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RESEARCH REPORT

Peripheral Neuropathy Research Registry: A prospective cohort

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The Peripheral Neuropathy Research Registry (PNRR) is a prospective cohort of peripheral neuropathy (PN) patients focused on idiopathic axonal peripheral neuropathy. Patients with diabetic, human immunodeficiency virus-, and chemotherapy-induced peripheral neuropathies are enrolled as comparison groups. The PNRR is a multi-center collaboration initiated and funded by the Foundation for Peripheral Neuropathy (FPN) with the objective to recruit a well characterized cohort of patients with different phenotypes and symptoms in each diagnostic category, and to advance research through development of biomarkers and identification of previously unknown causes of PN. The overall goal of the initiative is to find disease-altering treatments and better symptom relief for patients. We present the study design, types of data collected, and characteristics of the first 1150 patients enrolled. We also discuss ongoing analyses on this dataset, including untargeted-omics methodologies.

1 | INTRODUCTION

Peripheral neuropathy is a common neurodegenerative disease with many etiologies. Although diabetes, chemotherapy and human immunodeficiency virus (HIV) infection account for the majority of acquired non-inflammatory peripheral neuropathies, about 20%-50% of patients with peripheral neuropathy (PN) do not have an identified cause despite extensive testing and evaluations.[1,2] Furthermore, research into etiologies and mechanisms of axonal injury in peripheral neuropathies is limited compared to other neurodegenerative diseases. This is partly due to the large number of causes of PN but also the lack of comprehensively phenotyped cohorts with associated biosamples that could serve as useful research tools.

Based on cohorts for other neurodegenerative diseases,[3–5] we established a prospective cohort of acquired axonal PN patients, including those with small fiber neuropathies (defined as a subgroup of axonal neuropathies with only small fiber symptoms and/or abnormal epidermal nerve fiber densities). The Peripheral Neuropathy Research Registry (PNRR) is a multi-center collaboration initiated and funded by the Foundation for Peripheral Neuropathy (FPN). The primary goals of the PNRR are establishment of a carefully phenotyped cohort that includes an extensive patient questionnaire and standardized focused neurological examination and collection of blood samples for genotyping and biomarker research. Enrollment is ongoing and eventually will contain

Abbreviations: AAN, American Academy of Neurology; BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; cm, centimeter; CMP, comprehensive metabolic panel; DPN, diabetic peripheral neuropathy; EMG, electromyography; FPN, Foundation for Peripheral Neuropathy; HIV, human immunodeficiency virus; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPN, idiopathic peripheral neuropathy; kg, kilogram; NCS, Nerve Conduction Study; PNRR, Peripheral Neuropathy Research Registry; SIFE, serum immunofixation; SFN, small fiber neuropathy; SPEP, serum electrophoresis.

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extensive information on more than 2000 patients. Here we discuss the study design and characteristics of the 1150 patients phenotyped and biobanked to date.

2 | METHODS

A common protocol was developed and local institutional review board approval was obtained prior to enrolling any patients. Peripheral neuropathy diagnosis was made by an investigator based on a combination of symptoms and signs. Patients above the age of 18, diagnosed with diabetic peripheral neuropathy (DPN), HIV-associated peripheral neuropathy (HIV-PN), chemotherapy-induced peripheral neuropathy (CIPN), or idiopathic peripheral neuropathy (IPN) were included in the cohort. DPN included both established type 1 or type 2 diabetes mellitus and pre-diabetes, defined by either impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) or hemoglobin A1c. Eligible HIV-PN patients needed to have a positive serology for HIV and the PN had to be associated with the HIV infection and/or its treatment in the opinion of the enrolling investigator. For those with suspected CIPN, onset of symptoms had to be temporally associated with chemotherapy. Idiopathic PN was defined as a slowly progressive, symmetric, distal axonal polyneuropathy of unknown cause. Patients with any other confirmed causes of distal symmetric peripheral neuropathies, such as amyloidosis, chronic renal failure, alcohol abuse, vitamin deficiencies, or inherited neuropathies (based on genetic diagnosis or neuropathy in a first-degree family member) were excluded, as were primary demyelinating neuropathies. All participants gave written informed consent and were examined by a physician at one of the six enrollment centers, which included Johns Hopkins University School of Medicine, Icahn School of Medicine at Mount Sinai, Beth Israel Deaconess Medical Center, Northwestern University, University of Utah, and the University of Kansas Medical Center.

The following information was entered in the registry:

1. **Standardized questionnaire (Supplement 1):** The standardized questionnaire included questions regarding neuropathic symptoms experienced during the past 7 days. Common symptoms such as pain, numbness, muscular weakness, balance impairment, and autonomic symptoms were grouped in question blocks, but other common secondary symptoms such as sleep difficulties or muscle cramping were also assessed. The second part of the questionnaire captured medical, family, and social history. Participants were asked to identify if they had received any of 32 medical diagnoses known to cause or contribute to peripheral neuropathy. Free text data entry fields captured any other past medical diagnoses. Participants also provided a list of current medications with dosages, past surgeries, and past exposure to potential peripheral nerve toxins such as heavy metals, herbicides, fungicides and pesticides, smoking status, alcohol intake, and recreational drug use. The family history questions asked about other family members with possible neuropathies, auto-immune diseases, hyperlipidemia, and diabetes mellitus and any other medical conditions of immediate family members.
2. **Neurological examination (Supplement 2):** Information from the neurological examination performed by a trained physician at one of the enrollment centers was recorded. Examination data included cranial nerve involvement, bilateral muscular strength of all major muscle groups, deep tendon reflexes, gait, coordination, and sensory examination, including tandem-, toe-, and heel-walk for at least 5 steps, and Romberg (10 seconds). The required sensory examination included pinprick, vibration sense (using the Rydel-Seiffer tuning fork), and proprioception; evaluation of cold and touch sensation (Semmes-Weinstein monofilaments) were considered optional.
3. **Nerve Conduction Study (Supplement 3):** Conduction velocity, onset latency, action potential amplitude, and F-wave latency from median, ulnar, and peroneal motor nerves, and conduction velocity and action potential amplitude and peak latency from median, ulnar, radial, and sural sensory nerves were recorded if testing was performed within 3 years of enrollment. For some patients with suspected small nerve fiber (SFN) neuropathy, the intra-epidermal nerve fiber densities calculated from histological evaluation of a 3-mm punch skin biopsy at standardized sites at the distal leg, and in some cases distal and proximal thigh were captured together with the diagnostic interpretation, including if the skin biopsy showed a length-dependent or non-length-dependent pattern.
4. **Diagnostic laboratory testing results (Supplement 4):** Comprehensive metabolic panel (CMP), blood glucose, serum protein electrophoresis (SPEP) and/or serum immunofixation (SIFE), and vitamin B12 testing are recommended by the American Academy of Neurology (AAN) for the evaluation of peripheral neuropathy[6] and were required evaluations for all patients. Overall the results of 50 laboratory tests occasionally ordered by physicians for the evaluation of polyneuropathy were recorded when performed, including testing for inflammatory markers, vitamin deficiencies, and infectious diseases.

For returning patients, information from follow-up examinations was entered for longitudinal observations. Blood samples for future genetic screening and biomarker testing were also collected at least once, usually at enrollment. The PNRR-database and biospecimen repository are located and maintained at the Indiana University School of Medicine. Enrollment into the registry started in 2012 and is ongoing with the goal to phenotype at least 2000 patients to allow for all planned assessments. In 2017, a data quality monitoring protocol was established and all prior enrollments were updated. For this manuscript, participants who were enrolled until the end of 2016 were included in the data review.

The PNRR protocol was reviewed and approved by the Institutional Review Boards (IRBs) of all consortium members.

3 | RESULTS

Of the 1150 patients included in this data review, patients with idiopathic PN formed the largest group, accounting for 52% (n = 595) of participants. DPN was the identified cause for 31% of the enrolled patients (n = 360), 10% had HIV-PN (n = 115), and 7% had CIPN (n = 77).

3.1 | Demographics

The age of the study participants at the time of enrollment ranged from 22 to 93 years, with a median of 63 years. Eighty percent of participants were between 50 and 80 years old, and 5% were under the age of 40, (Figure 1). The median ages were comparable in the DPN, idiopathic PN, and CIPN cohorts, but lower in the HIV group, (Table 1). Participants with neuropathic pain were significantly younger than those without pain in all disease categories. Figure 2 depicts the race distribution of participants in the PNRR; majority of the patients were Caucasian/white (83%), while only 10% were African American/black. About 60% of the participants in the study were male and 40% were female. Same male:female ratio was also seen in the DPN and idiopathic PN groups, but more than 70% of the patients with HIV-PN were male. Only in the CIPN category more females were enrolled than males (Table 2).

Body weight at the time of enrollment ranged from 42 to 174 kg, with a median of 87.4 kg for the entire study population. The DPN group had the highest median body mass index (BMI, 30.9), while the median BMI in the idiopathic PN, HIV-PN, and CIPN groups were more than three points lower, (Table 3). Almost 40% of all PNRR participants were obese with a BMI of ≥30.[7] Those with DPN were more likely to be obese (57%) compared to the other diagnostic groups (36%).

The percentage of patients with recent onset of symptoms (within the past year) was the highest in the CIPN group, with 30% compared to less than 15% in the other three groups. In the DPN and CIPN groups 50% of the patients reported an onset of symptoms 1-5 years ago, compared to 40% and 45% in the HIV-PN, and idiopathic PN groups, respectively. Only 20% of the CIPN patients reported symptoms for more than 6 years. In the DPN group a third of the patients had long standing PN, 42% for idiopathic PN, and in the HIV-PN group those with symptoms of more than 6 years were the largest subgroup (45%).

3.2 | Standardized questionnaire

Numbness was the most common symptom, reported by 85% of all enrolled patients, followed by autonomic symptoms (80%); pain (70%), balance issues (66%), and muscular weakness (56%, Figure 3). The prevalence of numbness and balance issues were similar between all four groups. In the DPN group, 77% of the patients reported pain, compared to 64-70% in the other three groups, and 67% of the HIV-PN patients reported weakness, while perceived weakness was reported by 52-57% of DPN, CIPN, and idiopathic PN patients. Autonomic symptoms were also more commonly reported by HIV-PN patients with 91% of them reporting one or multiple symptoms, and less common in the other three groups with 70-81%.

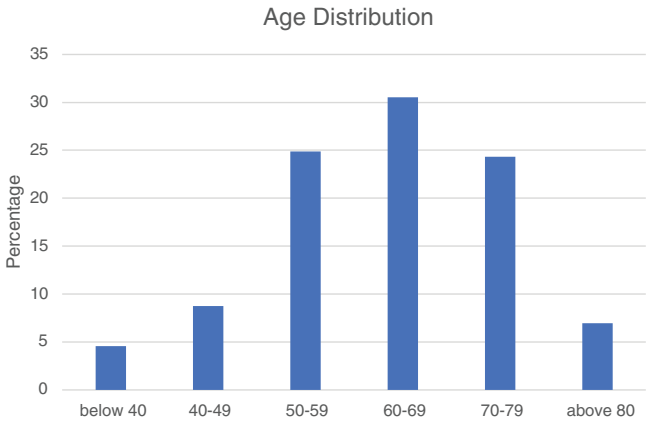

FIGURE 1 Age distribution of all patients enrolled in the Peripheral Neuropathy Research Registry (PNRR) study at the time of their initial visit

TABLE 1 Median ages for each category and for the subgroups of patients with painful and non-painful PN

Median age	Category	Pain	No pain
DPN	63	62	67
CIPN	64	65	63
HIV-PN	57	56	58.5
IPN	66	64	70
Entire study	64	63	68

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy; PN, peripheral neuropathy.

3.2.1 | Pain

Painful paresthesias were reported by 70% of the idiopathic PN and CIPN patients, 66% in the HIV-PN, and by 77% in the DPN group (Table 4). Painful sensations in the feet were reported by 93% of the patients with painful neuropathy, followed by 53% with paresthesias in the legs, 35% in the hands, 15% in the arms, and 19% in the back, torso, neck, or face. Painful sensations in the hands were more frequently reported by CIPN patients (48%) compared to the other groups (<35%), and non-length dependent pain distributions including the torso, back, neck, or face were more frequently reported by DPN and idiopathic PN (>23%) patients, compared to the CIPN and HIV-PN (<15%).

Patients' ratings of their pain intensities in reference to the Numeric Rating Scale (NRS) followed a normal distribution pattern in the DPN, HIV-PN, and idiopathic PN groups (Figure 4), with a peak at pain levels 7 or 8 and median rankings of 6 or 7. The median pain intensity was the lowest in the CIPN group.

Other evaluated descriptive pain characteristics were hot, sharp, dull, cold, or how itchy the painful sensation felt and if the patients experienced allodynia. Table 5 lists the mean and median ratings for all evaluated pain characteristic. The DPN and HIV-PN participants reported a more intense and sharper pain than the patients in the other two groups, and the HIV-PN patients also submitted the highest NRS-rankings for dullness and itchiness. Allodynia was more intense for patients with CIPN and HIV-PN, while the patients from the idiopathic PN group reported the lowest ratings. The CIPN participants described their pain more often as cold than those in the other groups. In regard to the time quality aspects for pain, constant stimulus-independent pain with occasional flare-ups was the most commonly reported type of pain in all four groups. Stimulus-independent, constant pain was the least frequently reported pain type for the DPN, CIPN, and idiopathic PN groups (<17%), but was reported by 27% of the HIV-PN participants.

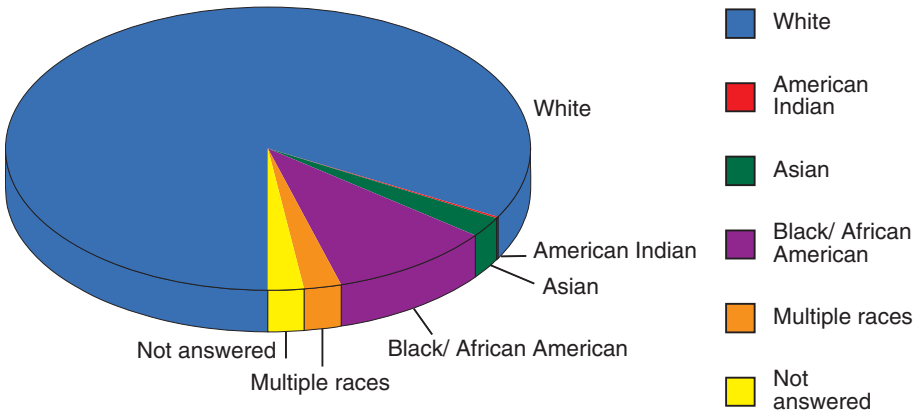

FIGURE 2 Ethnicity of patients enrolled in the Peripheral Neuropathy Research Registry (PNRR) study

3.2.2 | Numbness

In all groups, 92 to 96% of participants with numbness indicated their feet were affected. Figure 5 plots the areas of numbness reported, which follows the glove-and-stocking distribution for the idiopathic PN, DPN, and HIV-PN groups. In the CIPN group, 53% of the patients reported numbness in their hands compared to 30% in the legs (above ankle), making it the only category where more patients reported numbness in their hands than legs. Numbness in other areas, including the torso/trunk, back, neck, and head, was more frequently reported by DPN and idiopathic PN patients and only rarely in the HIV-PN and CIPN groups.

TABLE 2 Percentages of male and female patients enrolled in each category and in the entire study population and the resulting male: female ratios

Male/female ratio	Males (in. %)	Females (in. %)	Ratio
DPN	60	40	1.5:1
CIPN	44	56	1:1.3
HIV-PN	76	24	3.1:1
IPN	58	42	1.4:1
Entire study	60	40	1.5:1

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

3.2.3 | Muscle weakness

Fifty-five percent of all enrolled patients indicated that they had weakness. DPN, idiopathic PN, and CIPN patients most often reported frequent tripping, followed by proximal leg weakness and foot drop, and the percentages were very similar in all three groups. Participants with HIV-PN most often reported proximal leg weakness, followed by tripping and foot drop (Figure 6). About half of the participants who reported weakness in the lower limbs also reported weakness in arm and hand functions. For the CIPN group, problems with fine motor tasks was the most common issue, while a decreased grip strength was the main complaint in the other three groups.

3.2.4 | Balance

Balance issues were reported by approximately two-thirds of all study participants (Table 6). Prevalence of use of assistive devices and falls were largely similar across all groups.

3.2.5 | Autonomic symptoms

One or more symptoms suggesting autonomic involvement were reported by more than 70% of participants. The most commonly reported symptoms were dry eyes or mouth (Figure 7). More than a third also reported abnormal sweating, with night sweats more common than an overall increase for sweating. Abnormal bowel movements were reported by almost half of the HIV-PN patients, and most of them reported diarrhea, while constipation was more often reported in the other three groups. Erectile dysfunction or ejaculation problems were reported by almost half of the male patients.

3.2.6 | Sleep impairment

For the entire cohort, 62% reported sleeping difficulties. Seventy-one percent of patients with painful neuropathy reported sleep difficulties

TABLE 3 Median height, weight, and BMI recorded for each enrollment category and the entire study population

Median height, weight, & BMI	Median height (cm)	Height ranges (cm)	Median weight (kg)	Weight ranges (kg)	Median BMI	BMI ranges
DPN	172.7	147-201	94.8	42-174	30.9	18-52
CIPN	171.5	150-193	81.9	52-145	27.1	18-53
HIV-PN	175.3	150-198	81.4	44-140	26.4	17-49
IPN	175.3	142-201	84.6	43-154	27.5	16-55
Entire study	175.3	142-201	87.4	42-174	28.4	16-55

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

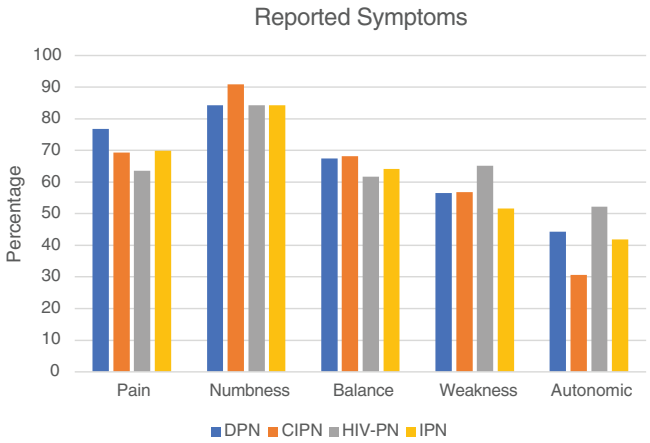

FIGURE 3 Percentages of patients in each enrollment category reporting pain, numbness, (muscular) weakness, balance problems, or impaired autonomic function as symptoms associated with their peripheral neuropathy

TABLE 4 Percentages of patients reporting pain in each enrollment category and the resulting pain to no-pain ratios

Pain:no pain ratio	% Of patients with pain	Pain:no pain ratio
DPN	77.0	3.5:1
CIPN	70.4	2.3:1
HIV-PN	66.4	1.9:1
IPN	70.4	2.3:1
Entire study	72.2	2.6:1

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

compared to only 53% of patients who reported no pain. Sleep disturbance was more common among those with DPN and CIPN compared to idiopathic PN and HIV-PN.

3.2.7 | Muscle cramps

Muscle cramps were reported by 72% of the participants. Frequent muscle cramps (daily) were reported by 21% of those with DPN and HIV-PN compared to <15% among those with CIPN or idiopathic PN.

3.2.8 | Medical history

Cardiac disease, hyperlipidemia, and hypothyroidism were the most commonly reported problems in the idiopathic PN, DPN, and CIPN groups, while the HIV-PN patients most frequently reported kidney problems and hepatitis.

3.3 | Neurological examination

3.3.1 | Muscle strength

All major muscle groups were evaluated bilaterally for muscular weakness. In the lower extremities, muscular weakness on exam followed a distal predominant pattern, and most frequently affected toe extension and toe plantar flexion. In the upper extremities, the intrinsic hand muscles and abductor pollicis brevis were most often diagnosed as weakened (Figure 8). In the DPN group, 36.8% of the patients were diagnosed with muscle weakness of at least one major muscle group, while in the HIV-PN group only 25% of the patients had reduced muscle strength.

3.3.2 | Reflexes

The evaluations for the biceps, triceps, and brachioradialis reflexes showed the same results within each group: the DPN patients had the highest percentages for areflexia, while brisk reflexes were most frequently reported in the HIV-PN group, and the idiopathic PN patients had the highest percentages of fully preserved upper limb reflexes. The patellar reflex was absent in 20% in the DPN and CIPN patients, 10% in the idiopathic PN group, and only 3% in the HIV-PN category. Ankle jerk was the most affected deep tendon reflex in all enrollment

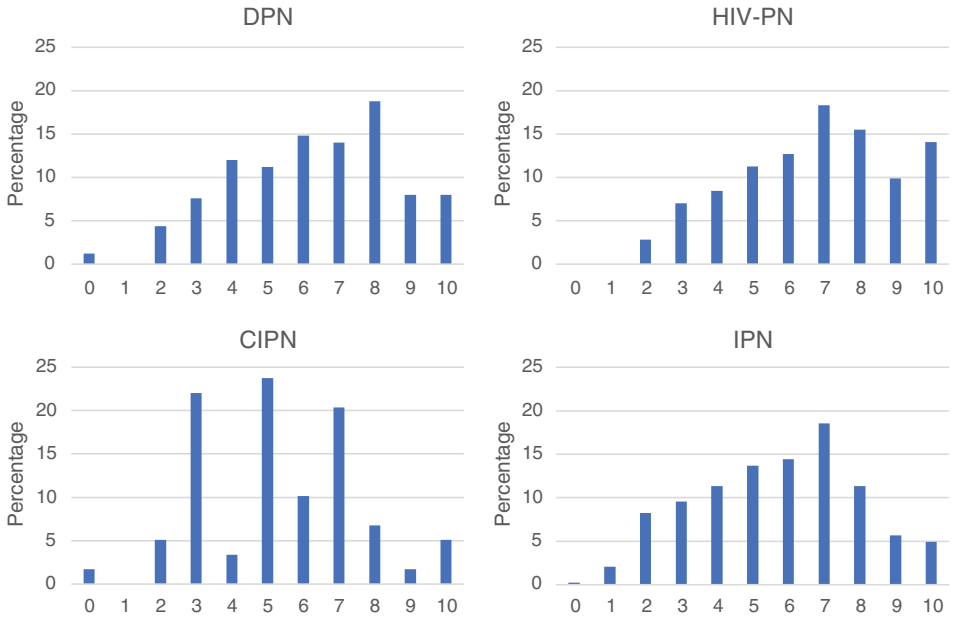

FIGURE 4 Pain intensities reported by the patients as a response to the question "How intense is your pain"; whereby 0 = no pain and 10 = the most intense pain sensation imaginable

TABLE 5 Mean and median ratings of different pain characteristics by the patients with painful neuropathy. The median ratings are in parenthesis

Pain characteristic	Intense	Sharp	Hot	Dull	Cold	Itchy	Allodynia
DPN	6.2 (6)	5.9 (6)	4.7 (5)	3.8 (4)	3.1 (2)	1.9 (0)	4.2 (4)
CIPN	5.4 (5)	4.7 (5)	3.5 (4)	3.9 (4)	3.5 (3)	1.7 (0)	4.7 (5)
HIV-PN	6.8 (7)	6.5 (7)	4.8 (5)	5.5 (6)	3.3 (1.5)	2.9 (2)	4.8 (5)
IPN	5.6 (6)	4.7 (5)	4.4 (5)	3.7 (4)	2.6 (0)	1.7 (0)	3.5 (3)

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

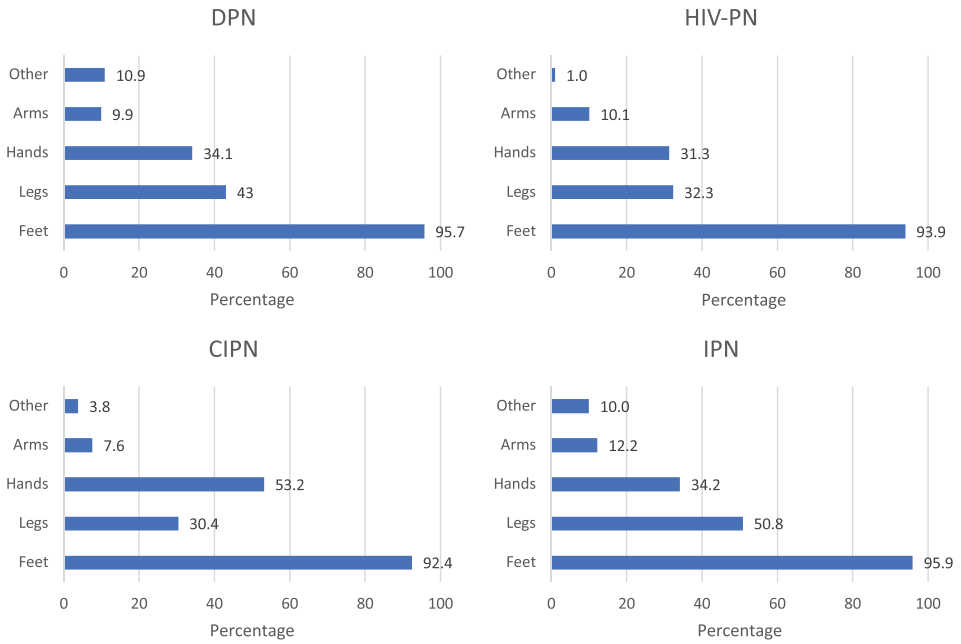

FIGURE 5 Areas of numbness reported by the patients in each enrollment category, whereby the wrist was considered the border between hands and arms and the ankle the border between feet and legs. "Other" summarizes reported numbness on torso/trunk, back, neck, and head

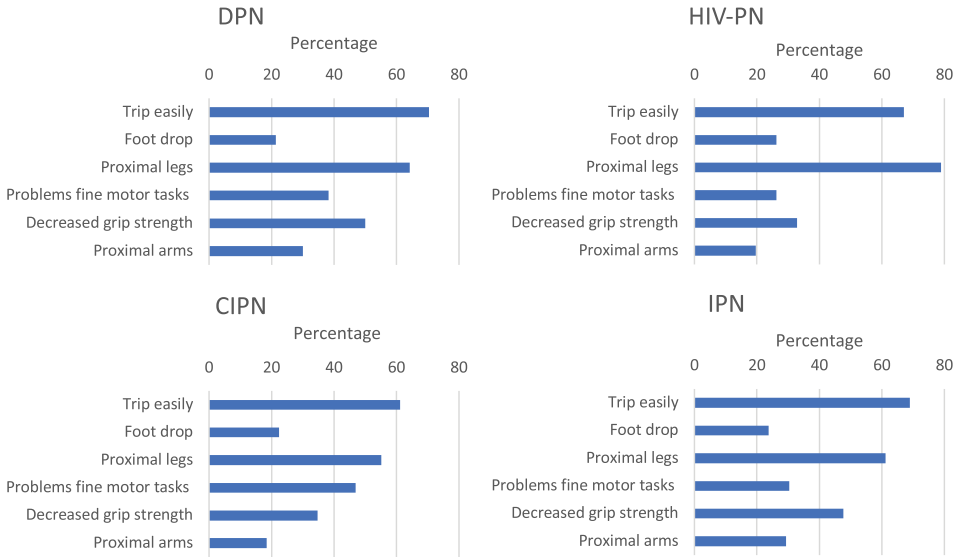

FIGURE 6 Patients indicating that they have muscular weakness were asked which activities were affected. The graphs show the percentages of patients with weakness reporting problems with the listed tasks. Multiple answers were possible

categories and was reported absent for 63-70% of the DPN, CIPN, and HIV-PN patients, and 45% of the idiopathic PN patients (Figure 9).

3.3.3 | Mobility

Figure 10 depicts the percentages of participants unable to perform the different mobility tasks. Tandem walk was the task that most patients

TABLE 6 Percentages of patients in each enrollment category reporting balance issues, using assistive devices for mobility and reporting falls as well as percentages of patients who report frequent falls of at least once a month

Balance impairment	% Reporting balance issues	% Using assistive devices	% Reporting falls	% Reporting frequent falls
DPN	77.6	26.0	40.7	9.3
CIPN	69.3	17.0	37.0	6.7
HIV-PN	63.8	31.0	41.4	9.5
IPN	70.0	22.5	34.0	6.1

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

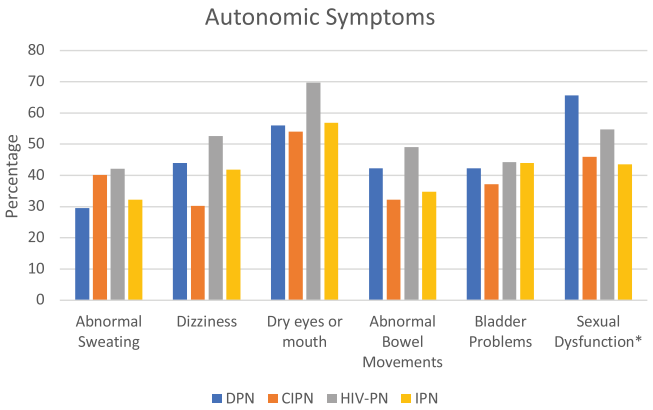

FIGURE 7 Autonomic symptoms reported by the patients in the standardized questionnaire for each enrollment category. *Only men were asked about sexual dysfunction, and the reported percentages represent the percent of men with sexual dysfunction in each enrollment category

had difficulties with, while a positive Romberg was observed in about 25% of all patients. The DPN patients had the most difficulties performing the five mobility tasks, while the CIPN patients had the least problems with Romberg, gait, and walking on their heels or toes; but 40% of the CIPN patients were unable to perform tandem walk.

3.3.4 | Sensory examination

On sensory evaluations, reduced or absent pinprick sensation distally was the most commonly encountered abnormality in all groups (Table 7). This was closely followed by reduced or absent vibration sense in the toes. Proprioception at the hallux was preserved in the majority of the patients.

3.4 | Nerve conduction studies

Over 80% of the participants had a Nerve Conduction Study (NCS) performed (Table 8). In the idiopathic PN and DPN groups the NCS results were abnormal for >65% of the patients, while the percentage of patients with only sensory nerves affected was higher in the HIV-PN group. In all enrollment categories, predominantly axonal nerve damage was the most common, but 20% of the DPN group had both axonal and demyelinating features (mixed), which is higher than the percentages in the other groups. The percentage of patients with a normal NCS on file was the highest in the idiopathic PN group.

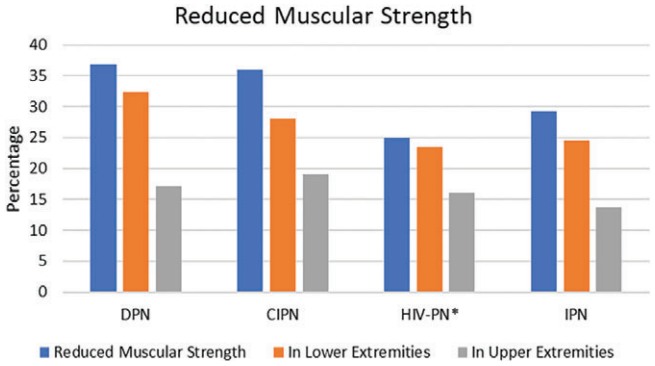

FIGURE 8 Percentages of patients with reduced muscular strength as determined by a neurologist during their enrollment examination. *Toe dorsi- and plantar flexion evaluation were not reported for a many of the HIV-associated peripheral neuropathy (HIV-PN) patients; the reported percentages are extrapolations based on the available data

3.4.1 | Skin biopsy

In the idiopathic PN group, when done, the skin biopsy was abnormal and interpreted as showing a length-dependent process for 80% of the patients. In the DPN group the percentage was 85%. In both the CIPN and HIV-PN groups less than 10 patients had an abnormal skin biopsy results entered.

3.5 | Diagnostic laboratory testing

The most common abnormal testing result was glucose, and for 80% of the DPN patients the most recent glucose screen was considered abnormal. The median HgbA1c for in the DPN group was 6.3 compared to 5.6 in the three other categories. About 30% of the patients enrolled in the CIPN and HIV-PN group had abnormal protein levels, either in form of monoclonal gammopathy or hypogammaglobulinemia, while the percentages in the DPN and idiopathic PN group were below 20%. The most frequently found paraprotein was IgA, and hypogammaglobulinemia was more common in the elderly and diabetic patients. About 7% of all the patients had a creatinine level above 1.3 mg/dL, and less than 1% had creatinine levels above 1.7 mg/dL. Only two of the enrolled patients had a vitamin B12 level below 180 pg/mL, 2% had a vitamin B12 between 180 and 200 pg/mL, and another 23% had a vitamin B12 between 200 and 400 pg/mL.

4 | DISCUSSION AND SUMMARY

This report describes an ongoing natural history cohort of patients with acquired, distal, symmetric axonal peripheral neuropathies at six academic tertiary care centers. In this initial report, we describe the nature of the cohort and collected information. The primary focus of this cohort is patients with idiopathic PN, DPN, CIPN, and HIV-PN. The collected blood samples will be used for a planned genomic study to identify any genetic causes or risk factors for idiopathic PN. Furthermore, the serum and plasma samples will be used for biomarker studies.

A major goal of this prospective cohort study is to be a resource for future research with specific hypotheses. Collaboration through this consortium is open to both academic and industry researchers.

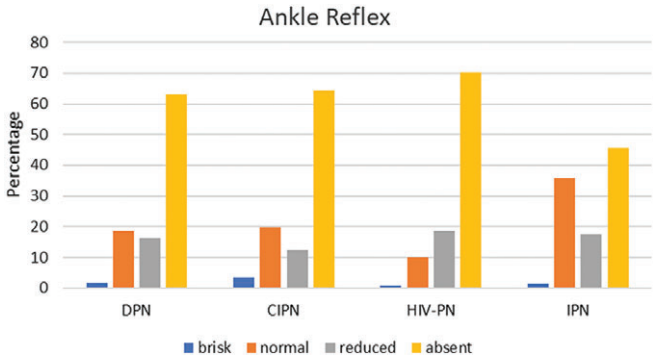

FIGURE 9 Percentages of patients with normal, brisk, reduced, or absent ankle tendon reflex as determined by the examining physician during the neurological examination

Investigators with specific projects can apply for access to the patient data and biological samples through the FPN or the chair of the Scientific Advisory Board (currently, Dr. Ahmet Höke). Applications will be reviewed by the Scientific Advisory Board and Consortium members and a decision will be made for access. As an example of the value of the PNRR data, investigators were granted access to a subset of the PNRR patients to investigate the prevalence of presumed pathogenic mutations in the SCN9A, SCN10A, and SCN11A genes[8] among painful vs painless neuropathy patients. In contrast to previous studies,[9,10] the investigators did not find an enrichment of gain-of-function mutations in these genes among patients with IPN or DPN irrespective of their pain status. Furthermore, they did not find sodium voltage-gated channel (SCN) genetic differences between patients with painful vs painless small fiber neuropathy.[11] The cause of discrepancy between the previous studies and the patients from the PNRR cohort is unclear and may reflect differences in patient populations or referral patterns. The PNRR was designed to enroll neuropathy patients seen in a general neurology practice in tertiary referral centers and the patient population may differ from the ones described previously where a high proportion of patients initially considered for the study had sarcoidosis, a rare cause of neuropathy.[9] However, PNRR also has limitations in that patients are enrolled through academic tertiary care centers and may not reflect the disease characteristics of patients in a community setting. Nevertheless, this initial study utilizing the patient samples from the PNRR highlights the utility of the PNRR as a clinical research tool for future studies.

TABLE 7 Percentages of patient with absent, reduced, or normal pinprick, vibration sense and proprioception at the metatarsophalangeal (MTP) joint of the hallux during the enrollment exam. Regarding vibration sense, Rydel-Seiffer Fork readings of ≥4.5 were considered normal for patients 40 and younger, for age 41-60 it was ≥4.0, age 61-85 ≥3.5, and for patients 85 and older ≥3

Pinprick				
HALLUX	**DPN**	**CIPN**	**HIV-PN**	**IPN**
Normal	16.1	22.4	26.1	20.8
Reduced	58.3	62.4	66.1	59.6
Absent	25.5	15.3	7.8	19.6
Vibration sense				
HALLUX	**DPN**	**CIPN**	**HIV-PN**	**IPN**
Normal	30.3	20	25	30.3
Reduced	20.7	23.5	29.2	20.7
Absent	49	56.5	45.8	49
Proprioception				
HALLUX	**DPN**	**CIPN**	**HIV-PN**	**IPN**
Normal	60.6	60.7	78.4	66.4
Reduced	28	29.8	19.8	24.3
Absent	11.4	9.5	1.8	9.3

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

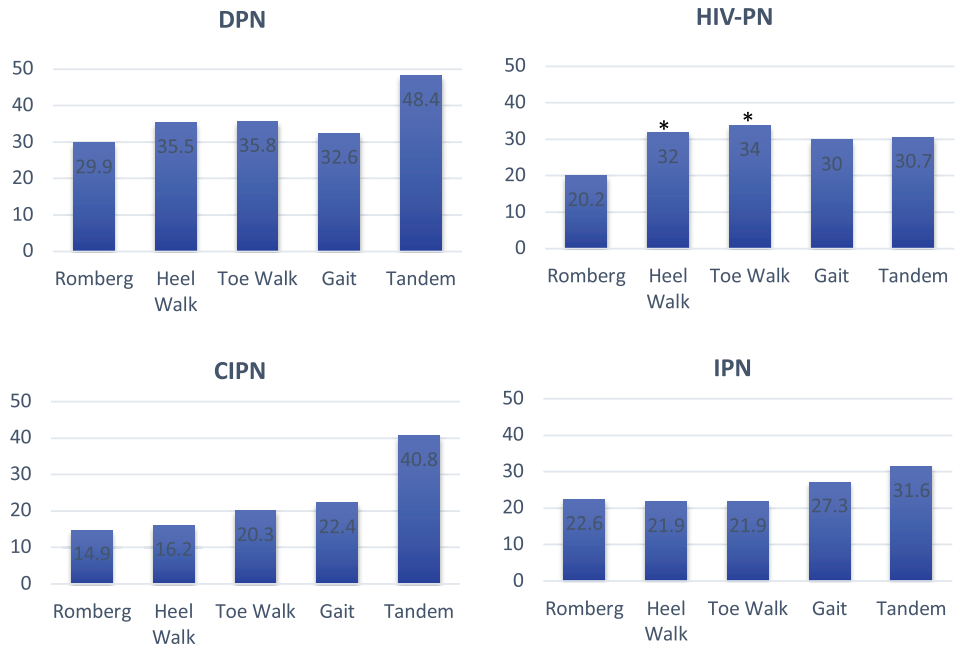

FIGURE 10 Percentages of patients who are unable to perform specific mobility evaluations during the neurological examination. *Heel and toe walk evaluations were not provided for many human immunodeficiency virus (HIV) patients and the reported percentages represent extrapolations from the available data

TABLE 8 Percentages of patients with normal, abnormal, or without Nerve Conduction Study (NCS) information on file, and NCS interpretation for abnormal tests. Percentages are listed together with the actual number of patients in parenthesis

DPN group				
Normal NCS:	17.5% (65)			
No NCS on file:	21.8% (81)			
Abnormal NCS:	60.7% (226)	See table below for details		
	Sensory	Motor	Sensorimotor	Total
Axonal	26.5% (60)	1.3% (3)	46% (104)	73.8% (167)
Demyelinating Mixed	0.4% (1)	0.9% (2)	0% (0)	1.3% (3)
Mixed	3.1% (7)	0% (0)	21.73% (49)	24.8% (56)
Total	30.1% (68)	2.2% (5)	67.7% (153)	100%
CIPN group				
Normal NCS:	21.3% (19)			
No NCS on file:	30.3% (27)			
Abnormal NCS:	48.3% (43)	See table below for details		
	Sensory	Motor	Sensorimotor	Total
Axonal	32.6% (14)	4.7% (2)	46.5% (20)	83.8% (36)
Demyelinating	2.3% (1)	0% (0)	2.3% (1)	4.6% (2)
Mixed	2.3% (1)	0% (0)	9.3% (4)	11.6% (6)
Total	37.2% (16)	4.7% (2)	58.1% (25)	100%
HIV-PN group				
Normal NCS:	18.1% (21)			
No NCS on file:	17.2% (20)			
Abnormal NCS:	64.7% (75)	See table below for details		
	Sensory	Motor	Sensorimotor	Total
Axonal	45.3% (34)	1.3% (1)	38.7% (29)	85.3% (64)
Demyelinating	0% (0)	1.3% (1)	2.7% (2)	4% (3)
Mixed	1.3% (1)	0% (0)	9.3% (7)	10.6% (8)
Total	46.6% (35)	2.6% (2)	50.7% (38)	100%
IPN group				
Normal NCS:	32.3% (199)			
No NCS on file:	15.1% (93)			
Abnormal NCS:	52.7% (325)	See table below for details		
	Sensory	Motor	Sensorimotor	Total
Axonal	25.9% (84)	1.5% (5)	52.6% (171)	80% (260)
Demyelinating	0.6% (2)	0.9% (3)	2.5% (8)	4% (13)
Mixed	4% (13)	0.3% (1)	11.7% (38)	15% (52)
Total	30.5% (99)	2.7% (9)	66.8% (217)	100%

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DPN, diabetic peripheral neuropathy; HIV-PN, human immunodeficiency virus induced peripheral neuropathy; IPN, idiopathic peripheral neuropathy.

In addition to the future genomic and biomarker studies, patients enrolled in the PNRR have been consented to be contacted for future clinical studies and will serve as a source of well characterized participants for therapeutic clinical trials. Finally, as patients enrolled in the PNRR are seen for their follow up evaluations, longitudinal data will be collected, which may help evaluate the efficacy of therapeutic interventions. Our goal is to utilize the PNRR as a useful tool and model to stimulate PN research.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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