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ORIGINAL ARTICLE

# Concept domain validation and item generation for the Treatment-Induced Neuropathy Assessment Scale (TNAS)

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## Abstract

**Purpose** Treatment-induced peripheral neuropathy (TIPN) is a difficult problem experienced by patients with cancer that can interfere with their ability to receive optimal therapy. The Treatment-Induced Peripheral Neuropathy Scale (TNAS) is a patient-reported outcome (PRO) measure developed to assess TIPN symptom burden. However, PRO validation is an ongoing process. The aim of this qualitative study was to define the conceptual model, establish content domain validity, and refine items for the TNAS based on patient input.

**Methods** Patients who received bortezomib, oxaliplatin, or platinum–taxane combination therapy reported their experience of TIPN in single qualitative audiotaped interviews. Themes of the TIPN experience were identified by descriptive analysis of the transcribed interviews.

**Results** Three groups of 10 patients each who had received bortezomib, oxaliplatin, or platinum–taxane combination therapy, for a total of 30 patients, reported their experiences. Two themes reported by patients were TIPN sensations and functional interference. Five sensations (numbness, tingling, pain, heat or burning, and coldness) and five functional impacts (using hands, walking, maintaining balance or falling, wearing shoes, and sleeping) were reported by at least 20% of patients and were selected for inclusion in the TNAS v3.0 for additional psychometric testing.

**Conclusions** The assessment of TIPN must be convenient, reliable, and practical for patients, who are the most reliable source of information about symptoms. The TNAS, developed with direct patient input, provides an easily administered and conceptually valid method of patient report of TIPN burden for use in research and practice.

**Keywords** Chemotherapy-induced peripheral neuropathy · Treatment-induced peripheral neuropathy · Patient-reported outcomes · Qualitative research · Symptom burden

## Introduction

Treatment-induced peripheral neuropathy (TIPN) is a toxicity experienced by patients with cancer that may limit patients' ability to receive optimal therapy [1, 2]. Chemotherapy-induced peripheral neuropathy (CIPN) is the most widely recognized form of TIPN, although it can also be caused by surgery or radiotherapy. Traditional methods for capturing the multifaceted nature of TIPN include a combination of objective neurological tests, clinician evaluation, and subjective patient report, which are not logistically feasible for multisite trials, clinical assessment, and repeated use for monitoring changes in TIPN over time. TIPN assessment must also be convenient, reliable, and practical for patients in clinical trials, who are the most reliable source of information on the efficacy and safety of interventions to prevent and treat TIPN.

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The Treatment-Induced Peripheral Neuropathy Assessment Scale (TNAS) is a patient-reported outcome (PRO) measure of TIPN symptom burden that was developed to address issues related to the adequacy of currently available measures [3]. The psychometric properties of TNAS v1.0 and v2.0 have been reported [3], and further validation and refinement of the TNAS is ongoing. The TNAS was conceived as a brief yet comprehensive and easily administered measure for assessing the severity and course of TIPN across various cancer treatments. To make the TNAS appropriate for use in clinical trials, we have striven to develop it in accordance with the US Food and Drug Administration (FDA) guidance on the use of PRO measures to support labeling claims [4]. The FDA guidance states that "content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use" [4, page 12]. The content domains of two of the most widely used measures of CIPN, the FACT-GOG/Ntx [5] and the CIPN20 [6], were not developed and validated by qualitative interviews with the patients. Further, the FACT-GOG/Ntx was originally developed for use with patients with non-small cell lung cancer receiving taxane therapy. It was subsequently modified for patients with gynecological cancers experiencing CIPN caused by platinum–taxane combination chemotherapy [5]. It was further modified to measure CIPN caused by oxaliplatin [7]. All of these modifications were made without qualitative input from patients.

Most measures of CIPN, including the FACT-GOG/Ntx and the CIPN20, are based on a quality-of-life (QOL) paradigm. In contrast, the TNAS's conceptual basis is the paradigm of symptom burden, defined as the patient's perception of both the severity of symptoms and the impact of those symptoms on daily activities [8]. Symptoms are the most direct patient-perceived, patient-reported indicators of physiological changes that occur from disease and treatment, and patient perception of the effects of symptoms is most proximal to changes in functioning caused by disease and treatment [9]. Symptom burden directly reflects two of the three components of treatment benefit/harm defined by the FDA as "the effect of treatment on how a patient survives, feels, or functions" [4, page 33]. Whereas, QOL is an important factor for evaluating the side effects of cancer therapies, symptom burden is more proximal to the physiological changes that cause side effects such as peripheral neuropathy [9], and therefore it is a more sensitive measure for research and practice.

Initially, the TNAS development team consulted clinicians caring for patients receiving neurotoxic drugs and conducted a literature review of CIPN and PRO neuropathy scales, giving special attention to symptoms and subjective reports of functional interference, as our intent was to develop a PRO symptom-burden measure. The results of this literature review are summarized in Mendoza et al. [3]. The initial content domain and candidate symptoms and functional impairments for TNAS v1.0 were developed from the consultations with clinicians and the review of PRO neuropathy scales.

The 11-item TNAS v1.0 was psychometrically evaluated longitudinally in 164 patients receiving either bortezomib for multiple myeloma or oxaliplatin for colorectal cancer [3]. After cognitive debriefing of the patients receiving bortezomib, two additional items were added to create the 13-item TNAS v2.0. The TNAS v2.0 was then psychometrically tested cross-sectionally in 309 patients receiving either bortezomib or oxaliplatin [3].

Because the content domain and item generation for TNAS v1.0 and v2.0 contained patient input only from limited cognitive debriefing interviews in patients with multiple myeloma, we determined that in-depth qualitative interviews with patients receiving major types of neurotoxic therapy were necessary to ensure that we had truly captured the experience of TIPN. A literature search identified six qualitative studies of patient's experience of TIPN. Women undergoing surgery for breast cancer [10] and patients receiving a variety of neurotoxic chemotherapies [10, 11] reported numbness as a significant problem that was more common than pain [11]. All studies found that at least some patients experienced TIPN-related interference with daily functioning [10–15]. In the trajectory of oxaliplatin-induced TIPN in the year following treatment, patients reported initially hoping that the TIPN would resolve, followed by doubting that TIPN would resolve, followed by beginning to adapt to TIPN, and finally learning to live with TIPN [14]. Patients with oxaliplatin-induced TIPN were willing to put up with TIPN when the treatment was effective in treating their cancer [15]. The studies concluded that comprehensive measures are needed to accurately assess TIPN and its effects [12]. Further, whereas the clinical paradigm of TIPN that focuses on pathological processes is important, for patients, focusing on the experience of TIPN and understanding its impact on daily functioning is critical [13, 14].

The aims of this qualitative study were (1) to delineate the patient experience of TIPN; and (2) to establish the conceptual model, further validate the content domain, and generate items for the TNAS, if necessary.

## Materials and methods

English-speaking patients with multiple myeloma, colorectal cancer, or gynecological cancer who received bortezomib, oxaliplatin, or platinum–taxane combination therapy and who reported developing TIPN during treatment were eligible for the study. The study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, and each patient provided written informed consent to participate.

**Table 1** Qualitative interview guide

| |
|---|
| What is it like for you to have neuropathy from your therapy? |
| What was it like for you when you first developed neuropathy with your therapy? |
| What other symptoms have you experienced that were related to the neuropathy from your therapy? |
| Is there anything else important about having neuropathy that you would like to tell me? |

### Qualitative interviews and analysis

Trained interviewers followed the study interview guide (Table 1) and asked probe questions, as needed, to elicit additional details based on specific patient responses. All interviews were digitally recorded and transcribed verbatim for analysis. The initial sample size was set at 10 patients from each group (multiple myeloma/bortezomib, colorectal cancer/oxaliplatin, and gynecological cancer/platinum–taxane therapy), for a total of 30 patients. If important new symptoms were still being identified after analysis of the 10 interviews from any of the groups, additional participants would be added to that group until saturation was reached—that is, until no further new symptoms were identified by 3 consecutive patients.

Qualitative analysis of the interviews was completed using the method of descriptive exploration [16] performed by two researchers (AGG and LAW) with more than 20 years' combined experience in conducting qualitative studies. Themes and underlying concepts were identified and employed to develop the conceptual model and content domain for an instrument that would measure the occurrence and burden of TIPN (Fig. 1). The number of patients reporting each concept, as the unit of analysis closest to the patients' own words, was tabulated to provide direction for the selection of specific items for the final measure [17].

## Results

Thirty-two patients with TIPN were interviewed between September 2013 and February 2015. Of these, 2 were excluded from further analysis because they did not meet the eligibility criteria: 1 had developed TIPN from thalidomide and 1 from vincristine. Participant demographic, disease, and treatment characteristics are shown in Table 2. Saturation was reached in each of the groups after interviews with 10 patients.

Seven main themes were identified in the qualitative analysis: sensations of TIPN, effects of TIPN on normal functioning, location of TIPN, timing of TIPN sensations throughout the day and relative to treatment, causes of TIPN, management of TIPN, and the future of TIPN. Two of these themes predominated: sensations and effects on normal functioning (Table 3).

The most common sensations reported by patients were numbness (23/30; 76.7%), pain (23/30; 76.7%), and tingling (18/30; 60.0%). Patients frequently described tingling, numbness, or both that became painful over time. Some patients reported TIPN sensations occurring along a temporal continuum, with the first sensation experienced being tingling, followed by numbness, and then pain. Other commonly reported sensations were those associated with temperature, either uncomfortable hot or burning sensations (11/30; 36.7%), or feelings of coldness (9/30; 30.0%).

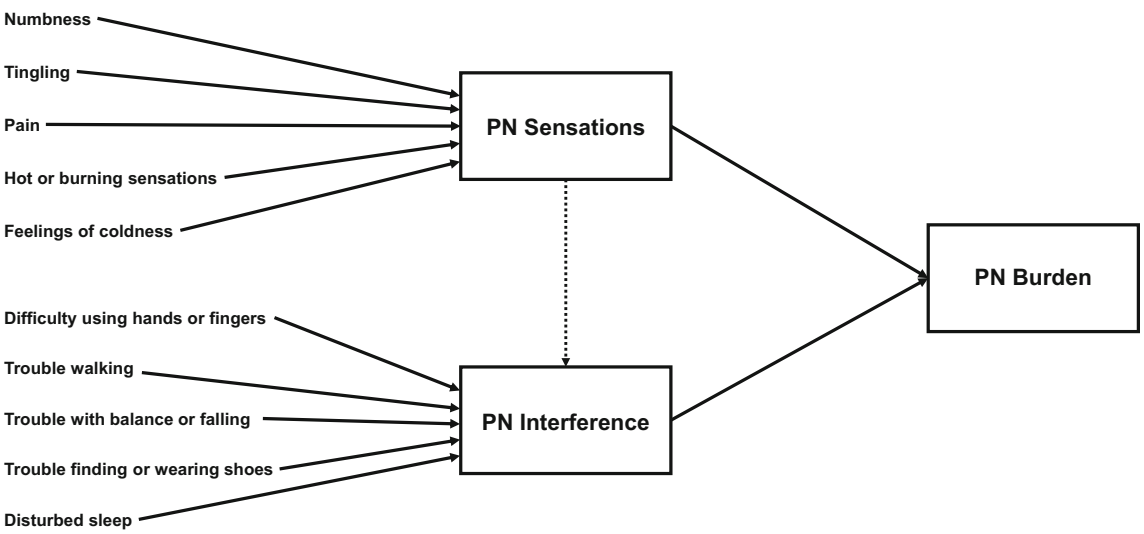


**Fig. 1** Conceptual model and content domain for patient-reported outcome measure of treatment-induced peripheral neuropathy. *PN*, peripheral neuropathy

**Table 2** Patient demographic and clinical characteristics, $N = 30$

| Characteristic | Mean | Standard deviation | Range |
|---|---|---|---|
| Age, years | 60.23 | 11.419 | 42–84 |
| Education level, years | 14.90 | 2.339 | 7–17 + |
| Time since diagnosis, months | 31.13 | 26.190 | 2–102 |
| Weight, Kg | 85.71 | 22.380 | 59.00–164.30 |
| | Number | Percentage | |
| Sex | | | |
| Men | 12 | 40.0 | |
| Women | 18 | 60.0 | |
| Race and ethnicity | | | |
| Non-White and/or Hispanic | 12 | 40.0 | |
| White non-Hispanic | 18 | 60.0 | |
| Marital status | | | |
| Married | 24 | 80.0 | |
| Not married | 6 | 20.0 | |
| Employment status | | | |
| Employed | 14 | 46.7 | |
| Retired | 9 | 30.0 | |
| Disabled | 7 | 23.3 | |
| ECOG PS score (research staff rated) | | | |
| 0 | 4 | 13.3 | |
| 1 | 17 | 56.7 | |
| 2–3 | 9 | 30.0 | |
| Disease | | | |
| Multiple myeloma | 30 | 33.3 | |
| Colorectal cancer | 30 | 33.3 | |
| Gynecological cancer | 30 | 33.3 | |
| Current disease status | | | |
| No evidence of disease | 11 | 36.7 | |
| Partial response | 6 | 20.0 | |
| Stable disease | 9 | 30.0 | |
| Progressive disease | 4 | 13.3 | |
| Current treatment status | | | |
| Active | 16 | 53.3 | |
| None | 14 | 46.7 | |
| Neurotoxic chemotherapy | | | |
| Bortezomib | 10 | 33.3 | |
| Oxaliplatin | 10 | 33.3 | |
| Platinum–taxane combination | 10 | 33.3 | |

*ECOG PS*, Eastern Cooperative Oncology Group performance status

The effects of TIPN on normal functioning most often mentioned by patients were difficulty walking (14/30; 46.7%), difficulty using hands or fingers (11/30; 36.7%), problems with balance or falling (10/30; 33.3%), difficulty sleeping (6/30; 20.0%), and difficulty wearing or finding comfortable shoes (7/30; 23.3%). Frustration or annoyance was mentioned by 9/30 (30.0%) of patients but was not included because many other factors could contribute to frustration and annoyance, and it might be difficult for patients to accurately rate the contribution of TIPN to the frustration or annoyance they were feeling. Patients reported difficulty walking, either because numbness prevented them from knowing where they were placing their feet, or because stepping on the ground was painful. Patients described that TIPN often caused sensations of walking on rough or uneven surfaces even when walking on level ground, causing them to lose their balance and

**Table 3** Patient quotations representative of sensations, interference, and patterns of peripheral neuropathy

| | |
|---|---|
| Sensations | |
| Numbness | Now it's just the numbness …. The other night I was lying in bed on my belly reading, and I had my foot on what I thought was my husband's foot, and I said, "Gosh, your foot feels really weird," and I turned around and realized it was the cat. You know, I cannot tell. I cannot distinguish what's what. And sometimes you play footsies with people under the table accidentally, and you do not know.<br>43-year-old woman who received oxaliplatin |
| | It was hard to pick out shoes because I couldn't really feel if the shoe fit properly because my feet were numb.<br>56-year-old woman who received a platinum–taxane regimen |
| Tingling | And the neuropathy, it gives me … some tingly, like when your hands and feet fall asleep. That's the feeling it gives you …. The best way I can describe it is when your hands and feet, like when they fall asleep on you. You know when … they're falling asleep, how it gives you that tingly and just pins, needles? Kind of like that.<br>46-year-old woman who received a platinum–taxane regimen |
| | It's just some tingling in the heels of both feet …. It's kind of like needles in the heels of both feet.<br>50-year-old man who received bortezomib |
| Pain | Sometimes it's like somebody's taking a hammer and just hitting my feet.<br>62-year-old man who received bortezomib |
| | In the morning it's just numbness, but as the day goes on it starts actually hurting. … It's numbness that progresses into pain<br>47-year-old woman who received oxaliplatin |
| Interference (effects on normal functioning) | |
| Trouble walking | I couldn't think about walking barefoot on anything …. Any type of carpet, mat, anything of that sort, it was off limits …. My feet were highly sensitive, and it was debilitating because you really didn't feel like walking anywhere.<br>45-year-old man who received oxaliplatin |
| | Over time it kind of affects my walk. I feel like I'm kind of walking angularly right now and not having a straight gait.<br>56-year-old man who received bortezomib |
| Difficulty using hands or fingers | I do a lot of writing at home. I write a lot of letters and things to people, notes and stuff, and I've had kind of a hard time writing …. You can imagine if your thumb was numb, you wouldn't have much feeling there to hang on to a pen and write.<br>84-year-old woman who received a platinum–taxane regimen |
| | When you put your fingers on the home row, it's hard …. You make a lot more mistakes because you're not feeling the keys like you would normally feel them. I'm making a lot more mistakes in my typing, which is time-consuming because you have to go back and correct it all …. When it started where it would onset and didn't go away, I just had to quit writing and typing for about a month because it was just such a shock to my system to have that sensation and try to sit there and type.<br>47-year-old woman who received oxaliplatin |
| Trouble with balance or falling | I tend to fall back when I'm standing and I stand for a long time. I have to catch myself. I tend to fall back.<br>64-year-old woman who received bortezomib |
| | Sometimes it messes with my balance. I might just be walking, and something normal that you might trip (on), but it's like an extra trip, because it's exaggerated and you have to balance yourself, and you know that your feet are not normal.<br>56-year-old woman who received a platinum–taxane regimen |

sometimes fall. This, in combination with numbness and pain, caused them to refrain from going barefoot, to restrict walking to smooth surfaces, or to forgo outdoor activities on uneven ground. Some patients also reported difficulty driving due to numbness, because they could not feel the pedals on the car. Some reported near-miss accidents when they had failed to apply enough force to the brake pedal, and some had stopped driving. Pain and other unpleasant sensations in the feet and legs, such as cramping and severe tingling or numbness, caused difficulty falling asleep or staying asleep. Women reported difficulty finding comfortable shoes and not being able to wear the shoes they preferred, such as ballet flats, high heels, and flip flops. Men reported that some types of shoes were more comfortable than others, but they did not report that this restriction in footwear was a problem for them. The most frequently reported problem due to numbness in the hands was the inability to accurately type on a keyboard. Numbness in the hands also caused difficulty in opening jars and bottles, putting on jewelry, and buttoning clothes.

The location of the TIPN was consistently reported as hands, fingers, arms, feet, toes, and legs; only 5 of 30 (16.7%) patients mentioned TIPN at any time as being associated with the head or face.

Patients treated with oxaliplatin frequently reported that infusion of the drug was accompanied by tingling that lasted for several days. This sensation resolved for some patients by the time of the next infusion, but for some patients it did not. Other patients receiving oxaliplatin reported that they had no TIPN symptoms during therapy but developed symptoms several months after the therapy was completed. Patients

receiving platinum–taxane therapy or bortezomib frequently described TIPN symptoms as developing after several cycles of therapy and then persisting.

Because bortezomib is not a standard chemotherapy drug, we looked for differences in the way patients described their experience of TIPN if they were receiving bortezomib versus oxaliplatin or platinum–taxane regimens. For all three groups, the most frequently mentioned sensations were numbness, tingling, and pain. Pain was the sensation most frequently mentioned by patients receiving bortezomib (7/10; 70%); numbness was most frequently mentioned by patients receiving platinum–taxane regimens (9/10; 90%); patients receiving oxaliplatin mentioned pain and numbness with equal frequency (6/10; 60%). Tingling was reported least frequently by patients receiving bortezomib (4/10, 40%) or oxaliplatin (5/10, 50%); patients receiving the platinum–taxane regimen reported pain the least frequently (7/10; 70%). All patients receiving oxaliplatin or platinum–taxane regimens reported either numbness, tingling, or both occurring before they began to experience painful neuropathy, whereas 3 patients (30%) receiving bortezomib reported that the first neuropathic sensation they experienced was pain. Although feelings of coldness in the extremities was reported by several patients receiving either oxaliplatin (3/10; 30%) or platinum–taxane regimens (4/10; 40%), only 1 patient (10%) receiving bortezomib reported this sensation.

### Modifications to TNAS v2.0

Because of the variation in the timing of occurrence of TIPN sensations [18], we deemed it essential to have a measure that could be completed frequently without undue burden to patients, especially during therapy as TIPN may be developing. Therefore, we aimed to keep the revised TNAS (v3.0) short, with only the most common sensations and interferences included.

We concluded from the above analyses that the conceptual model for a patient-reported measure of TIPN burden should include sensations and interference with activities, as was originally hypothesized for the TNAS [8] (Fig. 1). Thus, we identified 10 items for inclusion in the TNAS v3.0 on the basis of those most frequently mentioned: five sensations (numbness, pain, tingling, hot or burning sensations, and feelings of coldness) and five functional intereference items (difficulty walking, difficulty using hands or fingers, problems with balance or falling, difficulty sleeping, and difficulty wearing or finding comfortable shoes).

On the basis of the previous research with the measurement of symptoms [19] and our current findings on the timing of TIPN occurrence, we retained the 24-h recall period of the TNAS v2.0 to allow for frequent measurement if necessary. We also retained the measurement of occurrence and severity of sensations on an 11-point discrete numeric scale, with 0 being not present and 10 being as bad as could be imagined, from the TNAS v2.0.

## Discussion

Although we had developed, psychometrically validated, and refined a PRO measure of TIPN (TNAS v1.0 and v2.0) [3], we were concerned that the content domain of the TNAS was incomplete because of little direct patient input into its establishment. With this study, we intended to hear from patients about their personal experiences of TIPN and to incorporate this into the content domain of the TNAS, as recommended by the FDA.

Patients have been experiencing TIPN as a significant toxicity from cancer therapy for more than half a century [20]. TIPN is associated with a variety of drugs used in cancer treatment, including the vinca alkaloids, in use since the early 1960s; the platinum-containing drugs, in use since the late 1970s; the taxanes, in use since the early 1990s; and the immunomodulatory drug thalidomide and the proteasome inhibitor bortezomib, in use since the early 2000s [21]. Newer agents, such as the antibody–drug conjugate brentuximab vedotin, are known to cause TIPN [22].

Only a few studies have asked patients to describe the experience of TIPN. These studies report that patients describe the sensations of TIPN differently but most often report numbness and sometimes pain. Patients often report that TIPN affects common daily activities. However, none of these studies sought to elicit concepts, develop a conceptual model, or establish content domain validity for a PRO measure of the burden of TIPN.

Since the issuance of the FDA's guidance on the development of PRO instruments for use in labeling claims [4], a variety of instrument developers and professional societies have suggested methods and best practices for meeting the guidance requirements for achieving content validity in a PRO measure [17, 23–28]. The conceptual model determines the content domain of a PRO instrument and defines the major concepts contained in the phenomenon of interest. Establishing content validity is dependent on comprehensively determining the aspects that comprise those concepts. In PRO development, care should be taken to ensure that both the concepts and their aspects are those that are of the greatest importance to patients experiencing the phenomenon [26].

We interviewed 30 patients with TIPN to confirm the conceptual model and establish comprehensive content validity for a PRO measure of TIPN burden. Similarities exist between our findings and those of other studies of the experience of TIPN. However, many of the other studies included only patients who had received either oxaliplatin [13–15] or taxane [10]. The greatest number of patients in our study reported numbness and pain as the most severe and bothersome

sensations they experienced. Tofthagen [11] found that numbness was the most significant and prevalent symptom reported by a group of patients receiving a variety of neurotoxic chemotherapies, primarily platinum derivatives and taxanes; Bennett et al. [13] found that numbness was troublesome for patients receiving oxaliplatin. Bakitas [12], who interviewed patients experiencing TIPN from a variety of chemotherapy drugs, found, as we did, that pain was an important manifestation of TIPN. Besides patients receiving either oxaliplatin or platinum–taxane combination therapy, we also included patients receiving bortezomib, and these were the only ones to report pain as the first sensation with no numbness or tingling.

Other researchers found, as we did, that TIPN interfered with patients' lives in a variety of ways. Bennett et al. [13] and Tofthagen [11] also found that patients had problems walking on uneven terrain. Patients reported to both Bakitas [12] and Bennett et al. [13] that TIPN had necessitated changes in footwear, just as we found that especially women reported difficulty finding comfortable shoes. Some patients reported to Bakitas [12] that they had difficulty driving, as did some of the patients we interviewed.

Although we asked patients to describe their overall experience of TIPN, we focused our interviews and analysis on the patients' symptomatic experience and its effect on their daily functioning, so as to determine a valid and complete conceptual model and content domain for a symptom burden PRO measure of TIPN. We counted the number of patients mentioning different sensations and functional impacts and included in the TNAS v3.0 the sensations and functional impact items that were mentioned by at least 20% of the patients interviewed. Even though many of the items in the TNAS v1.0 and v2.0 were confirmed in the qualitative interviews, there were differences in the ways patient described the experience of sensations and functional impact of TIPN. A notable difference was that many patients in our study reported TIPN as being painful at times, yet pain was not included in the TNAS v1.0 or v2.0. Patients clearly separated the sensation of numbness from the sensation of tingling, and not all patients reported experiencing both sensations. Patients reported difficulty walking for reasons other than feet feeling numb, most often because of pain. Patients reported many effects from TIPN in the hands, other than difficulty grasping small objects.

The TNAS v3.0 containing five items representing sensations of TIPN and five items representing functional interference is currently undergoing psychometric testing to determine its validity, reliability, and sensitivity. The items will also undergo cognitive debriefing to determine if they are meaningful and understandable to patients.

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## Compliance with ethical standards

**Conflict of interest** Drs. Mendoza and Cleeland report a grant from Genentech during the conduct of the study. Dr. Williams reports grants from US Cancer Pain Relief Committee and from Genentech during the conduct of the study; and personal fees from Pled Pharma and Immune Design Corp, grants from AstraZeneca, Merck, Bayer Pharmaceuticals, and Bristol-Myers Squibb, and non-financial support from Amgen outside the submitted work.

**Research involving human participants and/or animals** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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