Table 1: Psychometric Property Definitions

Psychometric Properties	Definitions
Internal Consistency Reliability	Scale items measure the same construct
Equivalence Reliability – Inter-rater	Consistency of different raters
Stability Reliability – Intra-rater	Consistency of the same rater over time
Stability Reliability – Test-retest	Consistency of the test over time
Sensitivity Sensitivity & Specificity	Detects subtle differences, no floor or ceiling effects Ratio of a true positive to a true negative test
Content Validity	The content of a scale is representative of the intended conceptual domain.
Criterion Validity (2 types)	Compared to a gold standard measure
- Concurrent Validity	The measure can estimate present performance on a criterion compared to gold standard.
- Predictive Validity	Estimates future performance of a gold standard
Construct Validity (4 types)	The measure relates to other measures consistent with theoretically derived hypotheses.
- Convergent Validity	Correlation with similar measures
- Discriminant Validity	No correlation between dissimilar measures
- Contrasting Group Validity	Discriminates between contrasting groups
- Structural Validity	Scale items cluster related to a similar construct
Responsiveness	Detects change over time
Feasibility	Easy to use

Table 2. Sample Search Strategy in PubMed

Concept	Search terms
Peripheral Neurotoxicity	"peripheral neuropathy"[tw] OR neuropathic[tw] OR neurotoxicity[tw] OR CIPN[tw]
Chemotherapy	chemotherapy[tw] OR chemotherapies[tw] OR vincristine[tw] OR oncovin[tw] OR vinblastine[tw] OR vinorelbine[tw] OR vindesine[tw] OR vinorelbine[tw] OR "vinca alkaloid"[tw] OR "vinca alkaloids"[tw] OR oxaliplatin[tw] OR eloxatin[tw] OR cisplatin[tw] OR carboplatin[tw] OR platinum[tw] OR platinums[tw] OR taxane[tw] OR taxanes[tw] OR docetaxel[tw] OR paclitaxel[tw] OR ifosfamide[tw] OR ifex[tw] OR Ixabepilone[tw] OR epothilone[tw] OR Epothilones[tw] OR Bortezomib[tw] OR “proteasome inhibitor”[tw] OR “proteasome inhibitors”[tw] OR Thalidomide[tw] OR Lenalidomide[tw] OR procarbazine[tw] OR thiotepa[tw] OR podophyllin[tw] OR “topoisomerase inhibitor”[tw] OR teniposide[tw] OR etoposide[tw] OR vepesid[tw] OR vumon[tw] OR gemcitabine[tw] OR "Induction Chemotherapy"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Consolidation Chemotherapy"[Mesh] OR "Maintenance Chemotherapy"[Mesh]
Cancer	cancer[tw] OR oncology[tw] OR tumor[tw] OR tumour[tw] OR carcinoma[tw] OR malignancy[tw] OR malignancies[tw] OR malignant[tw] OR neoplas*[tw] OR "Neoplasms"[Mesh]
Pediatrics	Infant[MeSH] OR Infant[tw] OR Infants[tw] OR infancy[tw] OR Newborn[tw] OR Newborns[tw] OR Baby[tw] OR Babies[tw] OR Neonatal[tw] OR Neonate[tw] OR Child[MeSH] OR Child[tw] OR children[tw] OR Schoolchild OR "School age"[tw] OR Preschool*[tw] OR Kid[tw] OR kids[tw] OR Toddler*[tw] OR Adolescent[MeSH] OR Adolescent[tw] OR Adolescents[tw] OR Adolescence[tw] OR Teen[tw] OR teenager[tw] OR teens[tw] OR Boy[tw] OR boys[tw] OR Girl [tw] OR girls[tw] OR Minors[MeSH] OR Minors[tw] OR Pediatrics[MeSH] OR Pediatric[tw] OR Pediatrics[tw] OR Paediatrics[tw] OR youth[tw] OR "Young Adult"[Mesh] OR childhood[tw]

Table 3: Summary of Pediatric CIPN Measurement Evidence

Author and Year	Study Design & Purpose	Sample & Setting	CIPN Measure	Methods	Reliability Results	Validity Results	Sensitivity, Responsiveness & Feasibility Results	Limitations
Gilchrist 2009[1]	Design: Descriptive, prospective, cross-sectional correlational Purpose: Develop the ped-mTNS and test feasibility for use in school-aged children	Children with Cancer: *N*= 20 - 55% ALL - 25% lymphoma - 20% solid tumors - Ages 5-18 years old: $\bar{X}$ age = 10.6 years - 85% received vincristine, 15% cisplatin Therapy: 85% had been receiving vincristine or cisplatin for >30 days; 15% had been off therapy for ≤ 2 months	ped-mTNS	Pilot study involving the modification of adult TNS to develop pediatric ped-mTNS. A single examiner administered ped-mTNS once using standard symptom questions, assessment of pin sensibility (Medipin), vibration sensation (Rydel-Seiffer tuning fork and biothesiometer), strength (MRC scale), and deep tendon reflexes. Reliability: internal consistency assessed via Spearman inter-item correlations. Feasibility: assessed via patient participation rate, administration time, and providers' ability to complete scale items. Face validity: One neurologist evaluated the appropriateness of the content and scoring rubric of the interview and 4-part neurologic exam for children ages 5-18. Experts clinicians (*N* = 3) evaluated the content of the pediatric-mTNS and the ability to perform the test in the clinic among children ages 5-18. Construct Validity: assessed via Spearman correlations between two vibration sensation assessment techniques (Rydel-Seiffer tuning fork and Biothesiometer)	Reliability: Pin and vibration sensibility scores did not correlate with each other (*r* = -0.285) or with sensory symptoms (*r* = -0.142, 0.126, respectively). Motor symptoms were moderately correlated with strength (*r* = 0.544), DTRs (*r* = 0.456), and vibration sensation (*r* = 0.613).	Face validity: Results not reported Construct validity: Convergent validity was demonstrated when comparing tuning fork to biothesiometer scores, which were moderately correlated (*r* = -0.72 at finger, -0.63 at toe).	Sensitivity: Possible floor effects for items with scores that did not encompass the entire 0-4 range (sensory and motor symptoms, pin sensibility, deep tendon reflexes). Low mean scores 0.4 – 1.2) for 6 of the 7 ped-mTNS items. Sensitivity/Specificity: The tuning fork identified more (+4) abnormalities than the biothesiometer. Tuning fork sensitivity = 1.0; specificity = 0.6. Responsiveness: Not tested Feasibility: Demonstrated via successful completion of all test items in <10 minutes in all patients	1) Small sample size, lack of control group, single examiner 2) 85% of participants received vincristine, limiting the generalizability of the findings 3) Limited formal psychometric testing of reliability and validity 4) Face validity methods and results not provided 5) Limited assessment of sensitivity and specificity of individual items. 6) Cross-sectional design prevented assessment of responsiveness to change. 7) ped-mTNS examination procedures for evaluating light touch, pin sensation, strength, and reflexes varied from other published methods, and thus the findings may not be comparable across other studies 8) Lack of control for obesity, steroid-induced myopathy, and genetics.
Gilchrist 2013[2]	Design: Descriptive, prospective, cross-sectional correlational, case control Purpose: To investigate the reliability & validity of the ped-mTNS as a	Children with Cancer: *N*= 41 - 23 ALL - 6 lymphoma, - 12 solid tumors - Ages 5-18 years old: $\bar{X}$ age = 9.6 years - 40 were receiving vincristine, 1	ped-mTNS	Internal consistency reliability: assessed with Cronbach's alpha and item-total score correlations Intra-rater reliability: intraclass correlation coefficients were calculated using data from 10 patients who were tested twice by the same investigator using the ped-mTNS. There was ≥ 1	Internal consistency reliability: The ped-m-TNS demonstrated acceptable internal consistency with no items scoring less than 0.3 on the corrected item–total	Construct validity: 1) Contrasting group validity was demonstrated based on a statistically significant difference in mean total ped-mTNS scores between children receiving neurotoxic chemotherapy and	Sensitivity Analysis: - 9.8% of controls received score = 0 (lowest score) - No subjects or controls received the highest score of 32, suggesting that the instrument may have a floor effect.	1) Data regarding the sensitivity of individual item scores were not provided. 2) 96% of participants received vincristine, limiting the generalizability of the findings 3) Time between intra- and inter-rater reliability testing may have been too short to eliminate rater recall bias

	measure of CIPN in school-aged children and adolescents	vincristine & cisplatin, 1 cisplatin Gender- and age-matched controls: *n* = 41		hour between the two tests. Inter-rater reliability: intraclass correlation coefficients were calculated using data from 10 patients who were assessed by two different trained physical therapists using the ped-mTNS. There was ≥ 1 hour between the two tests. Construct Validity: 1) Contrasting group validity: assessed by comparison of mean ped-mTNS scores from children receiving known neurotoxic chemotherapy and age- and gender-matched controls 2) Convergent validity: assessed based on the correlations between ped-mTNS scores and BOT2 measures of balance and manual dexterity. Sensitivity Analysis (ceiling and floor effects): assessed based on the number of cases receiving the lowest and highest ped-mTNS score.	correlation and an overall Cronbach's alpha of 0.76. Intra-rater reliability: The ped-mTNS has acceptable intra-rater reliability based on an ICC of 0.99 (95 % CI 0.96–0.99). Inter-rater reliability: The ped-mTNS has acceptable inter-rater reliability based on an ICC of 0.98 (95 % CI 0.95–0.99).	controls (subjects, 8.7±4.2; range: 2–18; controls, 1.4±0.9; range: 0–4; p<0.001). There were no significant differences in autonomic symptoms and pin sensibility item scores when comparing the two groups. 2) Convergent validity was demonstrated based on statistically significant negative associations among ped-mTNS mean scores and BOT2 balance (*r* range: 0 −0.626, p < 0.001) and manual dexterity (r range: 0−0.461, p<0.001). No correlation between ped-mTNS total scores and cumulative vincristine dosage		4) Use of the Biothesiometer to assess vibration thresholds limits the generalizability of the findings and feasibility for use in settings where this equipment is not available. 5) Cross-sectional design prevented assessment of responsiveness to change. 6) ped-mTNS examination procedures for evaluating light touch, pin sensation, strength, and reflexes varied from other published methods, and thus the findings may not be comparable across other studies 7) Lack of control for obesity, steroid-induced myopathy, and genetics.

Gilchrist 2014[3]	Design: Descriptive, prospective cross-sectional correlational Purpose: Comparison of CTCAE v.3.0 and ped-mTNS scales' sensitivity and specificity, and assessment of CTCAE construct validity when compared to the ped-mTNS	Children with Cancer: $N = 60$ - 50% ALL - 23.3% lymphoma - 26.7% solid tumors - Ages 5-18 years old: $\bar{X}$ age = 10.7 years -59 were receiving vincristine, 3 cisplatin, 2 vincristine & cisplatin	ped-mTNS, CTCAE v.3.0 (retrospective-ly abstracted from clinical notes by a trained rater)	A single ped-mTNS assessment was carried out following chemotherapy administration (3-4 months post commencement in solid tumors or lymphoma, 2 weeks post delayed intensification treatment phase in ALL) followed by clinical review within 24 hours. CTCAE scores were retrospectively obtained by a single trained abstractor, based on medical notes taken at the clinical review. Specificity and sensitivity: based on motor and sensory CTCAE score comparisons to ped-mTNS strength and light touch items Construct Validity: Assessed based on the correlation between combined sensory/motor CTCAE and ped-mTNS scores	NA	Construct validity: Convergent validity: There was no correlation between ped-mTNS scores and combined motor and sensory CTCAE scores. The only ped-mTNS item that correlated to CTCAE scores was strength testing ($r = 0.43$; $p < 0.01$).	Sensitivity ped-mTNS: - Detected more patients with neurotoxicity than the CTCAE. - 84% of patients receiving a combined score of 0 on CTCAE demonstrated a score of ≥5 on the ped-mTNS. Sensitivity/Specificity Sensory CTCAE: - Compared to light touch evaluation, sensitivity = 0., specificity = 0.8 - Failed to detect sensory neurotoxicity in 40% Sensitivity/Specificity of Motor CTCAE: - Compared to manual muscle testing, sensitivity = 0.7, specificity = 1.0 – Failed to detect motor neurotoxicity in 15%	1) Lack of prospective CTCAE grading 2) 59 of 60 participants received vincristine, limiting the generalizability of the findings 3) Site-specific idiosyncrasies (such as automatic referral practices for ankle foot orthoses) which may affect the documentation of neurotoxicity in the medical record, and the subsequently derived CTCAE grades. 4) Cross-sectional design prevented assessment of responsiveness to change. 5) ped-mTNS examination procedures for evaluating light touch, pin sensation, strength, and reflexes varied from other published methods, and thus the findings may not be comparable across other studies 6) Lack of control for obesity, steroid-induced myopathy, and genetics.
Gilchrist 2018[4]	Design: Descriptive, prospective longitudinal, correlational Purpose: Although not designed as an instrument development study, one aim was to explore the association between CIPN and balance impairment using the ped-mTNS and an established balance measure.	Children with Cancer: $N = 86$ - 28 ALL - 32 lymphoma - 26 solid tumors - Ages 5-18 years old: $\bar{X}$ age = 10.0 years -65 were receiving vincristine, 2 bortezomib	ped-mTNS, BOT-2 balance items	Longitudinal evaluations of balance were carried out at different time points, given different treatment schedules. ALL patients were first evaluated within 2 weeks of the end of delayed intensification (6 months into treatment), lymphoma and solid tumors within 3 months after treatment initiation. At 6 months a follow-up evaluation was performed. BOT-2 was administered according to standard procedures. Neurotoxicity was evaluated via ped-mTNS. Concurrent validity: assessed via Spearman correlations between ped-mTNS and BOT-2 balance scores during and 6 months post chemotherapy treatment	NA	Construct validity: Convergent validity: ped-mTNS and BOT-2 scores during treatment were moderately correlated during ($r = -0.34$; $p = .005$) and 6 months post-chemotherapy treatment ($r = -0.31$; ($p = .01$)	NA	1) No control for non-CIPN causes of balance deficits (e.g., cranial radiation, intrathecal chemotherapy, limited ankle range of motion, steroid myopathy 2) 65 of 86 participants received vincristine, limiting the generalizability of the findings 3) 24% drop-out rate 4) ped-mTNS examination procedures for evaluating light touch, pin sensation, strength, and reflexes varied from other published methods, and thus the findings may not be comparable across other studies 5) Lack of control for obesity, steroid-induced myopathy, and genetics.

Lieber 2018[5]	Design: Cross-sectional, observational study Purpose: To compare quantitative sensory testing (QST) to nerve conduction studies (NCS) and rPed-mTNS© and assess correlations with CIPN risk factors	Children with Cancer from 2 study centers: *N*=46 - ALL diagnosis - Ages 6-18 years old: $\bar{X}$ age = 9.8 years - Vincristine treatment completed - Sample included patients 3 months to 10 years post treatment. Therapy: >12mg/m2 vincristine treatment	Reduced Ped-mTNS©, NCS, QST	A single assessment was undertaken using QST protocol, nerve conduction velocity of sensory nerves, and reduced ped-mTNS© (r-Ped-mTNS©: 5 of 8 items only, omitted vibration, light touch and pinprick items). Construct validity: evaluated by testing the correlations between the CIPN measures and known risk factors for developing CIPN (i.e., age at diagnosis, gender, and time interval after completion of chemotherapy). Contrasting group validity: assessed by comparing mean QST parameter scores from cases to published normal reference values Sensitivity/Specificity: QST parameters (vibration and mechanical detection thresholds) were compared to r-Ped-mTNS© and sensory nerve conduction velocity (NCV)	NA	Construct validity: Neither QST parameters, NCV, nor rPed-mTNS© correlated with known risk factors for developing CIPN (i.e., age at diagnosis, gender, time since last chemotherapy). Contrasting group validity: Mean scores for several QST parameters were worse than published mean reference scores from healthy controls (*p* range 0.019 to < 0.0001)	Sensitivity/Specificity of QST: - QST parameters vibration and mechanical sensation tests were sensitive (detected true positive finding) in 86% and 57% of patients with slowed NCV. - QST detected true negative vibration and mechanical detection abnormalities in 31% and 36%, respectively Sensitivity/Specificity of r-Ped-mTNS©: - Detected true positive in 29% of patients with slowed NCV. - rPed-mTNS detected true negative findings in 67%	1) r-Ped-mTNS© omits all objective sensory testing and only leaves symptom report, weakness and deep tendon reflexes. 2) QST findings were compared to sensory nerve conduction velocity testing, which is not a valid measure of vincristine-associated sensory and motor function abnormalities 3) Small sample 4) Lengthy QST battery that requires patient attention and cooperation 5) Lack of control for obesity, steroid-induced myopathy, and genetics.

Smith 2013[6]	Design: Multi-site, descriptive, prospective longitudinal, correlational Purpose: To examine the sensitivity, reliability, validity, responsiveness and clinical feasibility of several VIPN measures for use in children with ALL.	Children with Cancer from 4 academic centers: *N*=65 - ALL diagnosis - 1-18 years: $\bar{X}$ age = 6.4 years Assessments: *N* = 806 Therapy: 100% were receiving vincristine -Mean vincristine cumulative dosage = 12mg/m2	TNS©-PV, NCI-CTCAE, Balis grading scale, FACES Pain Scale	TNS©-PV^, NCI-CTCAE, the Balis grading scale, and the FACES Pain Scale were obtained by trained assessors at baseline and with each vincristine dose over 15 weeks Blood was obtained at several time points to quantify pharmacokinetic Parameters (AUC). Sensitivity: assessed via item and total scores means, ranges, and SDs Internal consistency reliability: assessed with Cronbach's alpha and item-total score correlations Inter-rater reliability: weighted kappa coefficients were calculated using TNS©-PV data from 19 patients who were assessed by a trained rater and a neurologist Construct Validity: Convergent validity: assessed based on the Spearman ρ correlations among the TNS©-PV, Balis grading scale, NCI-CTCAE, and the FACES pain score, cumulative vincristine dose, and AUC Responsiveness: assessed via Mann-Whitney tests of changes in mean scores over time from baseline to week 15 and effect size (*es*) Feasibility: based on the % of VIPN assessments that were obtained in children ≤ 3 years of age	Internal consistency reliability: The Cronbach's α for a reduced, 5-item TNS©-PV (i.e., worst subjective symptom, temperature, vibration, strength, and reflex items) was .84. Poor item-item correlations for laryngeal and constipation items (all $r < 0.13$) Inter-rater reliability: The TNS©-PV scores obtained by trained raters correlated moderately strongly with neurologist TNS©-PV scores (*Kw* range = 0.54-0.99) (*n* = 13-19) except paresthesia item (*Kw* = 0.15).	Construct validity: Convergent validity: The TNS©-PV scores correlated with cumulative vincristine dosage ($r = 0.53$; $p = 0.01$), pharmacokinetic parameters/AUC ($r = 0.41$; $p = 0.05$). The TNS©-PV positively correlated with the CTCAE and Balis grading scale scores (r range = 0.46 - 0.52; $p = 0.01$). The CTCAE sensory and Balis motor grading scale scores positively correlated with vincristine dosage ($r = 0.31$, $p = 0.05$; $r = 0.35$, $p = 0.05$, respectively). Grading scale scores did not correlate with pharmacokinetic parameters/AUC FACES scores positively correlated with the TNS-PV neuropathic pain item ($r = 0.48$; $p = 0.01$).	Sensitivity: Supported based on scores from the following measures which encompassed the entire score range: - All TNS©-PV items - Balis motor scores - FACES pain scores Responsiveness: - TNS©-PV was responsive to change based on statistically significant changes over time ($p < 0.0001$) and moderate *es* (.49) - CTCAE (sensory) was responsive to change based on statistically significant changes over time ($p < 0.0001$) and a moderate *es* (.48) Because the vibration and reflex items were the most responsive TNS-PV items, a 2-item TNS-PV total score was computed (V-Rex). The simpler 2-item V-Rex was the most responsive measure VIPN measure ($p < 0.0001$; *es* = 0.65). Feasibility: - Vibration & temperature sensibility scores were not attainable in 84% and 87% of children ≤ 3 years of age, respectively - Reflex & strength scores attainable in 91% and 78% of children ≤ 3 years of age, respectively - FACES scores attainable in 95% - TNS©-PV scores attainable in nearly all children ≥ 6 years of age	1) Findings are only generalizable to patients with ALL who are receiving vincristine 2) No control group 3) Retrospective data collection was used to obtain laryngeal and constipation scores (children/parents were asked if experienced over the past week) 4) TNS©-PV use requires assessor training and may not be feasible for use in busy clinical settings 5) Lack of control for non-CIPN pain, obesity, steroid-induced myopathy, and genetics.

Wright 2017[7]	Design: Descriptive, cross-sectional, case control The purpose of this study was to describe the gait characteristics of children and youth treated for CIPN due to vincristine treatment for ALL compared to healthy controls using 3-DMA and EMG.	Children with Cancer: N =17 - ALL diagnosis - > 5 years of age: $\bar{X}$ age = 11.2 years - CTCAE CIPN grades ≥ 1 Healthy Controls: N = 10 Therapy: received (n = 10) or currently receiving (n = 7) standardized vincristine dosing	Temporal-spatial, kinematic, and kinetic data obtained using 3-DMA, EMG, goniometer, strength (MRC) examinations, and hopping scores	*Subjects performed a minimum of six barefoot walking trials along an eight-meter walkway. A 3-DMA camera/software system recorded each walking trial. Simultaneous surface EMG data were collected during the walking trials. Passive ankle dorsiflexion range-of-motion was measured using a goniometer. Dorsiflexor strength was measured using MRC guidelines. Plantarflexor strength was based on unipedal hopping scores. Gait Deviation Index was used to quantify magnitude of gait deviation Construct Validity: Contrasting group validity was assessed via comparisons of CIPN cases with healthy control data, and analyzed using chi-square and t-tests.	NA	Construct validity: Contrasting group validity: supported by statistically significant differences between CIPN cases and healthy controls in 1) various stages of knee, plantar-, and dorsi-flexion; 2) hip extension; 3) step length; and 4) ankle movement and power.	NA	1) Cross-sectional design prevented assessment of responsiveness to change. 2) Insensitive measure (CTCAE) used to define presence of CIPN 3) Evaluator training or fidelity procedures are not described 4) No power analysis 5) Risk of type 1 and 2 error due to multiple testing and small sample size. 6) It is unclear which data in Table 1 were obtained from 3-DMA, versus the other testing approaches (goniometer, MRC testing hopping scores). 7) Lack of control for obesity, steroid-induced myopathy, and genetics. 8) Lengthy test battery that requires patient attention and cooperation

NA = not applicable: $\bar{X} = mean$

References

1 Gilchrist, LS, Tanner L, Hooke MC. Measuring chemotherapy-induced peripheral neuropathy in children: development of the Ped-mTNS and pilot study results. *Rehabil Oncol* 2009; 27: 7–15.

2 Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. Support Care Cancer 2013; 21: 847–56.

3 Gilchrist LS, Marais L, Tanner L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. Support Care Cancer 2014; 22: 359–66.

4 Gilchrist LS, Tanner LR. Short-term recovery of balance control: association with chemotherapy-induced peripheral neuropathy in pediatric oncology. *Pediatr Phys Ther* 2018; 30: 119–24.

5 Lieber S, Blankenburg M, Apel K, Hirschfeld G, Hernáiz Driever P, Reindl T. Small-fiber neuropathy and pain sensitization in survivors of pediatric acute lymphoblastic leukemia. *Eur J Paediatr Neurol* 2018; 22: 457–69.

6 Lavoie Smith EM, Li L, Hutchinson RJ, et al. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *Cancer Nurs* 2013; 36: E49–60.

7 Wright MJ, Twose DM, Gorter JW. Gait characteristics of children and youth with chemotherapy induced peripheral neuropathy following treatment for acute lymphoblastic leukemia. *Gait Posture* 2017; 58: 139–45.