the different models. So the dose that works for diabetic neuropathy may be less than the dose that works for post-herpetic neuralgia. So if you do lump them together, they all just get the same dosing. You may miss that as well.

DR. FREEMAN: Maybe to editorialize a little, I think there really are three issues. One is when you're doing a proof-of-concept trial, you want to remove as many confounders as possible, and one of the first steps in doing that is to have your populations and the study as specific as possible.

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The next point -- and I'll maybe only make two points -- is that even within a specific disease -- let's just say PHN or small fiber neuropathy -- a number of us have been focusing on different pain phenotypes as a way to address the underlying mechanism. And I think even in a disorder like PHN -- and I won't go into details -- as you say, a relatively pure disorder, the pain phenotype varies. And to me, there's no question that the response to an intervention is going to be different depending on the phenotype because that phenotype has to in some way reflect the underlying pain mechanism.

Then finally, osteoarthritis, I imagine if we put a group of obsessive, compulsive neurologists on to osteoarthritis, we would spend hours discussing the different pain characteristics that exist in that population. I do think that it's not as simple as all that.

Chris?

DR. GIBBONS: I actually want to get back to Karin's point, which I thought was really critical,

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the issue you raise, which is genetic testing and quality control. I think that's actually something very simple that this group could accomplish in short order, which is you have very well characterized patients with mutations. They really should be tested across the different commercial labs. We need to know who is viable as a place to get our testing done, without which, clearly, we're going to be in a complete quandary.

DR. HOKE: If I can comment, I work with GeneDX. If you use their whole exome sequencing to get at the Nav channel mutations, they say that their sensitivity is only about 90 percent. So if you're really interested in Nav channel mutations, you have to specifically ask for sequencing of those genes.

DR. FABER: And you would need single sequencing, but even -- I had a bad experience where they said they do single sequencing, but still missed some parts of it, and they didn't correct for that.

DR. FREEMAN: It was Nurcan, and then

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Giuseppe.

DR. UCEYLER: First of all just another comment on the genetic aspect, as another European center with less patients but very well characterized also clinically, we do next-generation sequencing in all of our patients and still would have much lower, as I commented early in the morning, numbers, the published ones. I don't know what the reason can be

One thing I wanted to ask here is, in your patient cohort -- so this was prospectively recruited patients -- you did not maybe also include -- for instance, after having one index patient, then the siblings, which would increase the number, of course, in the study population.

DR. FABER: The number of families are extremely low, so, no, that's not included in the 12 --

DR. UCEYLER: So you did not further recruit them when you have an index patient, that you say, okay, do you have siblings --

DR. FABER: Of course, we do family

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investigations. We do that, but that's something else; or the co-segregation, we do that. But these are single patients, and the number of family members are extremely low, so the percentage is really for probands.

DR. UCEYLER: So the percentage is without including further siblings after having found one in those patients.

DR. FABER: Yes.

DR. FREEMAN: Giuseppe?

DR. LAURIA: We've been analyzing the exome sequencing from around 15 families, in which we got 3-years DNA sampling and so on. But I want to bring your attention to the fact that we should not follow the idea that this is a monogenic condition. I think it is quite important because this is a condition in which -- our understanding or our hypothesis actually -- let's put it in this way -- is that there is possibly -- and based on the data which are relatively different from those that Ahmet presented there is a susceptibility background, a genetic susceptibility, clustering a

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different subgroup of patients. We decided to divide into painless and painful. Of course, there's a lot of work to do in terms of subdividing the painful groups by phenotype and whatever.

As to the analysis, the number of patients in which you would find one single pathogenic mutation, assuming the time that you need to define that mutation, that the variant that's pathogenic, which is a long time, is clearly low. So assuming that the quality of any commercial company will be fine, I don't know whether we are going toward the right direction with this discussion.

DR. FREEMAN: Eva, and then I want to ask a question.

DR. FELDMAN: Eva Feldman, University of Michigan. Maybe this will sound like heresy, but I think in 99 percent of the patients, this really isn't an issue, and I'm almost surprised we've spent this much time talking about genetic testing in that.

I think that we all have the experience primarily that the variants are not affecting our

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clinical practice. I also think that we all agree that the sodium channel is a target. You can use an analogy of myasthenia gravis. We know the acetylcholine receptor is a target, and we target it. We don't see multiple genetic variance in that particular receptor. And maybe that's not the best analogy, but we understand scientifically and mechanistically that the sodium channel is a target. I think we probably have a consensus that whether or not there is a variant in that channel, we shall move forward with clear, well-defined populations and potential new clinical trials.

So whether or not there is a variant or isn't a variant, I don't think should really drive further discussions necessarily at this meeting.

DR. FREEMAN: I'm sure we will come back to this, and I think we have enough, how should I put it, foment for discussion. Let me come back to something for which I have less clarity, and I'd like to get a little bit more clarity. That is the immune factors in small fiber neuropathy.

The way I see any intervention, and IVIG in

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particular given the expense associated with it. There two approaches. One is I would never ever give this therapy in the absence of a double-blind, randomized, placebo-controlled clinical trial for condition X, and here we're talking about small fiber neuropathy.

At the other end of the spectrum is this is such a devastating condition, patients have such impaired quality of life, I am willing to try anything, even if there is a chance, however small, that this will improve patients' quality of life, sense of well-being, even if it's the 22 percent placebo response, which Todd showed in his slide.

I would like to get a sense of where people stand on the spectrum. And having said that, then the subsequent step is if we stand somewhere in the middle, what are the criteria that you would use for deciding that this is reasonable to do? And I'm obviously most interested in a clinical trial, but I suppose as information to judge that, even in clinical practice. And we've got a couple of minutes left. I'd just like to raise that as a

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



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



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



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

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

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

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

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

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

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

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

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

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endings, they may no longer have inflammation, for instance, in the skin. And immunotherapy, not monolithic -- any therapy with regards to the inclusion criteria, you have to look at the costs and the risks. And the more expensive and potentially dangerous the therapy, if somebody wants rituximab or bone marrow transplantation, you really have to have a very high threshold. And also I think you have to prescribe very short courses.

So I'll say I'll consider a trial for you, and I try to follow the ICE for IVIG, and do not prescribe more than a 3-month trial, and I see that person back, and I'll evaluate, and I will not continue unless there's clear evidence.

DR. FREEMAN: This was a terrific session. I'll leave you to ponder bone marrow transplant --

(Laughter.)

DR. FREEMAN: -- for small fiber neuropathy at lunch.

(Whereupon, at 12:13 p.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N

(12:13 p.m.)

DR. DWORKIN: I think it's time to get started. Roy has asked me to serve as moderator for this afternoon session, so my objective for the next three hours or so is to do half as good a job, at least half as good a job as what Roy did this meeting. So I hope I succeed.

Two quick things before we get started. This morning I mentioned, in talking about the history of ACTTION, the kind of absolutely pivotal, critical role of Bob Rappaport, who's now joined us for this meeting. So I just want to reiterate what I said this morning, Bob. Without your vision, we wouldn't be here, and we all appreciate it a great deal. Thank you.

The second thing, for those of you who missed it, Francis Collins, the director of NIH, just this morning announced the HEAL Initiative. That acronym stands for -- let's see if I can remember this -- Helping to End Addiction Long Term. And as part of the announcement, he said

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that NIH's budget for fiscal year 2018 will be increased half a billion dollars from what it was in 2016. And that half a billion dollars will be devoted to two broad sets of questions addressing opioid use disorder, kind of the development and treatment of addiction and improving the treatment of pain so that fewer patients will need to try opioid analgesics.

Improving the treatment of pain will involve prospective studies apparently of the transition from acute to chronic pain; setting up a clinical trial network dedicated to studying pain; et cetera, et cetera. It's all online, and I think it's hard to imagine how this isn't anything but good news for many of us in the room who are interested in understanding pain and its treatment.

So without any further ado, it's my pleasure to introduce Dr. Simon Haroutounian. Simon is an assistant professor of anesthesiology at Washington University in St Louis, and he has done a comprehensive systematic review of the criteria that have been used in studies of small fiber

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neuropathy and is going to, for the next half hour, present what he's found in his systematic review to us.

Presentation – Simon Haroutounian

DR. HAROUTOUNIAN: So much for this introduction. I think before we start with the slides, I want to present one slide from another systematic review we just finished and going to submit probably sometime this week, where we looked at distal symmetric polyneuropathies and tried to look at the associations between intraepidermal nerve fiber density and other parameters such as neuropathy score symptoms and various QST parameters or some of the other more objective functional measures.

Just quickly to go through this slide, again, this is distal symmetric polyneuropathies in general, not only small fiber neuropathy. I just hope this can contribute to the discussion. In general, this pie chart shows what percentage among the studies that have included studies of small fiber -- distal symmetric polyneuropathy have

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

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

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

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

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We built this database where we systematically applied certain criteria to see if we're extracting the full data from those papers or that we're putting them aside. And we're primarily excluding nonhuman studies. Again, sometimes papers state that this is idiopathic or small fiber neuropathy study, but all patients are diabetic, so those would be excluded in that case

We also excluded studies with less than 10 subjects, which would actually exclude some of the clinical trials that were done in small patient populations. But we ended up having 123 papers in this group for which we extracted the full data on patient characteristics, biopsy findings, QST findings, et cetera.

Out of this group, there were 38 that was either reviews or guidelines. Only 11 studies met the characteristics that they were called idiopathic small fiber neuropathy, and actually it included patients for whom the etiology was unknown, so kind of completely idiopathic.

The largest group was what's called mixed

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small fiber neuropathy, so these were small fiber neuropathy patients, but the study group included a variety of either mixed etiologists, and then I think maybe and Gordon's presentation that will follow afterward will help us kind of figure out who are the patients who we can call idiopathic or we can give other names.

This is this a lot of data, so I will present only kind of semi quantitative analysis of those. The way I'll present it is basically a I'll present those 11 iSFN papers and those 74 mixed small fiber neuropathy papers. This is kind of mapping where we looked at the variety of parameters, the QST, a skin biopsy, symptom measures, sign measures, et cetera. And we map them or color code it in a way that green would be the expected association, no difference between controls or association. In the unexpected, opposite direction, all the results were unclear and mixed.

You will see that some of the boxes have this kind of cross-line, which means that the study

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compared patients to healthy controls. And if it's coded in this way, it would be the comparison is either to some kind of historic group or just with inpatient -- if it's a patient with distal symmetric polyneuropathy findings in the painful side versus non-painful.

I'll start with the guidelines. If we look at a variety of recommendations of what we should include in the diagnosis of small fiber neuropathy, there have been about 38 different guideline papers on this topic.

We separated the data to sensory symptoms; do we need sensory symptoms in this length dependent distribution; things like burning pain; paresthesia for the diagnosis of small fiber neuropathy; abnormal pin prick in length-dependent fashion; abnormal QSART; autonomic testing results' abnormal thermal perception; autonomic symptoms; abnormal skin biopsy that is with reduced intraepidermal nerve fiber density; and normal nerve conduction study to confirm this is small fiber neuropathy; or a battery of autonomic tests;

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and variety of laboratory tests to exclude other causes of neuropathy.

So the findings are, in general, in the different guidelines for SFN, you can see that about 87 percent of guidelines recommend that we should include sensory symptoms in the appropriate distribution as a part of our diagnosis.

Seventy-one percent of guidelines recommend that we include normal nerve conduction studies as a part of SFN workup. About 84 percent of guidelines recommend to use a skin biopsy to confirm small fiber neuropathy. And as you can see, there's a variety of other parameters, about 40 percent recommend using a normal pin prick as a criteria; 24 percent recommend using a quantitative sudomotor axon reflex; 66 percent recommend using abnormal thermal perception like QST; and then about 40 percent using autonomic symptoms; and smaller percentages of guidelines recommend using either kind of a full battery of autonomic tests or exclude patients by doing laboratory diagnosis

So this is just too small to figure out

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anything, but this is the way we mapped the studies, this set of the studies. It's 11 studies of idiopathic small fiber neuropathy. You can see that each study is here on the left side, and we looked at each of those parameters that were assessed in those patient populations: skin biopsy, distal proximal, or other CCM; corneal confocal microscopy; and then a variety of QST parameters; cold detection, warm detection; neurosensory alignment; et cetera; vibration, et cetera, et cetera; nerve conduction data; additional tests like laser Doppler; flare or synthetic skin response; skin wrinkling; contact heat evoked potentials; laser evoked potentials; and then a variety of autonomic tests.

I think the striking part is there are a lot of white boxes, which means that those parameters were not assessed in those studies. So I think Nurcan is leading the way with the study that has assessed most of the parameter. But in any case, this is a representation of those findings; so, again, 11 studies that are called idiopathic small

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fiber neuropathy and have included patients in whom the etiology is really unknown.

In terms of skin biopsy, 73 percent of the studies, 8 out of the 18, have looked at distal skin biopsy, and all of them are green, so confirm that those patients have reduced intraepidermal nerve fiber density. Only 3 of those 11 studies have looked at proximal biopsies, but again, all of the data was in the same direction.

In terms of nerve conduction, EMG versus NCV, only two of the studies have looked at basically normal EMG. And then in terms of nerve conduction velocity, three of the studies have shown negative or normal NCV, and one has shown mixed results.

In terms of QST, you can see that most of the parameters have been assessed in very few studies, so there's not much data we can draw from it. I think the three parameters that are probably worth discussing are the cold detection, warmth detection, and vibration detection thresholds.

In terms of cold detection thresholds, there

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are eight studies that have looked at cold detection. In 5 out of 8, the patients have impaired cold detection, but you can see that in two studies, the results were mixed, and in one study, 2 patients did not have any difference from controls.

In terms of warm detection, five studies have looked at it and four have found impaired warm detection in inpatients with idiopathic small fiber neuropathy, and one has resulted in mixed results.

In terms of vibration detection, six studies have looked at it; four have found normal vibration detection thresholds in this population, and two have found abnormal. But the rest are really -- the interesting thing is studies that have looked at pinprick in the idiopathic small fiber neuropathy, all the results are mixed. So it doesn't seem that pinprick is really separating small fiber neuropathy from controls.

In terms of additional tests, again, very few studies have actually looked at those things. I don't think it's even a point in focusing on

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those.

(Laughter.)

The second metrics -- again, I just presented it to look at the number of white empty cells. There's so much work to do to try to understand what are the different associations. You can see those columns that are filled primarily. These are the distal skin biopsies that most of the studies have performed. This is proximal skin biopsies. These are called detection and warmth detection, and these are the nerve conduction of muscle, and this is vibration.

Again, to kind of summarize the data from this ugly metrics, we're looking at the same parameters in this group of -- again, these are all small fiber neuropathy, but the populations are mixed in a way.

In terms of skin biopsy findings, you can see that 70 or 80 percent almost have distal skin biopsy, and in the vast majority, the skin biopsy was different from healthy controls, kind of to confirm small fiber neuropathy. A smaller amount

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of studies, about 40 percent, have looked at proximal biopsies. Only seven percent of all the studies have looked at a corneal confocal microscopy, but all of those five have shown differences from healthy volunteers and in production.

In terms of nerve conduction, again, you can see in some, the results are mixed in terms of excluding patients. There are probably some subgroups of patients with large fiber involvement because in a proportion of those studies, the results are mixed.

In terms of QST, there doesn't seem to be a very consistent pattern in those patients compared to controls. So even when we're looking at things they call detection warmth detection, we can see that only about half of the studies have shown clear differences between those small fiber neuropathy populations versus controls. And in the other half, the data or the endings have been mixed.

The same with vibration detection, it's only

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about half of the studies where the vibration detection was normal in those patients compared to healthy controls, but in the half of the studies, there were differences or the results were not as straightforward.

So I think just by looking at the data, we came to realize that it's even more complicated than we thought it is, but nevertheless, these are the findings.

In terms of additional tests like autonomic, et cetera, you can see the picture is vastly mixed in terms LDI flare, which is just heating up the skin and laser Doppler response, sympathetic responses. Autonomic testing results, again, only a small proportion of studies have looked at QSART, 11 percent, but about half have found consistent differences between SFN and healthy controls, and about half have found mixed findings, and autonomic testing has been also not very consistent.

The thing is, though, you can see those three tests, like contact heat evoked potentials, laser evoked potentials, and histamine skin

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response, again, there have been testing in a very small proportion of studies, 5 percent, 4 percent. I don't know if there's a reporting bias or not, but those seem to be pretty consistently separating small fiber neuropathy versus healthy controls.

I think one of the discussions maybe should be around those special tests, is there room for expanding those and maybe having more data in larger patient cohorts, or what might be the publication bias associated with those.

As almost another search, we looked at clinical or therapeutic trials of small fiber neuropathy and looked just at the inclusion criteria, not the characterization of patients. We just looked what kind of criteria people use in clinical trials for enrolling patients with small fiber neuropathy. Most of them are therapeutic clinical trials. There are a few that are overview of studies. And those too have the same patient population in a way, but most of them are therapeutic clinical trials in small fiber neuropathy.

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Interestingly, about 90 percent have relied on relevance symptoms to enroll patients in the study and about 70 percent have used some kind of pain severity cutoff, most of them 4 or more on a 0 to 10 numerical rating scale. And the interesting thing is that although most guidelines recommend to use keen biopsies for diagnosing small fiber neuropathy, if we look at SFN confirmation by skin biopsy, only 22 percent of the clinical trials have used skin biopsy to confirm small fiber neuropathy in these patients, and we had a discussion whether it's a useful or important tool for inclusion or not.

About half of the studies use nerve conduction to exclude abnormal nerve conduction as criteria for inclusion, exclusion of other predisposing factors, and then about a third of the studies use QST, again, to confirm small fiber neuropathy to enroll patients in the study.

This is kind of the overall high level, maybe semi-quantitative presentation of the findings from this systematic review, so I'll just

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try to summarize those. I know those histograms were pretty confusing.

Clinical trials, there were 27 clinical trials in SFN, and in terms of inclusion criteria they used, so neuropathy symptoms, inappropriate distribution that were used by most of the studies, and then certain pain severity cutoff, and then SFN confirmed by normal nerve conduction. So these were the main criteria most studies used.

DR. HOKE: Can I ask a question? How do they design a trial that excludes neuropathy? I mean, how did they include patients that didn't have the neuropathy symptoms? What was the definition of the -- like that 11 percent of the patients who --

DR. HAROUTOUNIAN: Sometimes it's mainly -- the main criteria could be, for example, small fiber neuropathy by skin biopsy, normal nerve conduction, and pain. It didn't clearly say that the distribution of the symptoms should be --

FEMALE VOICE: So more likely it was.

DR. HAROUTOUNIAN: We're kind of just going

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through the inclusion criteria of the studies and extracting this kind of specific information. There was quite a mix in terms of how people define the inclusion. [Inaudible – mic off].

So for guidelines and reviews, again, it's a separate group of papers, 38 papers. The key points are, in terms of what different guidelines recommend for diagnosing small fiber neuropathy, it's primarily looking at the appropriate distribution of sensory symptoms, skin biopsy findings in terms of reducing intraepidermal nerve fiber density, normal nerve conduction, and abnormal thermal perception. These are kind of the main recommendations from most of the guidelines.

If we're looking at those clinical studies, it characterizes patients with small fiber neuropathy in this pure small fiber neuropathy, 11 studies. I think the main take-home messages are that mostly it's the distal skin biopsies that were abnormal in those patients. And this is in 73 percent of those studies In terms of proximal skin biopsies, there are much fewer data.

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These are the percentages that use nerve conduction. About three-fourths, the results were as expected. In terms of cold detection and warm detection testing, you can see that more than half of the studies confirmed that there were differences between SFN and healthy controls, but it's not straightforward, clear-cut that you can find that there are warm detection or cold detection differences.

DR. FREEMAN: Can you clarify something for me? And that is, these were the pure idiopathic small fiber neuropathy, and 3 out of 4 had nerve conduction abnormalities, so 25 percent didn't, and vibration detection, one-third did not.

What I'm confused about is these are obviously launched fiber modalities, whether the result was unexpected. How did they use that information? Because some would say -- not all, but some would say that that is no longer pure.

DR. HAROUTOUNIAN: So the inclusion -- these are studies that characterize those patients, so in terms of inclusion criteria, they say we're

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enrolling patients that have idiopathic small fiber neuropathy with certain criteria and no other known causes of neuropathy. But the extent to which they tested that this is indeed idiopathic and indeed small fiber, quite differs from the studies.

So not all of them used vibration detection to exclude patients.

DR. FREEMAN: I see. So it's not that they did that in a population they were then excluded, but these were included in that --

DR. HAROUTOUNIAN: Were included as idiopathic small fiber neuropathy, but the findings --

DR. FREEMAN: Were as they were.

DR. HAROUTOUNIAN: -- was QST, et cetera. And you can see. Among the 11 studies, only 4 have done vibration detection, right? Only 5 had done warm detection, only 8 have done cold detection.

I mean, we would love them to all those, but it's just some of the data are not there.

DR. UCEYLER: Maybe just a comment on this question. So with the nerve conduction, velocity,

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I think it doesn't matter of definition, also how in these studies normal was defined. According to Lacoma [ph] and Stewart, I think marginally abnormal conduction studies will not exclude small fiber neuropathy.

Another aspect -- I will present data on this tomorrow -- a very interesting finding, I think -- what we see also in others, large fiber neuropathy should be excluded. So we do the clinical examination. We do the nerve conduction studies. This is all normal.

Interestingly, when we do QST, we do find mechanical detection threshold changes in these patients, which we do not understand. But we see this in several studies, and other people also do see this. So we have to think about that. As I said, I will show some data on this. Large fiber or what actually do these fibers sense, this is another question.

DR. HAROUTOUNIAN: And I don't know about the association between NCV findings and mechanical detection threshold, how consistent they are and

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what's the kind of specificity.

DR. HERRMANN: I think your review highlights one thing. All of these studies use somewhat different inclusion criteria for the patient of suspected small fiber neuropathy that's included. And then one of the problems with understanding what the diagnostic yield is of cold detection threshold or skin biopsy is this concept of incorporation bias.

So many of the tests you're looking at are incorporated in your inclusion criteria for the study. So I think that's just the challenge that you have to face when you interpret data, at least diagnostic yield for any of these tests, is just to understand the limitations when the test is actually part of the inclusion criteria, like pinprick, well, some studies require it to be abnormal; some don't.

DR. HAROUTOUNIAN: Those are the methodologies. Some use just a safety pin, but others use Von Frey filaments; others use the MRC German Neuropathic Pain Network weighted pins.

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Actually summarizing these findings was extremely hard because of the heterogeneity of the approaches and methods that people use. So even lumping them into as many categories might do some disservice to some high-quality studies versus highlight some of the findings of the lower-quote studies.

DR. LAURIA: The problem is actually the lack of a gold standard. Right? So the point is that if you don't have one, you don't know –

DR. HERRMANN: You have to used –

DR. LAURIA: -- anyone to find the gains [indiscernible]. That's the reason why at the time, we decided that -- since there isn't anyone, we decided to combine some.

That's in any case, a big issue because this creates an intrinsic limitation that cannot be overcome unless we define that something is the gold standard.

DR. SMITH: The other issue is there's a Bayesian problem here too. It's one of my concerns about how nerve conduction studies are used. In a

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low population prevalence, they work very well. The negative predictive value is quite high. But if you look at a population prevalence where in diabetes, half of patients have neuropathy, the negative predictive value is terrible. And this is compounded by the fact that it's not clear what gold standard one would use to make those kinds of comparisons.

DR. HAROUTOUNIAN: I think maybe the best example of the gold standard is the skin biopsies because before the EFNS guidelines on taking skin biopsies, if you look at the heterogeneity on how people have taken and analyzed biopsies, 3 millimeter, versus 4 millimeter, versus doing 30 micron cuts, versus 40, versus 50, versus 60, what to fixate in, what kind of anti -- there was a huge variability, but actually in the past seven or eight years, skin biopsy findings have been somewhat more consistent where people have followed the guidelines.

So I think it is possible with data to convince users or researchers to use more universal

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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actually accepted a clinical diagnoses of definite neuropathy.

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

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

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

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in the 7 percent who had thyroid dysfunction is causing neuropathy. But what it does show is that the prevalence of many of the things that we routinely test for in patients who we suspect have just a distal symmetric length-dependent axonal polyneuropathy are infrequent and likely not that much more frequent than in the general population.

You can look through these. The big players, of course, are diabetes, vitamin deficiency, and individuals who have immune disorders, and I'll talk more about that and show some of the work that many of the people in the room have done.

This is data that Rob was referring to that we published now almost 15 years ago. This is a group of about 140 individuals who are gathered prospectively, and for each test, this is the percent of individuals who had that test, and this is a busy academic neuromuscular clinic, and this is the frequency with which those tests were abnormal.

For instance, 81 percent of people had a

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TSH, and out of 140 people there wasn't a single abnormality. What you'll notice is that measures of glucose metabolism are the most common abnormalities and everything else really is no more frequently abnormal than one would expect in the general population in this group. So 3 percent had an abnormal ANA. I think it's about 12 percent of blood donors have an abnormal ANA, so that's clearly less frequent than one would see there. The frequency of monoclonal gammopathy was quite low.

So I think it's these kind of data, the perception of these kind of data, that lead to the consensus criteria that I'll show later in terms of diagnostic evaluation for patients with neuropathy.

One vitamin that seems to get a lot of attention certainly in our clinical practice is a pyridoxine. I don't know what it's like in Virginia, but Utahans love vitamin supplements, so we're always on the hunt for people who are using too much vitamin B6, usually because they're taking multiple multivitamins. And we'll often test this

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and find someone whose level is high and go, aha, this may be important.

This was actually a really nice paper where it was fairly significant numbers, 245 patients with neuropathy without ataxia, 33 with ataxia, a sensory motor neuropathy, 133 and 140 controls. And turns out there's no difference in pyridoxine levels across these populations. And there are a number of people, again, across these populations that have high B6 levels.

So no one's really talked about B6, but I think it's a good example of the value of looking at good data in informing your thinking because without this, I think our biases to look at the person who has sensory motor neuropathy and an elevated B6 and think, okay, this may be meaningful; whereas in this data, I'm less clear whether it is.

This isn't to say that someone who's taking megadoses and gets a non-length-dependent ataxic neuropathy doesn't have pyridoxine toxicity, but one needs to be cautious in interpreting these data

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in individuals with a distal symmetric polyneuropathy.

There are a couple of papers, one of which has been referenced explicitly in another. I think Henry has referenced, circumferentially perhaps, about idiopathic small fiber neuropathy. So I just want to go through these because they're perhaps most directly germane to today's conversation.

Anne Louise's study involved 213 patients who had small fiber neuropathy based on skin biopsy, autonomic testing, or nerve biopsy. What they did -- and this is a busy slide, but I can walk you through it -- they did a very comprehensive laboratory evaluation as you can see here, and then compared the frequency of abnormalities to publish a prevalence of abnormalities within that particular test. And then those who are I think green, there was a significant increase in risk in patients who had idiopathic small fiber neuropathy. So for instance, 4 percent had hyperthyroidism, whereas the population prevalence in NHANES was 0.5

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percent.
So you can peruse this. You'll see a few surprising things, which is that diabetes didn't float to the top. Now, a lot of these data are obviously susceptible to referral biases and whatnot, both in negative and positive ways. But you'll see that there are a number of measures of auto immunity that are overrepresented in this population compared to the published population. Now whether or not they are really more common than they would be in another wise matched similarly referral bias population, we don't know.
So for instance, complement levels were abnormal in 11 percent, whereas only 3 percent in a published a study. So take these data for what they are, but they I think show some of the complexity. And we can really cross-reference this with Karin and Ingemar's study that was talked about earlier and Rob showed.
This is a paper that was just published involving 921 patients with pure small fiber neuropathy. And I think for a study of this size,

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this was very, very carefully done. These individuals had abnormal skin biopsy or thermal testing with large fiber modalities being normal and normal nerve conduction study. So you can get into this with the normal skin biopsy, but you couldn't have large fiber abnormalities, and you had to have abnormal thermal testing.
These patients also all underwent a very comprehensive evaluation, as you can see here, including things that you already know aren't going to be useful like alpha galactosidase activity. We'll revisit briefly the sodium channel, but very briefly because I don't want to get -- that's not quicksand, that's a black hole of discussion, and so forth.
This I think Rob already showed, the histogram of abnormalities. The first point is amongst this group of patients with a small fiber neuropathy, 53 percent were truly idiopathic. So there is a population that's sizable in this neuropathy phenotype who do not have evidence of any other abnormality. But keep in mind this

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population has some referral bias. We heard earlier this morning they don't see a lot of patients who have diabetes. And if you go to Eva's clinic, we already heard that most of her patients have metabolic syndrome and prediabetes.
The most common abnormalities are similar to those from the other papers that we've talked about, so B12 deficiency, diabetes, and prediabetes, although less frequent than what we might expect was common. Sodium channels, sequence variants were common. And then auto immune disorders, keeping in mind, though, this is an aggregate of a whole bunch of different auto immune disorders, so sarcoidosis, Sjogren's, celiac, and other.
Sod does a 0.5 percent prevalence of celiac disease really represent a higher number than the normal population? I don't know. Those with a known risk factor -- and this goes to I think Todd's point about people having multiple different risks leading to a common phenotype -- over a quarter had more than one risk factor, so B12

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deficiency and alcohol use. So trying to identify what's causing the neuropathy in any individual patient can be quite challenging.
We've already talked about this and the registry, so I'm just going to skip over that. I did want to talk about this study, which is a little bit far afield, but I think perhaps is a call for common sense in terms of how we think about genetic neuropathies.
This is a study that over about 100 patients who were suspected to have a hereditary neuropathy underwent an almost 200-gene next-generation panel. The first point is there were 6 patients with chronic idiopathic axonal polyneuropathy included, which is intriguing to me why they did, but none of these patients had any disease-causing mutations or variants of unknown significance, so small number.
Well, what's interesting, even in people who one is suspecting phenotypically have a hereditary neuropathy, what's clear is if the age of onset was over 40 and there was no family history, even with the suggestive phenotype, the likelihood of finding

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something on genetic testing was 5 percent, whereas those less than 40 with family history, 33 percent.

I think Karin commented on this earlier, is that one needs to think about the sodium channel, the narrative, and really the whole issue of genetics and small fiber neuropathy with clinical common sense and phenotype and family history.

So just because Ahmet has access to $100-exomes that insurance companies uniformly cover, it doesn't obviate the need for him to exercise a good clinical judgment, which I know he does on a daily basis. I'm just going to start saying in my referrals, I'm from Johns Hopkins, and I'm sure it'll get covered now.

The next thing I want to delve into -- and I can go through this fairly quickly -- is thinking about the intersection between metabolic syndrome, obesity, prediabetes, and neuropathy. There are two reasons to do this. One is I'm kind of a one-trick pony, so if I were to show you my vacation slides, I'd still talk a little bit about this.

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Again, I want to cover it again fairly quickly because I just want to think about it and flip it around. And don't think about it as whether or not this is a meaningful cause for neuropathy, but how would you integrate this and your thinking about designing a clinical trial for idiopathic painful small fiber neuropathy.

The first study I want to talk about is a very carefully done study by Richard Hughes that I'm sure most of you are familiar with where they recruited 50 patients and controls from the same region and did a thorough evaluation. And what they found is in a monovariant analysis, those who had painful neuropathy were more likely to have an abnormal glucose tolerance tests, more likely to have abnormal serum triglycerides in fasting insulin. But in the multivariate analysis, the only thing that percolated to the top was hypertriglyceridemia.

There aren't very many studies that were this careful, and I'll quickly go through many of the same slides that Rob did that I think

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convincingly demonstrate a relationship between prediabetes, metabolic syndrome, obesity, and axonal neuropathy. I think one needs to be cautious about attributing, again, an individual patient causation with these, and these were probably maybe potent risk factors.

I think the first point -- and this is an old slide -- there are over 90 million, probably 100 million Americans now, with prediabetes. About 1 in 3 adults has prediabetes. So again, if you're going to do a study of idiopathic small fiber sensory neuropathy and you're going to exclude all patients who have prediabetes, you have to ask yourself what that does to your enrollment and does that actually make any sense whatsoever?

This is one of more colorful slides. This is the slide that Rob talked about. In the core study, Dan Ziegler's study, there's an increasing prevalence of neuropathy with increasing severity of glucose dysregulation and particular painful neuropathy.

I think one thing to keep in mind, though,

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7.4 percent of the control population had neuropathy and 1.2 percent had painful neuropathy. So again, from a clinical trial perspective, keep that in mind.

I'm going to skip over that. I'm going to skip over that. and I want to come to this slide, which Rob also showed a, which is the data comparing a prevalence of metabolic syndrome and chronic idiopathic axonal neuropathy, and painful chronic idiopathic axonal neuropathy compared to control, so a convincing increase in the prevalence of metabolic syndrome, yet it's still quite high in the control population.

We'll skip over that as well

This is data from our bariatric surgery cohort in Utah to emphasize the frequency with which morbidly obese individuals who are candidates for bariatric surgery have subtle abnormalities of neurological examination and also the presence of neurological or neuropathy symptoms.

So this is the prevalence of an abnormal UENS and the bariatric candidates and controls and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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suggestions that the patient might have a sodium channel mutation, at this point, routine screening is probably not useful.

There's a quote from an epidemiology article earlier that I really liked that I thought I'd put on a slide because I think it really captures the issue, and I'll actually read it.

"Since polyneuropathy probably is a multifactorial disease, it's not entirely appropriate to attribute the development of polyneuropathy to only one factor. These factors should be considered as proponent causes and not as one sufficient cause." And I think several people have made that point today, and I think it's the challenge in determining what's idiopathic and what's not idiopathic.

This is a trial. And I'll just tell you how we approach this. And this, again, is not a small fiber neuropathy trial, although patients with small fiber neuropathy can be included. This is a study of topiramate as a disease-modifying therapy for CSPN. And the idea behind this is that

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topiramate, as you know, causes weight loss and improves insulin sensitivity. It is a sodium channel blocker, which suggests another potential mechanism.

There are a data suggesting that get to Rob's question about epigenetics, that at least in diabetes models, abnormal sodium channel function not only can contribute to neuropathy phenotype, but can then subsequently lead via effects in terms of calcium homeostasis and others to axonal degeneration; so another potential mechanism for this messy drug.

So the way we handled this was because the intent was to impact metabolism in this population, we only included patients who had metabolic syndrome. And in fact, so we're only including patients who are overweight or obese. And the idea here is to try to narrow the population into those who have metabolic syndrome as a risk factor, a major risk factor, for their neuropathy, not arguing that it is positive and to weed out some of those patients who might have other causes, genetic

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causes and so forth.

We obviously needed to exclude other causes of neuropathy, and we did this in two different ways. One was to try to capture clinical judgment, any identified alternative cause of peripheral neuropathy and not limited to -- and [indiscernible] examples. So we didn't require everyone to get hepatitis B or C, but we asked investigators to use their common sense and thinking about these things. This has already engendered a few calls with good questions that I'm happy to share with you; what do we do about this individual patient?

We felt it important to do testing for the guideline -- mandated is too strong a word, but the tests that are suggested by John England's paper. So everyone gets a B12 SPEP immunofixation actually they're only getting an immunofixation. Actually, they're only getting immunofixation in the study and an oral glucose tolerance test, which is in part to exclude diabetes and in part is just an endpoint of the trial; no family history, no

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history of alcohol and drug abuse.

We are biobanking, and I think that's something that we ought to be doing in these studies. It's low-hanging fruit. So here we're just gathering DNA and banking it with the idea that we'll be able to go back and then look at sodium channel sequence variance. If there's an effect, we can look at whether or not any of these sequence variants or polymorphisms seem to predict treatment response, which is somewhat a different question as to whether or not these are risk factors for neuropathy.

So that's kind of how we dealt with it, but one can easily see Todd or Anne Louise doing a study of some sort of immune immunomodulatory therapy in patients with idiopathic small fiber neuropathy that they think have a greater likelihood of having autoimmune mechanisms and constraining the population based on serologic testing or other clinical features that would be fit with their concept.

So that's it. I don't know if that's what

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you're looking for, Roy, but I think I saved a little bit of time, so that's good.

DR. DWORKIN: Questions for Gordon.

DR. OAKLANDER: Great talk, Gordon. With everything [inaudible – off mic].

DR. SMITH: Can we stop there?

(Laughter.)

DR. OAKLANDER: Also factor into our recommendations diagnostic testing. And I think you already – [inaudible – off mic].testing kids and what you need to look for in kids is fairly different; not entirely different [inaudible]. And then number 3 is the cost of the test as well as the diagnostic yield.

DR. SMITH: I agree with everything you said.

(Laughter.)

DR. LEVINE: Just to follow up on what Anne Louise said, if the goal is to try to define an idiopathic group, my thought and listening to you talk there was also limiting age, but in the other direction.

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So you see the curve really start to increase at 60. So if you're trying match the natural history of a disease, defining the age group as a younger population of patients -- I mean normally we cut off 75-80, but then we're talking about 20, 30 percent of the patients that will have it through whatever that disease course, just natural aging as opposed to taking 20 to 60 year olds where the difference may be much easier to see.

I was just wondering what your thoughts were on that. I know we don't usually set the cutoff that low, but it seemed like it might be a logical thing to think about.

DR. SMITH: I'm just going to go. I think I mentioned -- and what other people think of that. I think it's a very sensible suggestion. We certainly see patients who have -- I'm just thinking of the diabetes world, and you'll now see patients who have obesity and type 2 diabetes in their late teens and early twenties who may have neuropathy. But I agree that if I see a

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25-year-old person who has a small fiber neuropathy, my antenna go up.

I don't know that we've got good data on what that means, but I agree it's a sensible thing.

DR. LEVINE: I agree with you exactly. See, there's the curve. It starts to go up at 60, but I think all of us feel differently when you see a 25 year old with a neuropathy than when you see a 75 year old with neuropathy.

DR. SMITH: This curve starts at 50.

DR. FREEMAN: Can I --

MALE VOICE: Last question.

DR. FREEMAN: Can I do that? Thank you.

A couple of questions. That was, as always, a terrific talk. I want to focus the discussion a little on the major reason we're here, and that is the clinical trial. And obviously a clinical trial is a little difference to clinical practice. And you made a statement on one of your slides about clinical trials may be a little different or words to that effect. And I think clinical trials are very different.

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So two points. The one is that we are beginning to, I think, develop the concept that small fiber neuropathy, axonal peripheral neuropathy has multiple potential factors that may work in conjunction and that many of the factors also have a very high prevalence in the population, and in a particular subject may or may not be the causative factor or even one of the component causes.

So with that in mind -- and you have a clinical trial that's ongoing, and a number of people in the audience, including some from pharma, are beginning to develop clinical trials. We need to be fairly explicit about what is acceptable and what is not acceptable and what to look for and what not to look for. And this applies, one, to the screening tests for inclusion and exclusion; and also, as I'm becoming increasingly aware of, treated potential abnormalities like treated thyroid disease, or treated B12 deficiency, or elevated methylmalonic acid or homocysteine levels.

So this is a very broad question, but we're

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going we need to be fairly explicit by the end of the day and certainly at the time of paper writing. Elaborate a little on what do you think is obligatory in a clinical trial, must be done at must be normal?

DR. SMITH: This issue is one of the things that has come up, and I'll give you an example. There's a participant at one of our sites who had celiac disease, had been treated. Their antibodies were undetectable. Their neuropathy started some time after that celiac disease.

I'm setting up a strawman, but we decided that patient was fine to screen because clinical common sense would dictate a neuropathy that started years after a successful treatment for celiac disease that was in remission essentially at this point was appropriate.

On the other extreme, we aren't allowing people -- and I think it would be imprudent to allow people into a clinical trial obviously who have diabetes and neuropathy, or who have a new diagnosis of vitamin B12. The way we're dealing

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with this in another trial we have ongoing right now is patients with diabetic neuropathy trial. Patients who are B12 deficient, we're allowing treatment and rescreening, a bit of a messy solution, but this is a lifestyle based study. So I think part of it may depend on the particulars of the trial.

That's sort of a really vague answer and an intentionally vague answer because I agree with what you're saying.

DR. FREEMAN: So there's a lot of agreement all around. Maybe just a follow-up question. One of the critical questions with all of these trials, impaired glucose tolerance. A lot of people in the audience, pharma, are doing trials on small fiber neuropathy. Do they need to do an oral glucose tolerance test? You said 1 in 3 people in the United States has impaired glucose tolerance.

How do we deal with that inflammation in a clinical trial?

DR. SMITH: I think it depends on the idea behind the clinical trial, the agent's hypothesis.

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So in a trial where we are specifically targeting metabolism, we want to know what the glucose tolerance looks like as a marker of the underlying physiology which are addressing.

I think I kind of think of this in the same way I think of blood pressure and stroke, and I think we may learn a lot from thinking about other multifactorial, complicated conditions with very clear, very potent risk factors. So I think of prediabetes in the same way, is poorly controlled blood pressure to stroke as it is to neuropathy. So if one's doing a stroke trial, you measure the blood pressure, but it doesn't necessarily mean you're going to do something different with it.

So I think my advice would be for a idiopathic small fiber neuropathy study, I would not frankly look at oral glucose tolerance tests unless there was some very compelling reason to exclude patients who had very mild diabetes. I would probably do a standard diabetes screen and not look at it. I don't see the reason one would. On the other hand, I've already given the example,

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where we're doing something to intervene with prediabetes, we of course want to know if that's successful.

But I think the idea that in many of the things that we're measuring now, and this is probably true for the autoimmune markers, to the extent that they're relevant, they're probably not -- and I think it's true in this population for many of the sodium channel variants. If they're relevant, they're probably relevant to the same sort of way prediabetes is, as a risk determinant rather than the primary cause. So that's my bias.

DR. DWORKIN: So let's carry on so we can get coffee. Thanks, Gordon.

Our next speaker is Dr. Chris Gibbons who is an associate professor of neurology at Harvard Medical School, and he's going to be talking about diagnostic instruments used [inaudible – off mic] of cryptogenic sensory polyneuropathy.

Presentation – Christopher Gibbons

DR. GIBBONS: So again, another dubious lecture that I'm slightly honored and slightly

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Actually to go back, everybody's included the standard kind of reliability, construct validity testing almost in everything these days. So I think everybody hits those marks. So the differences really are in these categories primarily and what that means going forward.

One of the ways we ask questions, any particular questionnaire, and highlight what we do is, first of all, what have you looked at? Who are you studying and why? So what are the control groups? What are the disease groups? How do you make the diagnosis of small fiber neuropathy? What are exclusion criteria? These are just sort of the basis for all the talks that we heard about earlier.

Some include controls prominently; some do not. Some control a specific to disease, either impaired glucose tolerance or newly diagnosed diabetes, some mixed disease, some specific things like sarcoid, so very specific diagnoses that may in fact be very relevantly different across disease states when you're comparing these.

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Then looking at how we make a diagnosis, this is pretty critical and this is sort of the topic of discussion for this whole group, how do we decide somebody has a small fiber neuropathy and whether it's truly pure or is it mixed?

Do we include a sign and symptom approach with one abnormal test? Do we say symptoms? Do we say multiple symptoms? Do we say either one test or another abnormal without symptoms? Again, these are pretty important topics that really make a big difference in terms of outcomes of these studies.

So as you can see, there are differences. Some people include controls; some people don't. Some add controls on at later study time points. The disease will vary between these studies, so even though we could think of this as a small fiber neuropathy, it may be small fiber neuropathy in something as opposed to an idiopathic.

Then finally, really, this question of how we make the diagnosis. This is pretty critical and I think one of the major topics for discussion as we go forward in this meeting. Then finally, as

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you just heard from Gordon, what do we exclude and why? And can we justify that going forward and comparing between these tests?

I thought I'd highlight some of these surveys. For people who aren't familiar with them, I thought it would just be useful to discuss a little bit about the questionnaires and what we're looking at. This is the survey of autonomic symptoms. It's a 12-questionnaire with kind of two parts.

The first is do you have the symptom? Either yes or no, during the last six months. And then the next question is, if you have it, how much does it bother you on a 5-point scale? So it's fairly clear, fairly easy to administer, 12 questions, and you kind of get these answers. And because these are really, again as noted in the title, autonomic symptoms, you're really focused in on those components. Some are sweating, some are kind of temperature feet, pale or blue, persistent diarrhea, constipation, urinary difficulty, erectile dysfunction, often what we would think of

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as a standard battery of questions for somebody who might be presenting with an autonomic problem.

Small fiber neuropathy ROD's questionnaire. This is, again, a Rasch-built disability scales, and this is looking at -- it's a 32-question scale, and as you look at the rating, it says 0 to 2 rating. And as you can see, not possible to perform; possible but with some difficulty; possible without any difficulty. So fairly clear in terms of how people complete this, and then the tasks. And these range from brushing your teeth and making coffee or tea, turning a key in a lock, et cetera, going down.

So these are the first 12, and I've included the next 15 to 32 here as well. Most of these are straightforward, and some increasingly more difficult. Again, this is a Rasch-built score, so it doesn't, unfortunately, have a standard numerical output, which is one of the challenges.

There's this symptom inventory questionnaire here, which is another way to look at small fiber

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neuropathy. This is, again, a 13-item questionnaire with a 4-point scale ranging from never to always; here are the questions coming down. And this again hits different domains as we talk about kind of autonomic sensory. Some include sweating, diarrhea, constipation, dryness, urination, palpitations, flushed, and then burning sensation in my feet; cannot stand the sheets on my legs. My legs are restless during the night. So again, this one covers a different selection of particular question.

This one is from the MGH group and their questionnaire. It's small Unfortunately, I'm not sure you can read this, but they also have domains focused here. And these are looking at changes in sweating pattern, or mental fatigue, physical fatigue, skin-burning pain; GI related things, public related discomfort, and again, ranging from never to always in terms of the scale.

So this particular, again, questionnaire, you've seen many of these questions have the same distribution in terms of number of questions or

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options, and then the different domains will vary a little bit in terms of the focus.

The NTSS-6, another one where this is a 6-question scale, however, it's a little bit different in that it's graded by both frequency and intensity in a 4-by-4 block. So the frequency goes from never to continuous and the intensity goes from not present to severe. So again, it's a 4 by 4 block, which is in fact a little bit more confusing if you're trying to administer this. It's not quite as simple checking across the criteria.

So what are the strengths of these scales? Well, in all of them, a large number of subjects that have enrolled. Some actually have large numbers of controls as well. So again, for any of these validated scales, I think this is what we sort of establish as a simple basic limitation, and in all cases, these fit this criteria. They're very well done. There is excellent internal consistency across almost all of them, excellent test/retest reliability; content validity, using many of the previously studied scales again as

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well.

So all of these hit these kinds of fairly high watermarks in terms of how well they've been evaluated. So again, a lot of strengths for each of these. So maybe now I'm going to get into some of the more provocative stuff.

Weaknesses. Why do they have weaknesses and what are they, and should we discuss this further? It comes up to the question, how do we know they have a small fiber neuropathy? What is our gold standard? In this case, we have some disagreement between these scales as to what we define small fiber neuropathy going in.

Is this defined by an abnormal test result, abnormal symptom, a sign, some combination of the above? I could really imagine very different results coming across depending on how you arranged your criteria for entry.

Now, is small fiber neuropathy in a single disease the same thing as small fiber neuropathy in every disease, or idiopathic small fiber neuropathy, or hereditary small fiber neuropathy?

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I see a lot of diabetes. I see a lot of autonomic neuropathies. Is this the same thing as a diabetic autonomic neuropathy or if it's an idiopathic neuropathy?

There are a lot of questions you can ruminate over in this process, and if you're studying a disease, perhaps such a sarcoid, is this actually relevant to any other small fiber neuropathy? So these are questions I think we do have to ask.

Even a bigger question, small fiber sensory neuropathies and autonomic neuropathies. Are these the same disease? Yes, no, maybe. It's an interesting question, but I would say that a patient with a severe isolated autonomic neuropathy is not the same as the severe isolated small fiber sensory neuropathy. And maybe there are some similar mechanisms. Maybe there's some similar problem, but I would say from a phenotype there are very different and probably the underlying etiology, if we ultimately discover what it might be would be very different.

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It does kind of get to this question for our questionnaire, if it's an autonomic questionnaire, we are looking at the apple, or are we looking at the orange, or are we looking at fruit? Which test are we doing for this particular scenario. and is it appropriate to apply this more broadly?

So do we need to be more specific in our definitions of a small fiber sensory questionnaire, is it a small fiber autonomic questionnaire, or is it a domain-specific questionnaire that we subdivide depending on how the result is put out? So these are important details that aren't really discussed.

There are other challenges to questionnaires. Not all are publicly available. Some are actually being developed. And one of the issues, of course, with any particular scale that's in validation, validation is an ongoing process. So maybe the most up-to-date version of the scale isn't available. But if we're going to use this in clinical trials, how do we access this information? How is this available? Can we make it available in

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the public domain? Are there going to be a few hurdles to acquisition of this? This is a problem.

Some questionnaires can't be analyzed simply. You may need a psychometric analysis to actually get into the detail. And if that's the case, is that a barrier to using this more broadly?

So when we ask this question, I think it's an important one if we're thinking about how to make this information widely available for everyone to use and potentially be consistent.

What about disease control subjects? Now this is a topic we sort of really haven't hit on, but people who are not well, who don't have neuropathy, do they have a particular bias, and do those underlying disorders, which may in fact crop up in our population, particularly as we just saw from Gordon slide, this aging population and multifactorial issues -- the questions that are being answered, are these the other diseases that are impacting us, or is this the neuropathy that these questions are being answered by?

So this really comes into a big internal

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conflict bias question that I have, and I sort of ruminate over this probably far more than I should, but do these reflect the patients that I see? So in other words, if I'm using this questionnaire in my patient population, does it mean anything? And I'm going to pick on one questionnaire because I can, and I'm up here, and I've got the mic, so that's what we're going to do.

This is the small fiber neuropathy RODS, so this is a disability score. And I find it fascinating because I look at the questionnaire, and I've kind of gone through the questions with my patients and I've wondered about this. So brushing your teeth, making coffee or tea, turning a key in a lock, picking up small objects, kind of going down through the whole list, I see a range of patients with small fiber neuropathy from very mild, a little burning discomfort in the toes, to the very severe, multiple amputations, really significant neuropathy to the point where, again, there are many complications that have been a result.

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I have yet to find anybody who's done anything saying they can do it all. There's nothing on this list they can't do. Maybe somebody will come up with one of these after an amputation and they haven't kind of regained mobility, but everybody signs this as a 2, which means they're normal.

I have yet to find any of my own patients with any disability if I look at a scale like this. And is this because my patients that I see are very different than the group that sees this with their population? I would say probably. Many of my patients have predominantly small fiber neuropathy from diabetes or diabetes related complications. Maybe that's a different disease. But if I'm looking at this, and I'm seeing no disability, despite amputations, I sort of see a mismatch.

So I struggle with this because it doesn't fit my own perceived bias of what small fiber neuropathy is. I suspect we all have these same perceived biases in what we're looking at, and this is something that maybe as a group we do need a

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better job in kind of discussing what it is we think we're seeing and how it fits to everybody else's practices and referral basis.

So obviously if you're at a genetic center, you don't see diabetes. I don't see much in the way of genetic because I see a ton of diabetes. So maybe there's just, again, this difference, but it's important to bring this to the forefront because I would never use this particular disability score for my patients; it just wouldn't fit, so it's an ongoing question.

So with that kind of discussion, I'm going to jump from diagnostic questionnaires to diagnostic examinations and kind of discuss that a little bit further.

This is a very busy slide, and Jen Gewandter has done a phenomenal job of putting this together. This is coming from an upcoming paper, but this looks at individual examination scores here. This is neuropathy in general scores, not specific to small fiber neuropathy.

This is looking at muscle strength, reflex

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testing, vibration touch, joint pinprick. And what you're seeing here is essentially the distribution of examination. Is it the full limb in the upper and lower, or just part of the limb, so just the distal toes?

So it just sort of gives you an idea of how much any particular test is measuring. Are you measuring everything or are you measuring just a few things?

Over in these columns here, you're seeing the percent of the max score as motor reflex, large fiber or small fiber. What you do immediately see is there, again, expected, depending on the type of score you're interested in, wide variability, up to 90 percent motor or zero percent. So again, big range in distribution of where the focus of the score may be.

Of course we're at a small fiber neuropathy meetings, so where are we here? Small fiber neuropathy, generally 20 to 40 percent or less for many of these. The only exception being the Utah Early Neuropathy score, which is at 60 percent, not

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surprisingly. And again, the distribution, widely variable, but what we're seeing in terms of small fiber focus, that's generally where we are. That would be the highest one, but there are a couple of others in here.

So is that relevant to the discussion? Well, I think it is because obviously if we're doing detailed muscle strength testing, that's probably unnecessary in an isolated small fiber neuropathy. We don't really want to consider the ones that spent a lot of unnecessary time focusing in on irrelevant details.

So kind of highlighting the UENS scale primarily because, first of all, it's publicly available, so it's easy to download. Everybody can get access to it. It is easy to understand. The instructions are simple. It's quite clear. How you rate with a pin kind of distribution on the legs. The motor examination is just great toe extension, pin sensation, allodynia, hyperesthesia, large fiber sensation. They do look at vibration and great toe joint position, and reflexes at the

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ankle.

So it's fairly clear how to do this. This is something that is very helpful if you're thinking about studies, because obviously clarity counts. If you can make a, a study easily accessible to a large group in a multicenter trial, that is helpful. The more complicated an examination, the more likely you are to get that inherent variability, which makes things a little bit messier to move forward with.

So here's what I'm going to pick on, the PNRR group, not necessarily in a bad way. But again, this is the peripheral neuropathy research registry. This is the examination involving this. It's a lot more detail. It's got a lot of data points here. This particular study is looking at more comprehensive neuropathy, so again, it's important to consider what is the goal of the study.

This I would say probably isn't appropriate for a small fiber neuropathy study; again, a lot of detail in areas that are not relevant necessarily

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to what we imagine a traditional small fiber neuropathy to be. However, it is trying to be adaptive to multiple different types of neuropathy in the same trial, and this is where it is a strength. It is comprehensive. Even though it's complicated, it's comprehensive, and it is clear. It's not difficult to complete. Everybody I think will be fairly familiar with the approach once they kind of read through the details.

So it's not a particularly challenging one. It is more complex in terms of the time and effort, but it's fairly clear on a standard neurologic exam what goes where when you review it. Unfortunately, it's not yet validated or publicly available in terms of study because it's -- isn't that correct, it's not yet publicly available?

DR. HOKE: We haven't published it, but hopefully soon.

DR. GIBBONS: So again, it's one of these that it's in an iterative process, so although widely used by many centers in this trial, it's not yet something that has widespread availability.

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So, again, one of the limitations.

This was a study that the Maryland group did kind of looking at examination scores in early neuropathy, in this case due to impaired glucose tolerance, and really looking at some of the details of whether small fiber function or structure was in any way related valuably to an examination.

So this is nerve fiber density at the distal leg, the distal thigh, QSART, cold detection thresholds. These numbers are probably hard to read. The p-values are all particularly nonsignificant mostly because the correlations were particularly bad.

James, am I summarizing that appropriately?

DR. RUSSELL: Sadly, that's true. I wish it weren't, but it is.

DR. GIBBONS: And I think it's an important point to raise because why? Why would all of these correlations have been so bad? And this is looking at multiple different examinations scores, including the UENS, the NDS, NIS-LL, the modified

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Toronto, et cetera.

So it's a lot of very good validated studies, which raises an important question, and I think we can kind of get into these details. All of the skills were terrible and correlating with tests of either structure or function. The modified Toronto correlated best with the diagnosis of neuropathy.

Why? Why do we think it correlated best? Well, because of the inclusion criteria, of course, for this study. Everybody had to have symptoms for less than two years without requiring any science. The modified Toronto is the only scale that asked questions of symptoms. There were no signs required for this, which meant it was probably either extremely earlier, essentially, from a pathology or functional point, probably proceeded many of the abnormalities. So in a very mild neuropathy, all your examination scores will be normal.

I would think we'd probably not be surprised. The only one that was correlating well

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was the modified Toronto because it had questions of neuropathy involved in the examination.

So again, how we want to kind of look at this depends a bit on our outcomes. Again, if we're looking at a defined small fiber neuropathy population that's incredibly early, maybe a nerve density isn't adequate because it's not going to be abnormal yet. Maybe this is a challenge we have to think through; what are the other alternatives.

So I think we have many steps ahead of us in this process, but I do think we need to come to some agreement by disease type or subtype. Are we going to be specific, in this case, for example, impaired glucose tolerance or other types of neuropathy? How do we define those disease states? I think that's really critical. Test questionnaire availability is important. If it's not available, we can't use it. It's as simple as that.

Simplicity utility, so the NTSS is widely used. It is more complicated. I think you'd get more errors in its use because of the complexity of a 4-by-4 block. People get a little confused about

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

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

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

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

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

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

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

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

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assumption being once you're at a certain point, you cannot improve.

Minimum scores I haven't seen too many of, but I think people have included, particularly for disease modification, a minimum requirement of neuropathy on an exam score as well. So some score above a threshold has been a definite definition.

Questionnaires inclusion, I don't think I've seen that particularly as an exclusion/inclusion on the -- the NTSS-6 has been used in some of the diabetic neuropathy trials as a minimum inclusion point, so you have to have a value above a certain amount to be included, an exclusion point above, which I have not seen or I don't know off the top of my head.

For the autonomic, again, we get into there are a number of autonomic scales, particularly if they're autonomic neuropathies. The COMPASS scores have been used. Some people use CAST scores, which we'll talk about -- or I guess David Herrmann will be talking about later in terms of autonomic testing.

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So these scores have been used and defined. I think getting back to your pain questionnaire, I tried to focus a bit more on the small fiber neuropathy specific as opposed to pain just because I thought it would grow into too complicated a topic. But clearly, those are, I think, multifaceted questions that, depending on the trial design and what your focus is on as a primary endpoint, could be a primary endpoint in inclusion/exclusion criteria. All of these could be the case. So yeah, it is dicey.

DR. DWORKIN: Thanks very much, Chris.

(Applause.)

DR. DWORKIN: We will reconvene here at 3:20.

(Whereupon, at 3:05 p.m., a recess was taken.)

Panel Discussion

DR. DWORKIN: We'll go to about 4:15. I'd like to welcome to the panel, in addition to the three speakers, Roi Treister –

(Pause.)

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DR. DWORKIN: -- Dr. Roi Treister, formally at the University of Haifa; and Dr James Russell, professor of neurology at University of Maryland; and Dr Michael Polydefkis, professor of neurology at Johns Hopkins. So welcome.

I think the very best way to start a panel discussion like this, I think is to ask the three people who you haven't seen yet because they weren't asked to be speakers, Dr. Treister, and Dr. Russell, and Dr Polydefkis, whether they have any questions or comments or thoughts about the presentations this afternoon from Dr Gibbons, and Dr. Haroutounian, and Dr Smith.

So starting with you, Roi, any questions?

DR. TREISTER: Sure. Many, many great open questions were raised today. I think what I believe would be the right pathway would be to try to be pragmatic and focus on the drug target, on the condition, on the outcome measure, excluding criteria which are obvious, while trying to answer most of the open questions by using exploratory measures that will be used in the phase 2 studies

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that are coming. Hopefully in the phase 3, there will be some open questions answered.

I have more specific comments regarding -- but I will wait to the right time for these.

DR. DWORKIN: Thank you. Dr Russell?

DR. RUSSELL: Perhaps I can say, you addressed where we are now. Where would you like to see us be on the future? You very systematically went through and you looked at all these measurements that are used and how they may be associated with various measures. But if you were to come up with an ideal measurement, what would you see as that including?

DR. HAROUTOUNIAN: I presented [inaudible - off mic].

MALE VOICE: I don't think you're on.

DR. HAROUTOUNIAN: I think one of the challenges was the huge heterogeneity in taxonomy and terminology that people use and also the inclusion/exclusion criteria of course for the studies. In terms of where I would like to see us

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in a few years, probably the ideal scenario would be can we come up with a set of criteria that have the optimal sensitivity and specificity that we could use for including and excluding patients in clinical studies and probably a different set of those that would be relevant to the clinical setting for diagnosing and then treating small fiber neuropathy.

I think just a more thorough analysis, quantitative analysis of what people have found in different studies looking a bit more thoroughly into what might be the key three or four parameters that could help us with good enough sensitivity and specificity to enroll patients to studies because obviously, there are dozens of various domains that are tested, and apparently most of the things people have done or not necessarily applicable to the setting of large studies or multicenter studies.

So the way I see is to have gold standards of well defined three or four criteria that we'd come to an agreement on the diagnosis of small

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fiber.

DR. DWORKIN: Anything else, James?

DR. RUSSELL: Let me take this a little further. You actually looked at all the diagnostic instruments, and I kind of have some fairly strong views about I think that they are a value in a sense, but perhaps not in a clinical trial setting.

So what would you say based on those instruments that you reviewed? I do appreciate mine are in there, so I won't feel hurt if you deeply criticize those neuropathy endpoints. So what do you think?

DR. GIBBONS: You promise you won't hit me if I say the wrong answer?

(Laughter.)

DR. RUSSELL: Chris, I'm very critical of my own instruments, I have to tell you, so feel free.

DR. GIBBONS: I do think actually the instruments will be a critical part of any clinical trial, and I think both examination and questionnaires are of incredible value.

The disease I like -- well mostly because

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I've spent a lot of time thinking about it, is treatment-induced neuropathy of diabetes, which is a predominantly small fiber, acute neuropathy in a situation where I found it particularly valuable as a construct because there is a dynamic change at the initiation of the problem followed by a period of recovery in people with type 1 diabetes, which means that I can conceptually validate some of these questionnaires and what responds. At least I see a dynamic range that changes, and I can see what happens.

I think there are a couple things that I do see. Examination scores do change. The UENS actually changes fairly dynamically; even the NIS-LL does change as well to a smaller degree. It doesn't have quite the same dynamic range, but what it would allow me to do is pick up any motor involvement.

So at least on my own thinking about this, I would include two examination criteria, one looking at more motor as well as one as small fiber, one to exclude or to define what was involved and one to

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really focus in on the small fiber component. But then on the questionnaire side, I think as you highlighted, I would include a small fiber sensory questionnaire specific and a small fiber autonomic questionnaire specific because I do think they both respond but also informed differently depending on the distribution of symptoms. And I think you need to know that going in from the get-go as to where the population will go.

In this particular population, the treatment-induced neuropathy, almost all our sensory and they have a big component to that. But there is a large autonomic piece, and many of the symptom scores, the autonomic symptoms scores, will respond dynamically to these changes.

So I think there's an incredible value in this, particularly as we're thinking about clinical trials with endpoints that would have patient-oriented outcomes or patient-centered outcomes. I think they need to be included; particularly once the FDA starts to consider clinical trial endpoints, I think it's a

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requirement. So I think we need to have these, but I think we need to be cautious about mixing which for one. But I would actually advocate, depending on the particular disease, having more than one.

DR. DWORKIN: I want to interrupt and assert a moderator's prerogative and push you hard, Chris.

DR. GIBBONS: Okay.

DR. DWORKIN: So I'm hearing that a distinction needs to be made between the questionnaire as an outcome measure, where we give a baseline and some endpoint and look at change group differences, and something administered at baseline to be inclusion criteria in a clinical trial, part of the diagnostic criteria.

I don't know if this is what James was asking, but I didn't hear anything in your talk, or Simon's talk, or any of the other talks that convinced me that there's a questionnaire out there that needs to be included with some kind of threshold score as an inclusion criteria and if we're going to do either a symptomatic or disease modifying clinical trial.

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Is there any sort of questionnaire, or can we just set that aside and leave the discussion of questionnaires for the next meeting of this group, which could be on outcome measures? And then we would talk about which of these questionnaires are reasonable, primary, or perhaps secondary outcome measures. But in the diagnostic inclusion/ exclusion criteria setting, is there anything?

DR. GIBBONS: This was Roy's point earlier, as he was prodding me for the same response, which is, yes, there are absolutely questionnaires that have been used and I think using criteria for threshold. I think the most widely used, at least in the neuropathy, is the NTSS-6, which has had a minimum threshold for inclusion in some studies. You have to have symptoms and it has to hit the score, so that has been used.

DR. DWORKIN: Would you recommend that if we were going to design a clinical trial tomorrow afternoon between 1 and 4, would you recommend that as inclusion criterion for our clinical trial?

DR. GIBBONS: So it would entirely depend on

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whether this was diseased modifying or symptomatic relief. If it was disease modifying, I'm not convinced that I would see a dynamic change. Maybe I would include it as a threshold for symptoms to be involved, but I wouldn't use it as an endpoint perhaps for recovery.

DR. DWORKIN: Use it for diagnosis.

DR. GIBBONS: Diagnosis.

DR. DWORKIN: In a disease-modifying trial?

DR. GIBBONS: I would be hard pressed to say to come up with a good rationale to say they had to be included. I think you would want it for many reasons that may not be scientific.

(Laughter.)

DR. DWORKIN: I'm not letting Michael off the hook. I want Michael that he gets to go.

DR. SMITH: I think for enrollment criteria, I would answer we're going to use whatever taxonomy we come up tomorrow. It seems to me unlikely we're going to tie our taxonomy to a specific instrument. We may include the domains, which is the flavor of the day that that instrument queries. But that's

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not something --

DR. DWORKIN: So that was my point, but said much more succinctly, Gordon. Thank you.

DR. SMITH: You're most welcome.

DR. RUSSELL: I would like to comment on that before we go on to Michael, and that is we have to be very careful with the symptoms scores. schools.

Symptom scores are quite sensitive, as Chris pointed on his lecture. The big problem with them is that there's a high variance, and the variance is the thing that kills you when you look at power analyses for an endpoint measure. So that's the thing that you really have to take into account if you're going to use symptoms scores as endpoint measures.

DR. HAROUTOUNIAN: Maybe if I can add, there's another point. If it's a disease-modifying agent trial and we use some of the symptoms scores to potentially correlate with outcomes, the questionnaires like NPSI, DN4, LANS, they have very little correlation or association with

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morphological changes in small fibers.
FEMALE VOICE: You said very little?
DR. HAROUTOUNIAN: Very little. So questionnaires like the Utah or the Michigan, the ones that are neuropathy scores, they correlate much better with the intraepidermal never fiber density, but symptom questionnaires, NPSI and DN4, they are very poorly correlated with biopsy findings.
So I think it's a caveat, and there's quite a bit of work to be done I think research-wise to understand the association between what is the difference between painful and painless neuropathy because morphology-wise, they're not much different, but symptom-wise, there's a huge difference between them, and what is it that mechanistically differentiates those two patient populations, and only then maybe we can use symptom measures in a meaningful way.
DR. DWORKIN: So I want to make sure that Michael has a chance to comment or question the speakers.

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

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

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

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

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

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

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

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

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

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

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of them as together.

DR. DWORKIN: First Todd, then David.

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

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

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

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

DR. DWORKIN: David and then Roy.

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

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

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is this distal small fiber neuropathy, chronic with a certain time course, probably a very different entity or group of entities from an acute small, non-length-dependent small fiber neuropathy or from a autonomic predominant small fiber neuropathy.

So we at least phenotypically going to have to define the entity and have a set of diagnostic criteria that could be applied across different trials, but then we're not going to enroll people who have no disability or no patient-reported impact in trials.

So while it may not be a diagnostic criteria, some measure of disability or some measure of patient-reported impact and degree of impact is going to have to be there as part of inclusion. So when you do pain studies, you'd take a numerical rating scale of 4 or greater. Well, depending on what you're studying, there's going to be some not diagnostic criteria, but patient impact or disability inclusion threshold. And that could be different depending on what, as Michael said, you're starting

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DR. DWORKIN: Roy?

DR. FREEMAN: So I actually rather like your approach to it, and I'm going to continue the analogy that you build up.

The way I think of a painful peripheral neuropathy trial is you start off and you say, okay, does this patient -- a diabetic painful peripheral neuropathy trial -- does this patient have diabetes? And that's the first question. And the equivalent of that is does this patient not have. And how much do we need to do to define that the patient does not have, well, Gordon is going to tell us exactly how much we need to do, and it's going to be not quite as discrete as the diagnosis of diabetes. But even that, the diagnosis of diabetes as we know is not quite discreet either.

The next step then is does the patient have neuropathy? And then we can talk about -- and David touched on that. But we can decide how we are going to define neuropathy. Will it be defined by a intraepidermal nerve fiber density? Will it be defined by symptoms? Will it be two out of three?

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Will it be proximal? Will it be distal? This is a discussion, but that's the point. Then the third and continuing the diabetic painful peripheral neuropathy trial, we will say does the patient in that case have pain, and is that pain neuropathic?

So we've gone through diabetes, neuropathy, pain, neuropathic pain, because, as we all know, there are many causes of pain in diabetic patients that are not neuropathic. So I rather like the idea of saying, okay, does the patient not have diabetes and everything else, too? Does the patient have a neuropathy? And this is a discussion of distal sensory proximal ganglionopathy pattern can go on in that, and lots of spaces to fill in. And then the equivalent of pain is over here. We are dealing with the diverse manifestations of a small fiber neuropathy, which can be sensory, can be autonomic, can be both.

Here is where I think the small fiber trial is unique. We're going to be talking about whether the drug is a drug directed against pain, or autonomic, or both, and whether the trial is

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symptomatic or disease modifying. So in brief, I like the tree.

(Laughter.)

DR. DWORKIN: How about Chris first, and then there were other people.

DR. GIBBONS: So I just wanted to throw out sort of a conceptual kind of process to kind of work through some of the challenges that we are going to face going forward when we're trying to bring together a consensus on this. We talked about some of the hereditary neuropathies in terms of their genetic components and what the implications of that were. What we really didn't touch on at all were the hereditary sensory and autonomic neuropathies, where clearly you have a population of patients that has a profound loss of small nerve fibers from an early age on.

I guess the question we can ask ourselves amongst those with really no sensory fibers whatsoever in their body, they are missing a set of symptoms that we widely attribute to maybe small fiber neuropathy. Is this in some way informing us

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about the relation of these symptoms to the disease or not? Can we infer something from those patients more broadly into the patients were asking you about? Do the dependent patients with hereditary sensory autonomic neuropathies, the Riley-Day syndrome, the classic ones, why don't they have fatigue? Some of our small fiber neuropathy patients, why don't they?

They clearly have severe mutations or amputations, auto amputations, many issues related to lack of pain, but why don't they have some of these other symptoms that we presume must be mediated by? So is that in some way helping us think about this?

So I'm just throwing that out there, again, as another point to examine.

DR. DWORKIN: I think another systematic review, actually. Other comments, questions from the audience? Yes, Nurcan?

DR. UCEYLER: Maybe one comment to what Roy just said with the tree. So when you look at what the patient does not have and then you go on

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looking for the neuropathy, and at the final stage actually ask for symptoms, the tree just to discuss, with this we would miss the patients I think who do have very typical small fiber neuropathy symptoms like burning pain in their feet and do not have any signs of neuropathy that we can get with the methods we have in hand at the moment.

So there is a segment of subgroup of patients who have burning feet, very, very typical history, and you do the skin biopsy, and you do the QST, and the CCM, and the prep and whatever, and you do not find any sign for neuropathy. You will find some when you do microneurography. This is what we have experienced, a large group of patients going through all this with burning feet. But the sensitivity is not high enough for all these techniques, and in the end you do microneurography and do see spontaneous activity. I like very much the pragmatic way of looking at it with this tree, but just for discussion, there are patients who have, I would say, small fiber neuropathy, but where we do not see the neurography.

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DR. FREEMAN: Absolutely. And I absolutely agree with you, and I have thought about that, and I think my response to you would be you're absolutely right. But I think the likelihood of any clinical trial of introducing patients who do not have neuropathic pain is greater, and that I'm prepared to make that compromise to say that, sure, I may be admitting -- and I don't know -- an unknown number of patients who truly have neuropathic pain, but I would rather do that than risk including patients with metatarsalgia, plantar fasciitis, calcaneal spurs, and all of the other causes of non-neuropathic foot pain. But I take your point in its entirety.

DR. UCEYLER: And maybe one has to distinguish here also, what we are trying to get a criteria for trials, and I think it is, again, something else. I'm thinking about criteria of small fiber neuropathy in general. So what are we using at the moment to make a diagnosis when we see these patients? So am I allowed to call the patient small fiber neuropathy patient if I do not

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find any science for neuropathy?

But I think here we have to distinguish, and for a clinical trial, this is a very pragmatic and good way to go ahead I would say also. And the other question would be for another panel maybe to think about new criteria or reformation of the criteria.

DR. DWORKIN: Rob, I think you had your hand up.

DR. SINGLETON: I think Roy expressed my sentiment quite well. The only other thing, going back a couple of comments, there are a lot of potential criteria and different aspects of small fiber neuropathy, but I think I would advocate that we should be inclusive but honed to somatic sensory exam and complaints.

I take your point there are any number of roles of small fibers, but kind of like Roy's point, there's a limit to how much we can take into account when we consider a practical set of eligibility criteria that will be useful for the majority of clinical trials.

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

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

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

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

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

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

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

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

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hugely complicated, and we can either try to address all those complexities or just say this is the path that's been laid out with mixed fiber, and we're just going to try to follow that path as best we can.

DR. SMITH: I just want to respond. I still am very skeptical of lumping patients with a particular phenotype into small mixed large. I just question why we aren't talking about painful neuropathy with small fiber pathology. There are a number of ways you can parse this, but I'll go back to is there fundamentally something different with patients who have very painful cryptogenic neuropathy, who have normal nerve conduction studies but have evidence of vibratory last on exam versus those who do not.

I see more of those patients than not, and I just worry that we're overcomplicating our criteria for small fiber neuropathy by drawing these really bright lights. I get the idea that there may be scenarios and the genetic data create one. It may be something unique about these very carefully

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defined subsets of patients who have isolated small fiber neuropathy that are different, but is that the taxonomy we're looking for as opposed to a broader painful neuropathy umbrella?

DR. DWORKIN: Simon?

DR. HAROUTOUNIAN: Just kind of to follow, when looking through the studies, there seemed to be almost a rudimentary set of findings that are common to those hundreds of different etiologies and perhaps we should think about a very basic inclusion type, and then each study or each subgroup of small fiber neuropathy we could recommend to do different ancillary type of tests to gain more knowledge.

It looks like the distribution of symptoms, potentially sensory symptoms, and skin biopsy, and perhaps warm detection threshold seem to be pretty consistent among all the trials; again, 80 percent, 75 percent, 90 percent, and the other findings are pretty specific to etiology or patient subgroups, et cetera. So perhaps we should try to focus on this maybe basic rudimentary group of --

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DR. DWORKIN: We have 10 minutes left.

Eva, go ahead.

DR. FELDMAN: Could I just ask a question? It's kind of we're coming full circle. So would you -- and you have really done a very beautiful, careful review -- include symptoms or not in the definition? I mean, really, that's where you start it, right?

DR. DWORKIN: I'm going to --

DR. FELDMAN: I mean, I'm asking him, not you.

(Laughter.)

DR. DWORKIN: Okay, because I was going to say let's talk about exactly that for the next 10 minutes. If I understood Roy's tree correctly, we're going to exclude patients with frank diabetes.

(Crosstalk.)

DR. FELDMAN: No, no --

DR. DWORKIN: The way those of us have been involved in the development of this meeting is that primarily what we would like to do is come up with

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diagnostic criteria for this condition that also include inclusion/exclusion criteria for a clinical trial, and the model here is DSM-V, the ISP diagnostic criteria. So secondarily, perhaps clinical practice, but primarily we're designing a phase 3 trial for NINDS, or a pharmaceutical company is designing a phase 3 trial to go to EMA or FDA. So primarily, diagnostic criteria to be used in clinical trials.

DR. OAKLANDER: Unfortunately, it ends up getting applied in clinical practice, which is what's happened to DSM. Given the absence of clinical diagnostic criteria, our criteria that we publish are going to end up becoming the de facto clinical criteria, and insurance companies are going to deny care reimbursement to patients because they don't fit into our action. I'm just saying at a practical --

DR. DWORKIN: I don't know what we can do about that except put a sentence or two in an article that the primary intent of the diagnostic inclusion/exclusion criteria in this publication

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are for use in clinical trials. I mean, I don't see how we can prevent insurance companies from doing their reimbursement mischief. Unless someone has a better idea of how to prevent that, boy, does that seem above my pay grade.

DR. HAROUTOUNIAN: Can I just take two minutes to address the symptom question?

DR. DWORKIN: Sure.

DR. HAROUTOUNIAN: If we're dealing with painful neuropathy, we have to address pain as symptoms. When we're looking at the specificity of things like burning pain or pins and needles or descriptors or DN4, NPS sites, none of the single symptom descriptors are specific or broadly applicable to different patient populations. So pain should be there, but it didn't seem that --

DR. OAKLANDER: The symptoms should be there.

DR. HAROUTOUNIAN: Pain.

DR. OAKLANDER: Pain.

DR. HAROUTOUNIAN: But I don't know if other symptomatic descriptors are kind of -- none of them

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was consistent enough amongst studies and none of them, both in terms of occurrence and severity, corresponded with the small fiber pathology.

DR. SINGLETON: How about distribution? Did you look at whether these questions about pain were -- did that matter whether it was length dependent or not?

DR. HAROUTOUNIAN: Could you repeat it?

DR. SINGLETON: You just said it doesn't matter what the descriptor is. My question is the distribution, the anatomic distribution. Does it matter whether it's described as length dependent, and was that something that the questionnaires that you evaluated, the measures that you evaluated, was that one of the things that was approached by these?

DR. HAROUTOUNIAN: So the distribution itself is not defined very well, but if you're looking at neuropathy questionnaire, like the Utah or the Michigan and the total score, they were pretty well associated, but not --

DR. SINGLETON: The exam skills had a

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questionnaire, right?

DR. HAROUTOUNIAN: No, we didn't look at the symptoms versus the exam skills.

DR. GIBBONS: So I know this is going to come full circle to your clearly leading question from the very get-go, but I think you did highlight kind of the nudge in that direction, which is we can define a small fiber neuropathy, and then we can define a symptomatic small fiber neuropathy, and it may simply be that we check the first box in order to move onto the second box. But I think defining a symptom as we sort of heard and I think many of us are familiar with, once you've defined a symptom, is it this symptom or that symptom? It can quickly move in a different direction, but I think the starting box has to be small fiber neuropathy.

DR. DWORKIN: We only have 7 minutes left, so let me continue to bark up the wrong tree. Couldn't one imagine symptomatic criteria? I realize there are other inclusion and exclusion criteria, but something like patient needs to have

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self-reported 2 of the following 5 symptoms; and those sensory symptoms are pain; and/or pins and needles, tingling; and/or self-reported, patient-reported numbness; and/or itching; and/or, I don't know, something else.

This is really the DSM-V model. So criterion one is two, it could be three, it could be one of the following five patient reported symptoms. So we don't have enough time to come up with that list now. This is why I left it to the end, but is that something that Roy does tomorrow afternoon starting at 1:00, that criterion one for our diagnosis of small fiber sensory or mixed peripheral neuropathy is a symptom list, and a certain number of those symptoms is required?

Or as I thought I heard Eva 45 minutes ago, maybe pain is so prevalent in this condition that it could be something like patient must have pain in the following distribution, and one of the following other three parasthesia/dysesthesia type symptoms, is that a model that's a reasonable one for tomorrow afternoon's discussion? David?

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

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

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

DR. HERRMANN: Yes.

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

DR. HERRMANN: Absolutely.

DR. DWORKIN: -- they can't have developed these symptoms a week ago. They should have had them relatively stable for six months up.

Amanda, and then Chris.

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

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

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

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

DR. DWORKIN: Chris?

DR. GIBBONS: I think you can take the approach of the symptomatic criteria, but you need to absolutely have qualifiers in there in addition. But I think the classic example that I see in practice is the bilateral plantar fasciitis. They have the exact same complaints walking in the door, but it is not a small fiber neuropathy and it's clearly not treated as such, so you have to have some criteria in there that either brings you in as a loss of functional modality or excluding something else.

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

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

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

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

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

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

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

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

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

Adjournment

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

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

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