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MASTER THESIS

Exploratory Analysis of Peripheral Neuropathy Patient Biomarker and Symptom Characteristics

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Abstract

Peripheral Neuropathy (PN) is a debilitating condition with a large prevalence worldwide yet it is under-recognized and lacks awareness. There exist a large number of different potential etiologies, but finding the underlying cause poses a difficult task. This thesis aims to add a step towards making a diagnosis by inferring the etiology from patient biomarker data such as symptoms, neurological evaluation, blood work and NCS. The data at hand is the American Peripheral Neuropathy Research Registry (PNRR) which is the largest cohort for Diabetic PN (DPN) and idiopathic PN (IPN). It covers over 400 patient parameters from 2600 PN patients. Systematic statistical bivariate analyses for three study populations (SFN, LFN, PN) compares DPN with IPN, and SFN with PN for multiple PNRR variables. We confirm anticipated differences and discover and quantify assumed or unknown sig. differences. This research is the first approach that analyzes multiple hypotheses in the PNRR. We identified variables that are able to differentiate between etiologies and PN type respectively. Targeting to measure these variables in clinic may pave the way towards faster and improved diagnosis making.

Acknowledgements

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Contents

List of Abbreviations

ANA	Antinuclear Antibodies
CBC	Complete Blood Cell count
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CNS	Central Nervous System
CRP	C-reactive Protein
DPN	Diabetic Peripheral Neuropathy
FPN	Foundation for Peripheral Neuropathy
IENFD	Intraepidermal Nerve Fiber Density
IPN	Idiopathic Peripheral Neuropathy
LFN	Large Fiber Neuropathy
MetS	Metabolic Syndrome Evaluation
MMA	Methylmalonic Acid
NCS	Nerve Conduction Study
PEF	Physician Examination Form
PEP	Polypeptide
PHQ	Patient History Questionnaire
PN	Peripheral Neuropathy
PNS	Peripheral Nervous System
PNRR	Peripheral Neuropathy Research Registry
PNW	Peripheral Nerve Work-Up
SFN	Small Fiber Neuropathy
SFPN	Small Fiber Polyneuropathy
SPEP	Serum Protein Electrophoresis
TSH	Thyroid Stimulating Hormone

This thesis is dedicated to all neuropathy patients who are striving to better understand their diagnoses, and especially to the patients of idiopathic neuropathy who are trying to pin down their underlying cause(s).

Chapter 1

Introduction to Neuropathy

1.1 What is Peripheral Neuropathy?

Peripheral Neuropathy (PN) is the terminology utilized for any type of a disorder in the peripheral nervous system, which is defined as the nervous system outside of the brain and spinal cord. "Peripheral Neuropathy itself is not usually a disease on its own but a symptom of an underlying illness" [1]. PN caused by underlying systemic medical conditions are referred to as polyneuropathies as they affect multiple nerves at the same time. Symptom distribution in most polyneuropathies are in a length-dependent pattern (affecting longer nerves first) with symptoms starting in the bottom of the toes and slowly progressing to a glove-and-stocking distribution pattern. Polyneuropathies are usually symmetrical (affecting both limbs equally) and axonal in nature (neuron or axon is damaged by the condition rather than the protective myelin sheet that is wrapped around the axon which can also leave to nerve destruction).

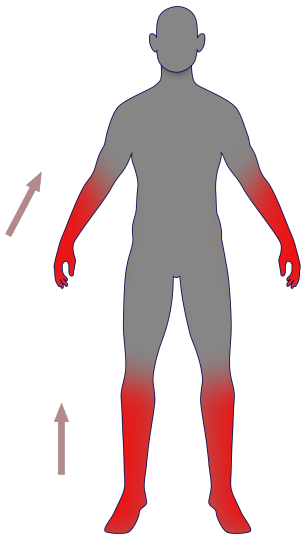

FIGURE 1.1: Glove and stocking distribution pattern of symptoms of a length-dependent PN. Source: Own illustration.

Incidence, Prevalence of PN. Visser et al. 2015 [2] report for the Netherlands an incidence of 77/100'000 persons per year in people of 18 years and older. Hanewinckel et al. 2016 [3] found a prevalence of 4.0% for definite polyneuropathy for the middle-aged and elderly population of the Netherlands. Adding to this share the cases of probable neuropathy results in a prevalence of 9.4%. Prevalence was higher in males

and increased with age. 49% of the cases were newly diagnosed which indicates that the presence of polyneuropathy is underdiagnosed. I estimate similar incidence and prevalence numbers for other European countries.

Hyperglycemia in form of Diabetes Mellitus (DM) is the most common underlying etiology associated with polyneuropathy, accounting for about 50% of all diagnoses. However, there are over 100 different conditions identified as potentially causing PN, including liver and kidney damage, exposure to nerve toxins in form of medications, chemotherapy or chemical agents or HIV-infection to name just a few. For about 30% of all diagnoses, no underlying cause can be identified despite extensive laboratory testing, these patients are labeled with having Idiopathic Peripheral Neuropathy (IPN).

Neurologists differentiate between small and large fiber polyneuropathies, defined by which sub-types of nerve fibers are affected by the condition.

1.2 Small Fiber Neuropathy

This thesis is devoted to Small Fiber Neuropathy (SFN), a subtype of PN that affects only the small unmyelinated nerve fibers. As these are mainly sensory nerve fibers, the most common symptom of SFN are abnormal sensations in form of pain or numbness and autonomic dysfunction (see Figure 1.2a). Initial symptoms are often tingling or itchiness, but can progress to intense burning and stabbing pain that impairs a person's ability to perform tasks of daily living. SFN is also often associated with autonomic dysfunctions such as irregular bowel movements, abnormal sweating, dry eyes or mouth, erectile dysfunction and fatigue and common in combination with other autoimmune diagnoses. In many patients with polyneuropathy, initially the condition only affects the small unmyelinated nerve fibers and only progresses over time to also affect larger, myelinated nerve fibers. However, in many patients, the condition never progresses and remains solemn SFN.

The condition is often diagnosed based on the symptoms reported by the patient as most neurological evaluations, such as sensory testing or electrophysiological testing in form of Nerve Conduction Study (NCS), are normal. The only assessment that regularly results in a confirmed diagnosis of SFN is through punch skin biopsy, when a 3 mm piece of skin tissue is examined under a microscope to determine the Intraepidermal Nerve Fiber Density (IENFD). As the IENFD naturally decreases with age, the normative values for a positive diagnosis are age adjusted.

SFN has only been known for about 40 years. Research funding is limited and therefore the condition is not well understood. Until today, "SFN remains underdiagnosed and the knowledge on the condition is limited among general public and health care professionals [4]."

The human body can regrow the small unmyelinated nerve fibers affected by SFN, however to do so, the underlying cause of the condition has to be identified and must be eliminated. As that is often not possible, disease management is most often limited to symptom control, such as pain management.

To date only two epidemiological cohort studies have been conducted to better understand SFN. Peters et al. 2013 [5] estimated a prevalence of 52.95/100,000 and a

minimum incidence of 11.73/100,000 in the **Netherlands**; and Bitzi et al. 2021 [6] a minimum prevalence of 131.5/100,000 and a minimum incidence of 4.4/100,000 for **Inner Switzerland**. The Swiss authors state that their calculated minimum prevalence is higher than in the Dutch study due to different calculation approaches.

Making a diagnosis for SFN is very difficult to establish. SFN is not detectable by standard neurological examination or NCS. Blood values remain normal in most cases. To diagnose a SFN necessitates skilled labs and well-trained pathologists to perform a skin punch biopsy (the gold standard), which is only available in large specialized clinics. Moreover, SFN can be caused by a very large number of different etiologies including multi-systemic conditions and pain syndromes. The vast number of different and seemingly unrelated symptoms are very difficult to interpret - even more for a physician who has never seen this pathology before. Lastly, SFN overlaps with other similar syndromes (see Figure 1.2 (B)). E.g. patients with ME/CFS often do also have SFN (and vice versa SFN patients suffer from enormous fatigue too). SFN has also been found in Fibromyalgia. And Postural Orthostatic Tachycardia Syndrome (POTS) is one symptom of SFN. For all these reasons, in over 30% of cases the underlying cause cannot be found and a very large number of undiagnozed cases is assumed. SFN expert Prof. Oaklander estimates a global affection of SFN over 100 million people worldwide [7].

(A) Symptoms of SFN. (B) Related syndromes to SFN.

FIGURE 1.2: WordClouds. Source: Own illustration.

1.3 Large Fiber Neuropathy

When the polyneuropathy also affects larger, myelinated fibers, neurologists refer to the condition as Large Fiber Neuropathy (LFN). When larger nerves are affected, the most common symptoms are balance problems, frequent falls and muscular weakness. LFN can usually be diagnosed via electro-physiological NCS testing. In patients with a predominantly sensory LFN, both the unmyelinated and myelinated fibers are affected, which means technically, the patients have both SFN and LFN at the same time. Only in pure motor neuron diseases, such as Amyotrophic Lateral Sclerosis (ALS), are the small unmyelinated nerve fibers not affected.

1.4 Problem statement and aim of thesis

In 30% of PN/SFN patients, no underlying etiology can be identified despite elaborate testing, i.e. these patients are then defined as having idiopathic polyneuropathy [8]. This also means that only the symptoms of IPN can be addressed, but the underlying condition causing the nerve damage cannot be treated that may halt the disease progression. For the patients who finally find a cause, it often takes very

long (several years since symptoms onset) until the diagnosis can be made. The earlier a diagnosis can be made, the earlier a treatment can be initiated, and therefore disease progression earlier potentially halted. It is additionally frustrating and burdensome for the idiopathic patients not to know (over years) what is the cause and having to keep looking for the needle in the haystack. As a result, improved and faster diagnostic methods and diagnoses are urgently needed.

This thesis aims to make a step towards a future research goal to infer the etiology behind idiopathic cases much earlier from symptoms, neurological measurements, blood work, disease development, and other features. The PNRR is the largest patient cohort for IPN and iSFN. This cohort could serve in the future to tackle this goal.

To date, IPN patient populations have barely been studied by means of modern statistical approaches such as Machine Learning. Little is known about diversity and characteristics of IPN. Does IPN form a diffuse cloud in a multi-feature space or do the data at hand allow to differentiate subgroups of IPN? Thomas et al. 2019 [9] have done descriptive statistics to compare the four etiologies of the PNRR (IPN, DPN, CIPN, HIVPN) regarding a chosen set of symptoms and the authors found merely subtle symptom differences between the subgroups.

1.5 Research Questions

Applying systematic bivariate statistical comparisons to over 400 PNRR variables in 3 sets of analyses (Analysis 1: "SFN diabetic versus idiopathic", Analysis 2: "LFN diabetic versus idiopathic", Analysis 3: "SFN vs. LFN")[1], in which of these variables do we find statistically significant differences between diabetic vs. idiopathic patients in Analysis 1) the biopsy-proven SFN patient study population, in Analysis 2) the LFN patient study population; and between SFN vs LFN patients in Analysis 3) the PN study population (union of SFN and LFN patients)? What insights do we discover how diabetic and idiopathic neuropathy, respectively SFN and LFN differ? How strong are the significance levels and how large are the effect strengths? Interesting and noteworthy results of variables of significant differences are described and interpreted.

1.6 Thesis structure

This thesis is structured in 10 chapters. After this chapter, Chapter 2 introduces the architecture of nerves, Chapter 3 introduces neuropathy, Chapter 4 gives an overview of the clinical evaluation of PN and Chapter 5 outlines current possible treatments. Chapter 6 introduces the data (PNRR), followed by the Method in Chapter 7. Results are presented in Chapter 8, the discussion follows in chapter 9 before the Conclusion. Additional results can be found in the appendices.

[1] Throughout this thesis when referring to the 3 analyses, Analysis 1 is shortened to "SFN", Analysis 2 to "LFN", and Analysis 3 to "SFN vs. LFN".

Chapter 2

Nerves

2.1 The Nervous System

The Nervous System is divided into the Central Nervous System (CNS), which encompasses the brain and spinal cord, and the Peripheral Nervous System (PNS), see Figure 2.1.

The PNS has a motor and a sensory division. In the sensory division, sensory nerve cells embedded in the tissue of the skin, muscles, joints and organs transmit signal back to the CNS when stimulated. These sensory inputs include pain, touch, vibration, pressure, temperature, and proprioception (the sense of the position of joints). This travel direction is called *afferent*. In the motor division, motor nerves transmit signals from the CNS to activate muscles and organs. This direction is called *efferent*. The somatic nerves send impulses for voluntary movements to our muscles. On the other hand, the autonomic nerves send signals to our organs autonomously, which means we are unconscious about it. They regulate our bowel motility, heart function, bladder function, muscle tone, glands, etc. The autonomic nervous system is divided into two systems of contrary functions, yet they need to be balanced out and work hand in hand with each other: the sympathetic nerves send signals to set us up for "fight or flight", and the parasympathetic nerves to settle us for "rest and digest" or "feed and breed". Sympathetic stimuli raise our heart rate, blood pressure, muscle tone, and slow gut motility, whereas the parasympathetic stimuli raise gut motility, salivation, sexual arousal, etc. More functions of the two systems are illustrated in Figure 2.2. Source: [10, 11].

2.2 Physiology of nerves

Figure 2.3 depicts the structure of a nerve cell called *neuron*. Each neuron has extensions, called *axons*, which are insulated and protected by the myelin sheath. An axon terminates for example at a neuromuscular junction. Hundreds or thousands of axons run alongside each other within a bundle in a connective tissue sheath. This bundle is called nerve (cf. Figure 2.4).

Neurons interact with each other in a sophisticated process. The end of an axon connects to the cell body of second neuron. An electrical impulse travels along an axon and when it reaches its end, chemicals called *neurotransmitters* are released into the *synapse*. The synapse is a small space where the two cells connect. The neurotransmitters then attach to receptors on the membrane of the second neuron. A

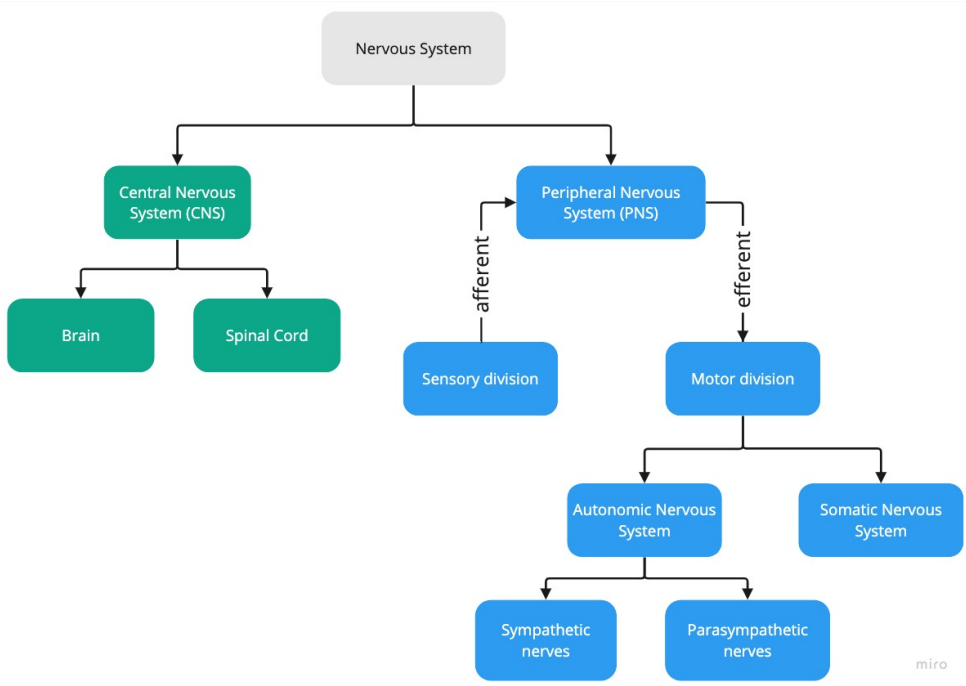

FIGURE 2.1: The Nervous System. Source: Own illustration, adapted from [10].

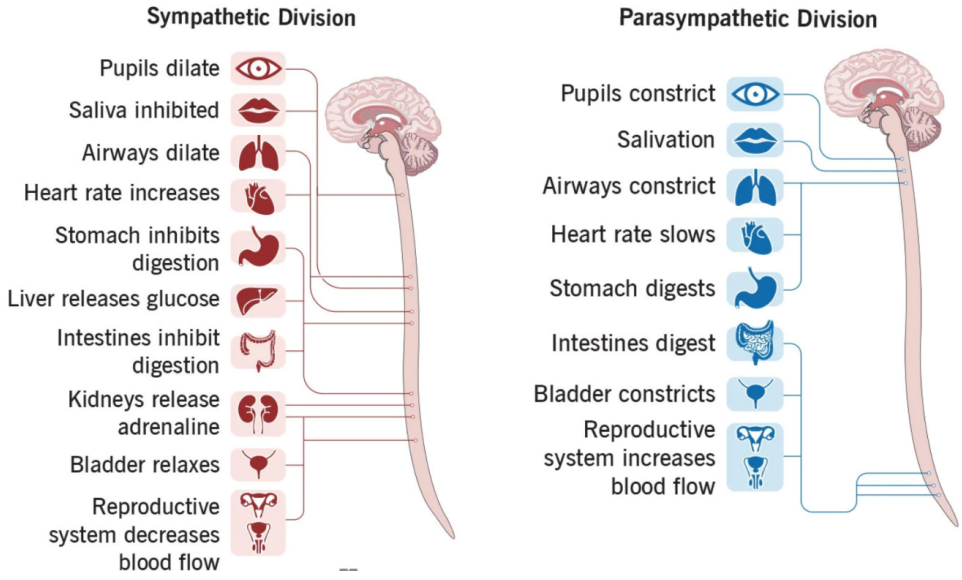

FIGURE 2.2: Functions of the Autonomic Nervous System. Source: [12].

neurotransmitter and a corresponding receptor can be understood like a lock and its key. When the neurotransmitter attaches to its receptor, an electrical impulse - the action potential - is released and it travels along the axon of the second neuron. This process continues from neuron to neuron [1].

Beside their functions, axons are also categorized by size and nerve conduction speed. Motor axons are the thickest, autonomic the thinnest, and sensory axons have varying size between. Axons are surrounded, insulated, and therefore protected by a fatty coating - the myelin. The more myelin there is around an axon, the faster the electrical impulse travels along the axon.

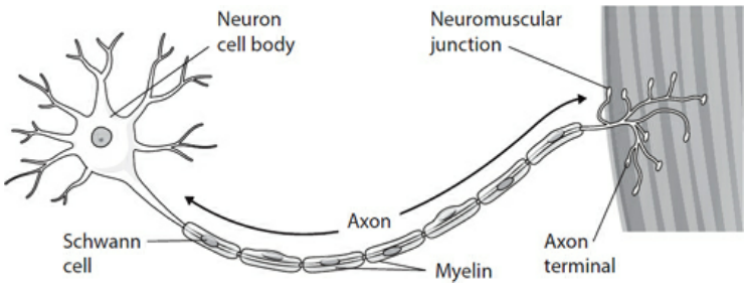

FIGURE 2.3: Nerve cell and neuromuscular junction. Source: [1]

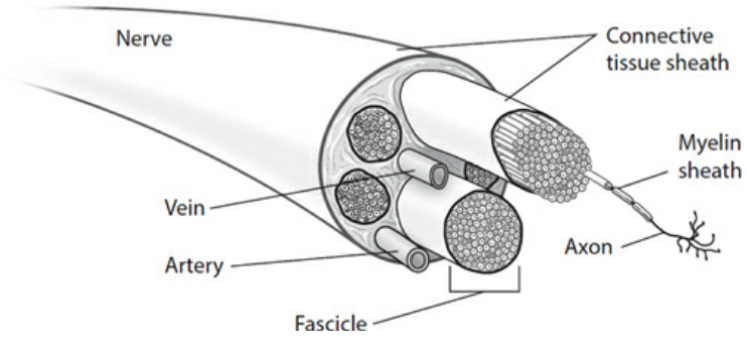

FIGURE 2.4: Graphic representation of a nerve. Source: [1]

Figures 2.5 and 2.6 show an overview of the different axon fiber types, their function, size, and conduction velocity. The sensory C fibers are unmyelinated and sense warmth and pain. The Aδ fibers are thinly myelinated and sense cold and pain. The Aα Aβ sensory fibers sense touch (pressure), vibration, and proprioception. Aα, the largest, control the muscles. The autonomic axons are of type Aδ and C. The different conduction speeds between the fiber types become obvious when we e.g. hit our little toe against a table leg: first we sense the pressure, conducted at 58 m/s; and then a bit later the pain, conducted at 9 m/s. Since the insulative coating on autonomic axons is thin, they are most susceptible to damage by toxins and mechanical forces, such as compression. The evolution of the sensory symptoms such as pain or dysesthesia during the development of neuropathy can be comprehended when we relate it to the anatomy of the different nerve fibers. [1].

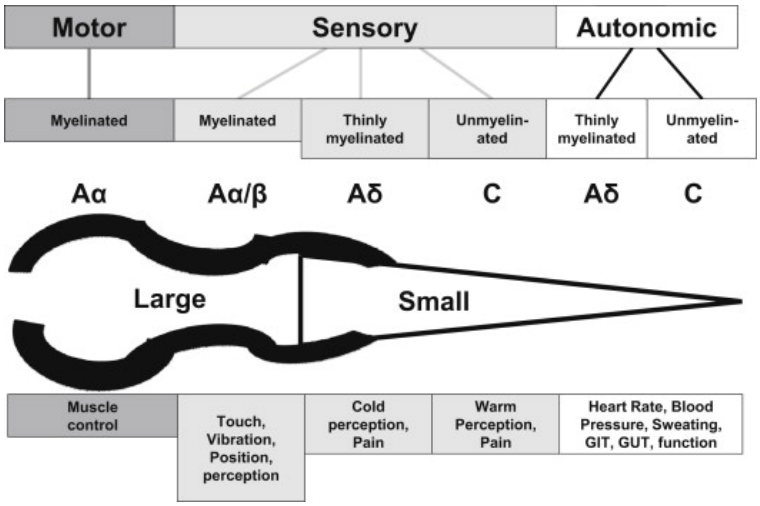

FIGURE 2.5: Categorization of peripheral fiber types. Source: [13].

Fiber Type	Diameter (m)	Conduction velocity (m/s)
A alpha	12 - 20	70 - 120
A beta	5 -12	30 - 70
A gamma	3 - 6	15 - 30
A delta	2 - 5	12 - 30
B	< 3	3 - 15
C	0.3 - 1.3	0.7 - 2.3

FIGURE 2.6: Erlanger and Gasser Classification of Nerve Fibers. Source: Own illustration.

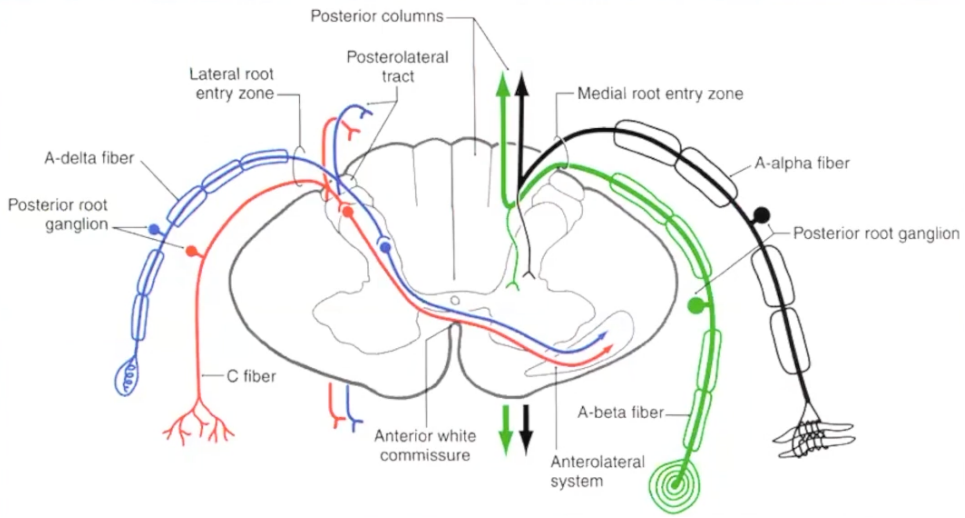

FIGURE 2.7: Small fiber anterolateral system. On the left side, the two small fiber types A-delta (in blue) and C (in red) are depicted. On the right side, the large fiber types A-alpha and A-beta are depicted. Source: Chemali 2022 [14]

Chapter 3

Types of Neuropathy

There exist several types of neuropathy. This chapter introduces the most important types.

Depending on the neuropathy process the disease effects sensory, autonomic, and/or motor nerves; and damage initiates either in the neuron itself (axons), or the myelin sheet that is wrapped around the axon; and either the small or the large fibers or both are compromised. A polyneuropathy typically affects multiple nerves and is symmetrical (e.g. nerves in both legs), while a focal or multifocal neuropathies affects one or several nerves while sparing all other nerves. In a Mononeuropathy only a specific nerve is damaged. Source: [11].

A pure autonomic or pure motor neuropathy is rare. Common are pure sensory or combined sensory/motor or sensory/autonomic neuropathies. When only the small fibers are damaged, we refer to it as Small Fiber Neuropathy (SFN). Although the often used term Large Fiber Neuropathy (LFN) refers by its name explicitly to damaged large fibers, the small nerve fibers are however also affected in varying degree in this type. A neuropathy of only the *large* fibers is rather rare [10].

3.1 Axonal and Demyelinating Neuropathies

3.1.1 Axonal neuropathies

In axonal neuropathies the nerve damage initiates in the axon. Initially, the myelin sheath is not compromised. This is the most common type of neuropathy that are caused by exposure to nerve toxins or systemic medical conditions. It usually is a length-dependent pattern, affecting the longest peripheral nerves first. Axonal neuropathies can affect both large and/or small fibers. There is no therapeutic treatment for axonal neuropathies besides curing the underlying etiology that causes the nerve damage.

Neurons do not regenerate. A neuron's cell body creates proteins and energy-containing molecules and these are to be transported from the cell body to the axon's end. Thus, if a neuron's health is impaired, it can no more support the end of its axon and that part degenerates first during the process. Thus, the first symptoms start in the feet. With exacerbating neuropathy, the nerve degeneration process spreads from the periphery back up to the calves, hands, and later further towards the torso. As a result, this type of neuropathy is often referred to as *distal symmetric polyneuropathy*, "glove

and stocking distribution" or *length-dependent neuropathy*. This pattern occurs usually in Diabetes induces PN. However not all axonal neuropathies occur in a length-dependent pattern, such as neuropathies caused by vitamin B12 deficiency, vitamin B6 toxicity, or anticancer medications. Source: [1, 11].

3.1.2 Demyelinating neuropathies

In this type the damage affects primarily the myelin coating. This occurs in about 10% of neuropathies. When the myelin sheet is damaged and becomes thinner, the axon becomes more exposed to the bodies environment and gets damaged. The conduction velocity of nerve slows down significantly. The most common cause of demyelinating nerve damage are dysfunctions in the immune system. "*Autoimmune means that you make antibodies against what is actually a normal protein in your body*" [1].

A common form of such an autoimmune neuropathy is the Guillain-Barré syndrome (GBS), which is an acute inflammatory demyelinating polyneuropathy, often caused by infections (influenza, pneumonia) or food poisoning. Another form is the chronic inflammatory demyelinating polyneuropathy (CIDP). While GBS is acute, and has fast progression to weaken patients to paralysis within several days, CIDP progresses much slower [1]. There are multiple treatments for demyelinating neuropathies, and patients are often stable or go into recession when treated.

3.1.3 Mixed neuropathies

Many polyneuropathies caused by systemic conditions such as Diabetes Mellitus (DM) or metabolic syndrome have both axonal and demyelinating features. However, they do not respond to the therapies established for demyelinating neuropathies.

3.2 Large Fiber Neuropathy

The term Large Fiber Neuropathy (LFN) includes the above mentioned subtypes Axonal neuropathies and Demyelinating neuropathies, and additionally Inherited neuropathies. LFN occurs usually in a length-dependent pattern, i.e. feet, lower legs, and hands are affected first. A typical cause for this type is DM.

Symptoms of Large Fiber Neuropathy include:

- Numbness in extremities
- Coordination difficulties due to loss of proprioceptive fibers
- Weakness due to damage of the motor (somatic) nerves
- Muscle cramps
- Muscle twitches
- Muscle atrophy (decrease in muscle size)
- Various sensory symptoms such as pain, dysesthesia, etc. [1]

[1] The sensory symptoms are the same as in SFN.

Source: [10].

3.3 Small Fiber Neuropathy

Small Fiber Neuropathy (SFN) - also coined *Small Fiber Polyneuropathy (SFPN)* - is a spectrum of disorders that only damage the unmyelinated and thinly myelinated sensory and autonomic nerve fibers (i.e., C and Aδ fibers types). SFN establishes itself in two main symptoms: (1) neuropathic pain; and (2) loss of sensory and/or autonomic function. If the disease damages specifically the autonomic nerves, it is also referred to as *autonomic neuropathy*. Sensory SFN usually occur in a length-dependent distribution over the body, meaning symptoms usually start in the toes and then slowly progress to involve feet and lower legs. However, some forms of SFN have a non-length dependent pattern, which means they affect all nerves at the same time, and are often caused by exposure to toxins, e.g. chemotherapy or other medications. The course of a SFN is variable; in some patients the disease severity stays stable at some point, in most it keeps progressing though, and very few patients manage to reverse it. Sometimes a SFN develops further into a LFN. SFN is associated with various disease groups. The pathogenesis and the mechanisms that lead to the axonal degeneration are still poorly understood. Source: [15, 16].

3.3.1 Symptoms of SFN

Neuropathic pain (1): Neuropathic pain is prevalent in more than 80% of patients. The most frequent pain type is burning. Further typical pain sensations are tingling, shooting, and pruritus. The pain can be a continuous background pain or it can severely flare-up triggered by certain activities. Allodynia is also common in SFN, which is a pain "elicited by a stimulus that does not normally provoke pain" [16]. Examples are discomfort from a fold in a bed sheet touching the body, or being uncomfortable wearing shoes. Similar is hyperalgesia, a pain stimulus that is felt much more intense than it would normally [16].

Loss of function (2) can encompass: loss of pain sensation, inability to correctly sense temperature, numbness, loss of sudomotor (sweating) function, loss of autonomic vasomotor function leading to skin color changes or loss of thermoregulation. Autonomic dysfunction - also termed Dysautonomia - resulting in: constipation, diarrhea, gastroparesis, urinary and erectile dysfunction, etc. Source: [10, 15].

Sensory system		Autonomic system
Spontaneous pain (burning, sharp)		Sudomotor (hypohidrosis, anhidrosis)
Evoked pain (allodynia, hyperalgesia)		Cardiovascular (orthostatic hypotension)
Pruritus (alloknesis, hyperknesis)		Gastrointestinal (diarrhea, constipation, dysphagia)
Paraesthesias		Genitourinary (retention, incontinence, sexual dysfunction)
Dysesthesias		Visual (blurred vision, light hypersensitivity)
Hypoesthesia (thermal and pinprick)		Mucocutaneous (dry eye, dry mouth, skin discoloration)
Restless legs syndrome		

FIGURE 3.1: Sensory and autonomic presentation in SFN. Note: List is not exhaustive. Source: [16].

Chapter 4

Clinical Evaluation of PN/SFN

In PN a cause cannot be found in up to 30% of cases. A missing cause results in no therapy and thus in disease progression. Therefore, finding the cause is key yet also very difficult. It often needs meticulous "detective work" by an experienced, thorough and passionate neurologist. These are the important features of a good neurologist that separates the wheat from the chaff. Such a neurologist will inquire about the patient's medical history, the diseases that run in the family, any happenings of events before onset of the PN, the occurrence, time-span and location of each symptom, the patient's lifestyle, etc [10].

4.1 Clinical evaluation of SFN

The diagnosis of SFN incorporates the evaluation of clinical signs (senses, reflexes, balance, coordination, etc), neurophysiological testing, and evaluation of intraepidermal nerve fiber density (IENFD).

4.1.1 Practical neurological examination

A practical neurological examination encompasses the following exams:

- Evaluation of sensory symptoms and signs: light touch perception, pinprick sensation, temperature discrimination, and vibration sense. Diagnosed abnormalities in SFN can be reduced or absent sensation to pinprick, hyperalgesia (i.e. an extreme sensitivity to pain), allodynia (i.e. pain evoked by a normally non-painful stimulus), reduced thermal sensation, and sometimes reduced vibration sense.

- Examination for skin changes such as skin color changes, dryness, loss of distal hair, or abnormal nail growth (Terry's nails).

- Evaluation of signs of dysautonomia: orthostatic hypotension (low blood pressure upon standing), pupillary reaction to light reflex, dry eyes (Schirmer test), dry mouth, abnormal sweating, gastrointestinal complaints such as constipation or diarrhea, bladder dysfunction, or erectile dysfunction. Many of these signs cannot be examined by means of standard neurological devices. Therefore it's crucial to deliberately ask the patient about these symptoms, because it's possible that a patient is unaware of these symptoms or may think they would not be related to his other neurological complaints.

- Reflex Testing to evaluate the function of the large nerve fibers: Evaluation of the deep tendon reflexes such as the patellar reflex and Achilles reflex. These are usually preserved in SFN (as opposed in LFN).

- Examination of muscle strength of fingers, hands, arms, feet, and legs show no abnormalities in SFN.

- Examination of balance and proprioception (i.e. the sense of body position and movement): to test the latter, the neurologist moves a patient's joint such as the big toe joint and asks the patient about the movement direction. The ability to maintain balance can be tested by asking to stand with feet close together and eyes closed (Romberg test). The sense for balance and proprioception is unaltered in SFN. Source: [4, 16, 17].

4.1.2 Neurophysiology: EMG and NCS

Nerve Conduction Study (NCS) and Electromyography (EMG) are standard diagnostic tests to evaluate the function and integrity of large nerve fibers and muscles. NCS measures the speed and strength of electrical signals as they travel along peripheral nerves. Electrical stimuli are applied to a nerve and the responses are recorded by surface electrodes. In this way, the NCS assesses the conduction velocity, amplitude, and latency of nerve signals. EMG assesses electrical activity in muscles at rest and during a voluntary contraction by a needle electrode that is inserted into a muscle. The EMG can detect a muscle dysfunction, e.g. muscle weakness [18].

NCS/EMG is the standard test to diagnose LFN. In contrary, SFN involves no large fiber damage and thus no (clinically relevant) abnormalities are detected by NCS/EMG. Yet practically, little large fiber involvement is still applicable for the diagnosis of SFN [15].

4.1.3 LD vs NLD

4.1.4 Skin biopsy to assess Intraepidermal Nerve Fiber Density

The gold standard to diagnose SFN is the skin biopsy. At two respectively three defined areas (at the distal leg, lateral distal thigh, and lateral proximal thigh) a 3 mm skin biopsy is punched off. The biopsy is then stained by an immunostaining (standard is the immunostaining with antibodies against the pan-neuronal ubiquitin hydrolase protein gene product 9.5 [PGP 9.5] [19]). This diagnostically important light microscopic procedure has however only been established since the 1990ies. This method allows to visualize the (reduced) skin innervation by the small fibers and thus to determine the intraepidermal nerve fiber density (IENFD). In most cases though a trained neurologist would be able to suspect (or diagnose) a SFN by history, symptoms, and standard neurological examination without skin biopsy. The latter may then be performed as a confirmation. The level of nerve innervation in the skin, i.e. the IENFD varies in a healthy population by age (natural reduction with age) and gender. Therefore, age- and gender-adjusted normative values have been established. Source: [15, 19].

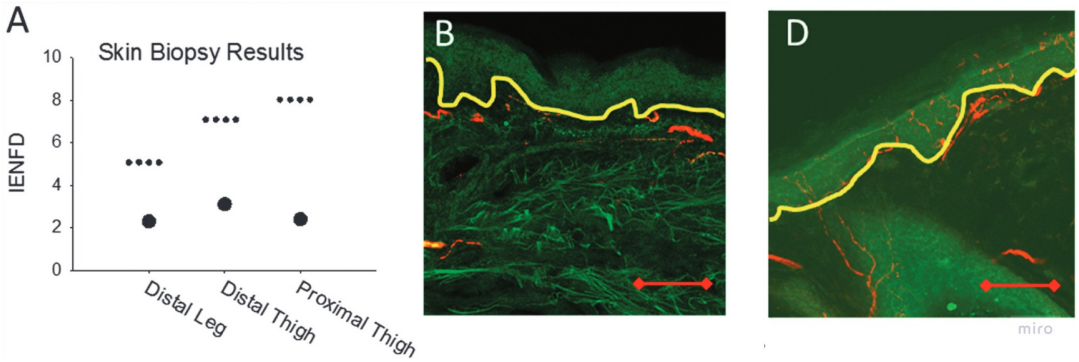

FIGURE 4.1: A) IENFD is reduced at all three sites (large black dots). Dotted lines define the lower threshold of the normal IENFD value. B) Biopsy from the distal leg with pathologically reduced IENFD. The nerve fibers (in red) do not enter the dermal-epidermal junction (yellow line). Red scale bar = 100 μm. D) Biopsy from the distal leg shows epidermal nerve fibers (in red) that cross the dermal-epidermal junction. Its corresponding IENFD value lies at the lower threshold of the normal IENFD. Source: [15].

4.1.5 QST and autonomic testing

There exist several further tests to help diagnose SFN. As these are not mandatory for the PNRR, I mention them briefly for the reader's overview. **Quantitative sensory testing (QST)** assesses a patient's sensory perception thresholds with applied thermal, mechanical, vibrational, and electrical stimuli. It allows to detect sensory abnormalities. **Autonomic Testing** examines the functioning of the autonomic nervous system, and there exist several tests. There are two main categories: the cardiovascular assessment of parasympathetic and sympathetic adrenergic function and the assessment of sudomotor (sympathetic cholinergic) function. Typical tests for the latter are the tilt table test which can diagnose orthostatic hypotension or postural tachycardia syndrome (POTS), the Quantitative Sudomotor Axon Reflex Test (QSART), or the Thermoregulatory Sweat Test (TST).

4.1.6 Laboratory screening

Laboratory screening includes blood values, antibodies, genetics, and further tests. There exist no clear guidelines for laboratory screening. Each hospital may approach it in it's own way. Laboratory screening depends also on the hospital's expertise, experience, costs, and willingness to find the cause. At an initial patient presentation though, laboratory screening for the main causes should be performed, i.e. for diabetes (incl. pre-diabetes) and other metabolic causes, the most important infectious diseases, immune-mediated causes (autoimmunity), paraneoplastic syndromes (cancer), toxic, and the most important genetic causes. In the list below Devigili et al. 2020 [17] suggest the needed laboratory tests for an initial SFN screening. However, often no cause can be identified, in this case it's suggested to repeat the screening two years later as with disease onset a cause may be found. Additionally, the neurologist should also move on to test for less common causes. Furthermore, a popular list of tests for treatable causes of SFN is kept by the Massachusetts General Hospital at Harvard on their website neuropathycommons.org [20].

Diabetes or pre-diabetes

- Fasting plasma glucose
- Oral glucose tolerance test
- Glycated haemoglobin HbA1c

Other metabolic causes

- Thyroid function
- Renal function
- Vitamins B12 (cobalamin)
- Folate

Infectious disease

- HIV test
- Hepatitis B and C serology
- Hematological disease:
- Serum electrophoresis and immunofixation
- Complete blood count

Immune-mediated

- Antinuclear antibody (ANA)
- Extractable nuclear antigen (ENA)
- Antineutrophil cytoplasmic antibody screening (ANCA)
- Cryoglobulin
- Rheumatoid factor
- Erytrocyte sedimentation rate (ESR)
- Anti-RO (SSA), anti-La (SSB) – (Sjogren's syndrome)
- Antibodies for gliadin, transglutaminase and endomysial – (Celiac disease)

Paraneoplastic syndromes

- Onconeuronal antibodies (anti-Hu, anti-CV2)

Genetic disease

- Sodium channelopathy - SCN9A, SCN10A, SCN11A genes
- Familial amyloidosis - Transthyretin gene
- Fabry disease - Enzymatic assay for alpha-Gal A activity or Genetic test of alpha-Gal A (GLA)

Source: [17].

4.1.7 Laboratory screening in the PNRR

Laboratory screening in the PNRR is divided into three tiers: The first tier is considered mandatory and contains the laboratory testing recommended by the American Academy for Neurology. Tests of the second tier are commonly conducted in patients with idiopathic PN to identify potential underlying causes. The third tier testing are for known causes of polyneuropathy, such as antibodies, vitamin deficiencies and infectious diseases.

FIRST TIER:

Screening for the most common causes of polyneuropathy: Creatinine level (kidney disease), Glucose screening by at least one of the following: Glycated Hemoglobin (HbA1C), fasting blood glucose, or Oral Glucose Tolerance test(hyperglycemia/diabetes), Serum Immunofixation (IFE) and/or (Serum Protein Electrophoresis (SPEP)) (paraproteins/immune system) and Vitamin B12 (vitamin B12 deficiency).

SECOND TIER:

Complete Blood Cell count (CBC); Erythrocyte Sedimentation Rate (ESR) [high values indicate inflammation]; Thyroid Stimulating Hormone (TSH); Lipid Profile (cholesterol, triglycerides, HDL- and LDL-cholesterol); C-reactive Protein (CRP) [high levels indicate inflammation]; Antinuclear Antibodies (ANA) test [is used to diagnose lupus, Sjogren's syndrome, rheumatoid arthritis, mixed connective tissue disease, polymyositis, dermatomyositis, autoimmune hepatitis and drug induced lupus]; Urine Immunofixation (IFE) and/or Urine Electrophoresis (UPEP); Methylmalonic Acid (MMA) [elevated levels are used to diagnose early or mild 12 deficiency].

THIRD TIER:

INFLAMMATORY / AUTOIMMUNE: Kappa / Lambda Light Chains; Angiotensin-Converting-Enzyme (ACE) [elevated levels can indicate: leprosy, hyperthyroidism, acute hepatitis, primary biliary cirrhosis, diabetes mellitus, multiple myeloma, osteoarthritis, amyloidosis, Gaucher disease, pneumoconiosis, histoplasmosis, miliary tuberculosis, or sarcoidosis. Too low levels can indicate: chronic liver disease, eating disorders, steroid therapy, therapy for sarcoidosis, or hypothyroidism.]; Anti-Double-Stranded DNA Antibodies [screening for lupus, rheumatoid arthritis, HIV, and others]; Anti-Endomysial Immunoglobulin G antibodies [screening for autoimmune diseases including celiac]; Anti-Ganglioside Antibodies (GM-1) [screening for autoimmune neuropathies]; Anti-Gliadin Antibodies (IgA / IgG) [testing for gluten sensitivity and celiac disease]; Anti-Neutrophil (p-ANCA and c-ANCA) [screening for autoimmune diseases, particularly vasculitis]; Anti-RO (SSA) Antibodies and Anti-LA (SSB) Antibodies [screening for Sjogren's syndrome and/or systemic lupus erythematosus (SLE)]; Anti-68 Kd Antibody (cochlear antigen) [screening for sensorineural hearing loss]; Anti-MAG Dual Antigen [screening for PN with purely sensory or mixed sensory and motor neuropathy with predominantly demyelinating features]; Anti-Parietal Cell Antibodies [parietal cells are critical to absorb vitamin B12]; Anti-Thyroglobulin Antibodies [to diagnose an autoimmune thyroid disease or thyroid dysfunction]; Rheumatoid Factor (RF) [used as a diagnostic test for Rheumatoid Arthritis and Sjogren's syndrome]; Tissue Transglutaminase Immunoglobulin A (IgA) Antibodies [used in screening for celiac disease, juvenile diabetes, inflammatory bowel disease and various forms of arthritis]; Cryoglobulins [screening for vasculitis and other autoimmune diseases].

INFECTIOUS: HIV; Lyme; Rapid Plasma Reagin Antibodies (RPR Ab) [Screening for Syphillis]; Hepatitis B; Hepatitis C.

GENETIC: Galactosidase Assay [screening for Fabry's disease], Charcot-Marie-Tooth (CMT).

PARANEOPLASTIC: Anti-Ri antibody; anti-Hu antibody [associated with subacute syndrome of encephalomyeloradiculopathy, sensory neuropathy, and autoimmune neuropathy]; Anti-Purkinje Cell (YO) antibody; Paraneoplastic Panel (Mayo Panel) [Autoantibodies: ANN1S, ANN2S, ANN3S, AGN1S, PCABP, PCAB2, PCATR, AMPHS, CRMS, STR, CCPQ, CCN, ARBI, GANG, VGKC].

OTHER: Creatine Kinase (CK) [Screen for myositis, inflammation]; Homocysteine [elevated level can indicate low B-vitamin intakes]; Heavy metals in urine; Vitamin E; Vitamin B1, Vitamin B6 [deficiency and elevated level can cause neuropathy].

4.2 Etiology

SFN etiologies can be classified into: genetic, metabolic, systemic, toxic, infectious, inflammatory, syndromic, and idiopathic categories. With perhaps over 200 different causes for SFN, it is very hard to pin down the underlying etiology, and oftentimes the cause remains idiopathic despite thorough evaluation. As a matter of fact, *idiopathic* unfortunately remains the most frequent "cause" of SFN, namely in 30-50% of cases [21]. The second most common cause is Diabetes and impaired glucose tolerance in about 36% of cases [22]. Yet even in the absence of diabetes, metabolic syndrome and obesity are at least risk factors if not direct causes for SFN [4]. Other frequent causes are alcohol abuse, chemotherapy (toxic for nerves), immune-mediated, and infections. Immune-mediated SFN can develop under different settings: as a manifestation of an underlying systemic autoimmune disease such as Sjogren's syndrome or Systemic Lupus Erythematosus, in connection with SFN related autoantibodies (e.g. TS-HDS, FGFR3 [1]) without a systemic disease, or postinfectious/postvaccination-triggered [23]. The cause of a SFN is oftentimes not detectable by blood tests. Perhaps it would be identifiable histologically, however this is barely done in practice. The list below gives an overview of all known etiologies. Sources: [4, 16, 21, 23–25].

Genetic:

Familial amyloid polyneuropathy, hereditary sensory and autonomic neuropathy (HSAN), Fabry disease, Tangier disease, Friedreich ataxia, Charcot-Marie-Tooth (CMT), Pompe disease, Hemochromatosis, Sodium channel mutations (SCN9A, SCN10A, SCN11A, etc.), COL6A5 mutations.

Metabolic:

Impaired glucose tolerance, diabetes mellitus, vitamin B1, B6, folate, B12, E deficiency, copper deficiency, dyslipidemia, hypertriglyceridaemia, hypothyroidism, chronic kidney disease, uraemia.

Infectious:

Hepatitis C and B, HIV, Covid-19, Herpes Zoster, Herpes Simplex 1 and 2 Lyme disease, leprosy, influenza, Epstein-Barr virus, Chagas disease, syphilis, mycoplasma pneumonia, rubella, cytomegalovirus, vaccinations (e.g. rabies, Covid-19 vaccines).

Toxic:

Vitamin B6 toxicity, antiretroviral agents, antibiotics, chemotherapy agents, flecainide, amiodarone, dapsone, phenytoin, statins, alcohol, organic solvents, heavy metals, recreational drugs (nitrous oxide, others), tumour necrosis factor α inhibitors.

Inflammatory and immune-mediated:

Sjogren's syndrome, sarcoidosis, celiac disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic vasculitides, amyloidosis, monoclonal gammopathy of unknown significance (MGUS), autoimmune autonomic ganglionopathy (AAG),

[1] trisulfated heparin disaccharide, fibroblast growth factor receptor 3

anti-potassium channel antibody, paraneoplastic syndromes, Hashimoto hypothyroidism, Guillan-Barre Syndrome (GBS), inflammatory bowel disease (IBD), Scleroderma.

Pain syndromes:

Fibromyalgia, Complex regional pain syndrome type I (CRPS), Ehlers-Danlos syndrome (EDS), Chronic pelvic and bladder pain, Irritable bowel syndrome (IBS).

Neurodegenerative disorders:

Parkinson's disease, multiple system atrophy, Amyotrophic lateral sclerosis (ALS), pure autonomic failure, motor neuron disease.

Other:

Acute intermittent porphyria.

Idiopathic:

If none of the above causes can be identified, the neuropathy is said to be idiopathic.

Chapter 5

Treatments for Peripheral Neuropathy

The treatment for PN focuses on the underlying cause of the neuropathy (if known) and on the symptoms, i.e. pain and/or autonomic symptoms. Small fibers have the ability to regrow, and perhaps - in a lesser fashion - larger fibers too. Thus, treating the root cause can heal the nerves and maybe reverse the neuropathy. For IPN, the treatment can unfortunately only address symptom relief and perhaps the protection of the nerves.

5.1 Treating Peripheral Neuropathy of a known etiology

The best treatment is to treat the underlying cause of the neuropathy. Diabetes-related PN is treated with glycemic control and lifestyle improvements, PN caused by vitamin deficiency is treated through supplementation of the deficient vitamin or substance (e.g. vitamins B1, B6, B12, E, copper), metabolic or hormonal unbalances are corrected (e.g. thyroid dysfunction), toxic agents are eliminated, and in Fabry's disease enzyme replacement therapy is the way forward [4, 17]. Autoimmune-mediated PN is treated with immunotherapy. Treatment options include here: intravenous immunoglobulins (IVIG), therapeutic plasma exchange (TPE), immunosuppression (Biologicals), and immune-mediated SFN occurring in relapses may improve on high dose intravenous or oral corticosteroids (prednisone, prednisolone). Regarding treatments for other etiologies, see Finsterer and Scorza (2022) who list the corresponding treatments for numerous SFN causes [26].

5.2 Treatments for neuropathic pain

Neuropathic pain (NP) is the most severe and frequent symptom in SFN and very difficult to alleviate. Despite existence of various pain medications, treatment of NP often remains insufficient and frustrating, also under combined drugs. The second problem are significant side effects such as sedation, dizziness, loss of libido, dry mouth, etc. The choice of the therapeutic agent(s) is based on several criteria: the presumed mechanism of the pain, minimal side effects, comorbidities, and drug-drug interactions. In the following, I list frequently prescribed agents for NP:

a) Serotonin and norepinephrine reuptake inhibitors (SNRI) such as Duloxetin or Venlafaxine. b) Tricyclic antidepressants such as Amitriptyline. c) Antiepileptic drugs such as $\alpha 2\delta$ Ligands of Voltage-Gated Calcium Channels (e.g. Pregabalin

or Gabapentin) and Sodium Channel Blockers (e.g. Carbamazepine, Topiramate, or Lamotrigine). d) Opioids such as Tramadol, Oxycodone, Methadone, or Fentanyl. e) Topical agents such as Lidocaine, Capsaicin, Phenytoin, Amitriptyline, or Ketamine. The latter advantages' are targeted application to painful areas and little to no side effects. f) Physical treatments such as transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), monochromatic infrared energy, pulsed magnetic fields, or dorsal root ganglia stimulation [24, 26]. g) Other agents such as Cannabinoids or low dose naltrexone (LDN). Source: [27].

5.3 Treatments for autonomic issues

The treatment of autonomic dysfunction depends on the type of dysfunction, and is often only managed symptomatically. Options may include adrenergic drugs or cholinesterase inhibitors (e.g. Mestinon). Gastrointestinal mobility disorders may be approached by prokinetic drugs to enhance cholinergic function and constipation may be eased with laxatives and diet change. Dryness of eyes may be managed with eye drops and mouth dryness with moisturizing sprays.

5.4 Treating concurrently occurring syndromes

PN and SFN often leads to respectively occurs concurrently with other syndromes such as gastrointestinal absorption and resorption problems or Mast Cell Activation Syndrome (MCAS). Unfortunately, these are not well-known among physicians. The small fibers are in direct contact with mast cells. In case of MCAS, the mast cells will "attack" the small fibers. Thus, it is important to treat an accompanying MCAS with antihistamines and/or mast cell stabilizers. Neuropathy with motility disorders can occur with or lead to microbiome dysbiosis (small intestine bacteria overgrowth (SIBO) and small intestine fungal overgrowth (SIFO)) and leaky gut syndrome, and can result in various absorption and resorption problems with vitamins, minerals, and amino acids. These problems may lead to a vicious circle aggravating the neuropathy. Thus, it is vital to treat an eventual microbiome dysbiosis and to check levels of the mentioned substances and supplement potential deficiencies.

5.5 Neuroprotective treatments

In studies and in animal models, several agents have shown to possess neuroprotective properties, such as Alpha Lipoic Acid, Palmitoylethanolamide (PEA), Resveratrol, or Vitamin E. It is wise to add such products to the diet, yet the study situation is very sparse. Source: [27].

5.6 Complementary therapies

A wide range of complementary therapies are popular among patients and are generally recommended to ease symptoms, increase overall well-being, and to improve nerve health. Moderate aerobic exercise training reduces neuropathic pain [28]. Aerobic training also improves blood circulation which increases oxygen flow to nerve tissue. A healthy diet is also very important, i.e. a sugar-free, low carb, anti-inflammatory, organic diet rich in omega-3 polyunsaturated fatty acids as well as

the renunciation of processed foods. Moreover, supplements and herbs with anti-inflammatory and antioxidant properties may improve nerve health too, such as Alpha Lipoic Acid, Vitamin C, Curcumin, Acetyl-L-Carnitine, L-Glutamine, Glutathione, N-Acetyl-Cystein (NAC), Ubiquinol, and other mitochondrial health promoting agents. Mind-body practices such as Meditation, Mindfulness, Yoga, Tai Chi, etc. promote stress reduction and contribute to the healing process [29]. Other treatments include medical cannabis and cannabidiol (CBD), cognitive behavioral therapy (CBT), and acupuncture [24]. Lastly, as pain is especially harsh during the night, natural sleep remedies such as Melatonin or sleep medication are also very helpful.

5.7 Novel treatments on the horizon

ARA-290 (Cibinetide), an erythropoietin (EPO) derivate, has shown promising results for small nerve fiber regrowth in clinical studies for sarcoidosis-related SFN [30]. Promising too are the phase 2 clinical trial results of a drug named WST-057 developed by a company named Winsantor. WST-057 stimulates nerve growth by addressing the mitochondrial dysfunction in nerve cells. The normal cell function is reestablished through inhibition of a GPCR (G-protein coupled receptor) found on the membranes of axon terminals of peripheral nerves [31].

Chapter 6

Data: The Peripheral Neuropathy Research Registry (PNRR)

6.1 The Peripheral Neuropathy Research Registry

The Peripheral Neuropathy Research Registry (PNRR) was initiated in 2008 and is funded by the Foundation for Peripheral Neuropathy (FPN), located in Chicago, United States. It is a cohort of a US patient population with PN. It contains four PN etiologies: Diabetic Peripheral Neuropathy (DPN), Chemotherapy-Induced Peripheral Neuropathy (CIPN), HIV/AIDS associated PN, and Idiopathic neuropathies. The PNRR helps the characterization of clinical phenotypes and genotypes of patients with PN and its goal is to improve the diagnosis, treatment, and prevention of PN [32]. More information about the PNRR can be found on its website https://thepnrr.org.

The PNRR is enrolling PN patients in seven neurological consortium partner clinics: Johns Hopkins University School of Medicine, Baltimore, as the leading institution, Mount Sinai School of Medicine, New York, Northwestern Medical Faculty Foundation, Chicago, University of Kansas Medical Center, Kansas City, University of Michigan Health System, Ann Arbor, University of Utah School of Medicine, Salt Lake City, and Washington University in St. Louis. Patient inclusion criteria for the 4 etiologies are distal, symmetrical, and axonal polyneuropathies, as well as length dependent and non length dependent SFN. Excluded are predominantly demyelinating polyneuropathies, patients with other identified causes of PN, and patients with also upper neuron involvement [33].

Data for the PNRR are collected by neurological routine examinations according to set standard operation procedures (SOPs) in seven visit information forms, each dedicated to a specific medical aspect:

- A. Physician Examination Form (PEF). It captures results of routine neurological examinations to diagnose and evaluate nerves, muscles, reflexes, and sensation in PN.
- B. Nerve Conduction Studies Form (NCS). NCS are performed on major motor and sensory nerves in arms and legs. It evaluated e.g. nerve speeds or signal strength (action potential).

- C. Peripheral Nerve Work-Up (PNW). The PNW measures various diagnostic blood laboratory. The first tier contains markers such Creatinine, Glucose, IFE, Polypeptide (PEP) or B12. The second tier contains markers such as CBC, ESR, TSH, CRP, ANA, or MMA. Further collections include autoantibodies, infections, genetics, paraneoplastic markers, autonomic testing, and biopsies.

- D. Patient History Questionnaire (PHQ). The PHQ is answered by the patients. It assesses symptoms, sleep, medical history, medications, life style, exercise habits, family history, etc.

- E. Metabolic Syndrome Evaluation (MetS). The MetS looks at various aspects of the Metabolic Syndrome: Obesity, hypertension, glucose metabolism, exercise. The MetS was added to the PNRR in 2020.

- F. Supplemental Data. This data is optional and encompasses diverse measurements. Currently, mostly only Johns Hopkins University captures this. It includes absolute values for certain markers such as immunoglobulins, blood work, or skin biopsies. It also assesses muscle, nerve and sensory measurements on a more fine-grained level.

- G. Blood Collection and Processing Form. This form captures details about the collected blood samples. This data is not necessary for our purposes, and we do not have access to them.

All forms together yield 917 measurement variables. The captured information from these paper forms are then entered in a REDCap database. Upon a complete patient's record, a Data Quality Assessment (DQA) is performed. For returning patients follow-up data entries are entered into the PNRR. Follow-up visits happen about with time lapse of 4-6 years. The first enrolments started in 2011. As of September 2022, the PNRR enrolled a total of 2336 subjects (644 DPN, 1363 idiopathic PN, 151 HIV/AIDS PN, and 178 CIPN).

The PNRR data (data dictionary and actual data) and its preprocessing are outlined in Appendix A.

6.2 Selection criteria of the study populations

This section describes the criteria to select the study populations from all PNRR patient records. The inclusion criteria of the PNRR records into the study populations are listed below.

- a) Record of a patient's initial hospital visit (i.e. if a patient was re-evaluated after 4 years, this observation was not included). The reason is that the study population shall not be biased towards patients who were examined multiple times.

- b) IPN (variable pef_diagnosis = idiopathic PN) or DPN (variable pef_diagnosis = diabetic PN) as underlying etiology.

- c) SFN population: Only biopsy-proven SFN. Normal NCS/EMG (variable pnw_1) and abnormal skin biopsy (variable pnw_2). Note that the SFN study population includes length dependent and non-length dependent SFN.

		etiology		
	population	**DPN**	**IPN**	**Total**
1	**SFN**	51	256	307
2	**LFN**	436	802	1238
3	**PN**	487	1058	1545

FIGURE 6.1: Size of study populations. Beige numbers refer to the SFN analysis, white numbers to the LFN analysis, and turquoise numbers to the SFN vs. LFN analysis.

- d) LFN population: Abnormal NCS/EMG (variable pnw_1).
- e) PN population is the union of the SFN and the LFN population.

The resulting study population sizes are shown in Table 6.1. Note that the LFN analysis has a much larger study population size than the SFN analysis. The SFN vs. LFN analysis features the largest population size with 1545 patients. The group sizes are unbalanced with larger IPN groups as opposed to DPN groups. It's noteworthy that the PNRR contains besides the skin biopsy proven SFN cases further SFN patients who however did not undergo a skin biopsy and thus could not enter the SFN population of this research. I tried to append these SFN patients to the study by applying Freeman's 2020 criteria for iSFN, yet corresponding PNRR variable definitions and data availability were not sufficient to make them enter into the SFN study population.

Chapter 7

Method

Bivariate statistical tests are performed for all PNRR variables except for the checkbox and descriptive text variables. A statistical test was only performed with a sufficiently large sample size. The threshold was set to 15. If at least one of the two groups contained less samples than the threshold, a test was not performed. According to the variable types and test preconditions five different bivariate tests were performed: Chi square, Fisher's exact, Student t, Welch, and Mann-Whitney U. Figure 7.1 shows the algorithm for the application of the statistical tests.

Due to statistical batch analyses, Benjamini Hochberg Correction [34] was applied. It corrects for the family wise error rate (FWER), as well as for the false discovery rate (FDR), and has more power respectively is less strict than e.g. the Bonferroni correction.

To interpret the effect strengths the medians (respectively the percentages for each variable level) of both groups, Cramer's V as a measure for the effect strength for the Chi square test, and Vargha Delaney's A for the Mann-Whitney U test are given. Vargha Delaney's A takes values between 0 and 1. A value of 0.5 indicates that the two groups are stochastically equal. A small effect can be interpreted for values between 0.56 - <0.64 and >0.34 - 0.44, a medium effect between 0.64 – <0.71 and >0.29 – 0.34, and a large effect for values >=0.71 and <=0.29. Cramer's V ranges between 0 (no association) and 1 (perfect association).

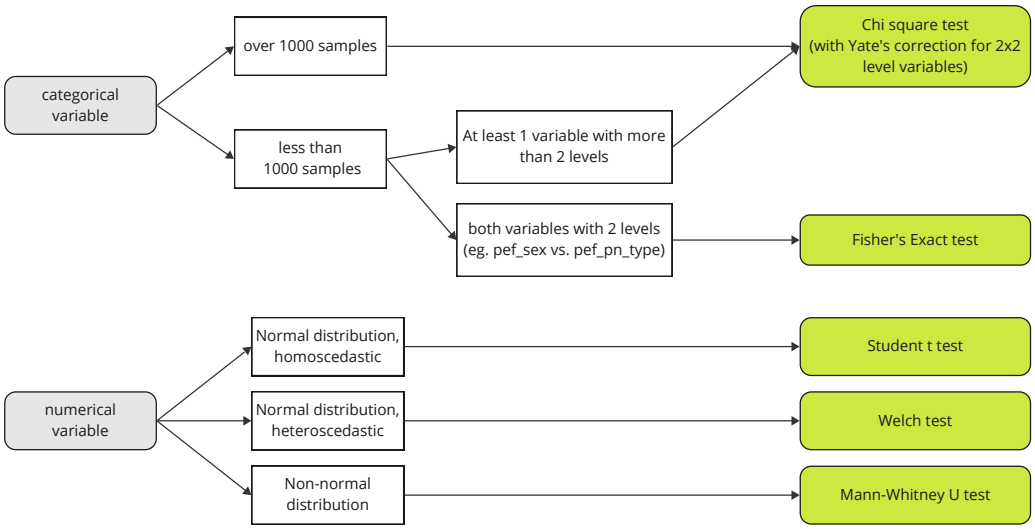

FIGURE 7.1: Algorithm for the application of the statistical tests

Chapter 8

Results

8.1 Baseline demographics

Table 8.1 shows the baseline demographics for all three analyses. Note that in order to make results readily interpretable, they are discussed here at the same time.

8.1.1 Analysis 3: SFN vs. LFN

Age: LFN is significantly older than SFN with a mean difference of 10.3 years. As SFN can progress to LFN with time, it is clear that LFN are older than SFN. **Sex**: LFN has a much higher share of males (70.7%) as opposed to SFN (51.5%). In the general population, we deem that diabetic and idiopathic SFN and LFN affect men and women evenly, and that the large share of males in LFN is caused by a bias: The higher shares of males can be explained - as we observe in clinic - due to more demanding behavior of men to get a second opinion or referral to a renowned clinic such as the Johns Hopkins Hospital than women and questioning their home neurologist more often. The same trend holds also in SFN, though much weaker. **Years since onset of PN**: The mean duration is significantly longer in LFN (7.5 years) than in SFN (4.7 years). This is well-explainable as SFN is often an initial neuropathy state which with time may proceed to a LFN. **BMI**: LFN has a significantly higher mean BMI (30.3) than SFN (28.4). The reason is that LFN has a much larger share of abnormal HgA1C than SFN. Obesity is a typical association with DM. **Height (cm)**: LFN yields a significantly higher height than SFN, and this difference is most likely artificial due to much higher share of males in LFN than in SFN. **Painful neuropathy (%)**: SFN has a significantly and much higher share of painful neuropathy than LFN. This is clearly understandable because pain is the hallmark symptom in SFN, while LFN patients are referred to neurology clinics also for (leading) issues such as balance or fall. **Glucose** related variables such as HgA1C (%), Fasting glucose level, and abnormal HgA1C (%) have all significantly lower values in SFN than in LFN. The cause can be attributed to the higher share of DM patients in LFN than in SFN. This bias may also explain the significantly lower HDL-cholesterol in LFN than in SFN. LDL-cholesterol levels have no impact on neuropathy. **Vitamin B12 value**: There is no significant difference in B12 between SFN and LFN, although SFN has a somewhat lower B12 mean than LFN. This is interesting because B12 adsorption gets small with age and LFN patients are significantly older than SFN as we have seen.

8.1.2 Analysis 1 and 2: SFN and LFN

Age: In SFN, DPN are older than IPN patients, though not significantly. In LFN it's opposite, IPN are older than DPN patients and significantly at **. We have no explanation for this difference. **Sex**: In both analyses 1 and 2, there are more males than females in DPN; though in LFN the share of males is quite higher with 64.9% than in SFN (56.9%). In IPN, the share of male and women is even with slightly more males (50.4%). In LFN, the share of males (73.8%) is much higher than the share of females. **Years since onset of PN**: IN LFN, disease duration is significantly longer in IPN (7.8 years) compared to DPN (6.7 years). Same holds in SFN, though the difference is not significant. **I cannot interpret this difference between etiologies. BMI**: In LFN, DPN has a significantly higher BMI than IPN; the same trend exists also in SFN though not significantly. This difference in BMI is well-explainable as DM is clearly associated with obesity. Same holds for Weight (kg). **Height (cm)**: In SFN, there is no significant difference between etiologies, however in LFN IPN is significantly higher than DPN, which is to some degree explained by the higher ratio of males in IPN than in DPN. However - as we will see later in the men's only LFN cohort - there is a positive association between etiology (IPN) and height. This can be explained by the fact that a longer nerve has more surface to be damaged than a shorter nerve. Thus, higher people have a higher risk for neuropathy. **Painful neuropathy (%)**: In LFN, DPN have a significantly higher share of being painful. This confirms existing observations that DPN is known to be more painful than IPN. In SFN, there is no significant difference. **Glucose** related variables show a clear trend. In both SFN and LFN, DPN have significantly higher levels for HgA1C, fasting glucose, and a higher share of abnormal glycated hemoglobin. These differences are even more pronounced in LFN than in SFN, which can be explained by longer disease onset, higher BMI, higher age in LFN as opposed in SFN. In LFN, DPN have significantly higher levels of triglycerides and lower levels of HDL-cholesterol ("good cholesterol") than IPN. This is as expected as DM is associated with these values. For LDL-cholesterol levels ("bad cholesterol"), DPN has significantly lower levels than IPN, though LDL is not important in the context of neuropathy. In SFN, there are no significant differences. **Vitamin B12 value**: In both SFN and LFN, IPN has higher levels than DPN, though not significantly. B12 adsorption is negatively correlated with age making low B12 levels a risk factor for neuropathy. The higher B12 in IPN might be explained by the lower age of IPN; however in LFN, IPN are older which is just the opposite.

8.2 Significant results

From a top-down perspective, Table 8.2 lists for each analysis the number of significant tests. In analysis 1 DPN differentiates significantly from IPN in only very few variables (2.1%). Analysis 2 has 19.5% and analysis 3 the most significant differences with 63.4%. SFN is well discernible from LFN due to clear clinical differences in Physician Examination and NCS. Differences between etiologies are mainly in the Diabetes-related variables; subtle in SFN and more frequent in LFN.

In the following sub-chapters, for each of the 3 analyses the shortlisted variables of significant differences are listed and discussed. The numbers at the beginning of each bullet point refer to the variable's index number and identify the given variable. See Appendix B for the list of all variables with significant differences. Note

	Analysis 1: SFN					Analysis 2: LFN					Analysis 3: SFN vs. LFN				
	DPN		IPN			DPN		IPN			SFN		LFN		
	mean	std	mean	std	Sig.	mean	std	mean	std	Sig.	mean	std	mean	std	Sig.
N	307					1238					1545				
Variable															
N (% of all)	51 (16.6%)		256 (83.4%)			436 (35.2%)		802 (64.8%)			307 (19.9%)		1238 (80.1%)		
Sex (% male)	56.9		50.4		-	64.9		73.8		**	51.5		70.7		***
Age (years)	60.9	9.5	54.8	14.7	-	63.4	11.8	67.5	10.9	***	55.8	14.1	66.1	11.4	***
Years since onset of PN	3.9	4.6	4.9	5.9	-	6.7	7.2	7.8	6.7	**	4.7	5.7	7.5	6.9	***
BMI	29.8	5.6	28.1	5.9	-	32.6	6.8	29.1	6.2	***	28.4	5.9	30.3	6.6	***
Weight (kg)	88.8	17.4	84.2	19.2	-	99.6	21.9	92.4	21.4	***	84.9	18.9	94.9	21.8	***
Height (cm)	172.6	8.7	173	10	-	174.8	10.5	177.9	9.7	***	172.9	9.8	176.8	10.1	***
Painful neuropathy (%)	80.4		84.4		-	78.0		65.2		***	83.7		69.7		***
HgA1C level (%)	6.5	1.2	5.5	0.4	***	7.2	1.7	5.5	0.6	***	5.7	0.8	6.2	1.4	***
Fasting Glucose Level (mg/dL)	110	26.2	89.3	10.9	***	122.7	60.7	96.2	28.1	***	91.8	15.1	102.6	40.1	***
Glycated Hemoglobin (HgA1C): abnormal (%)	66.0		19.4		***	85.4		26.1		***	28.2		48.6		***
Triglycerides level (mg/dL)	155.1	71.1	130.2	73.6	-	168.7	108.7	136.4	114.3	***	134.8	73.6	148.6	113.2	-
HDL-cholesterol level (mg/dL)	49.2	13.7	54.7	18.9	-	46.7	14.1	53.9	46.9	***	53.7	18.1	51.2	38.1	*
LDL-cholesterol level (mg/dL)	101.2	27	111.2	43.1	-	90.3	36.1	99	35	***	109.4	40.8	95.7	35.7	***
Vitamin B12 Value (pg/mL)	685.7	374.5	740.5	438.3	-	732	578.4	760.1	463.6	-	731.1	427.9	750.3	506.4	-

FIGURE 8.1: Baseline demographics for all three analyses. Significance levels: * p<0.05, **p<0.01, ***p<0.001. The greyed-out cells are categorical variables of two levels. Here, only data for one level are displayed.

			All variables		
	Analysis	**population**	**Total tests**	**Sign. tests**	**Sign. tests (%)**
1	DPN vs IPN	**SFN**	336	7	2.1
2	DPN vs IPN	**LFN**	436	85	19.5
3	SFN vs LFN	**PN**	437	277	63.4

FIGURE 8.2: Significant results per Analysis. Column "Total tests" shows the number of performed tests.

that significant variables from the baseline demographics were already discussed in Chapter 8.

8.2.1 Analysis 1: SFN diabetic vs idiopathic

- 208. Glycated Hemoglobin (HgA1C): As expected, IPN has a much higher ratio of normal vs. abnormal HgA1C than DPN. Fisher's exact test sig. at 0.001, Cramer's V = 0.39.
- 209. HgA1C Level: As expected, IPN has a much lower HgA1C level than DPN. Median IPN = 5.45, DPN = 6.05. Mann-Whitney U test sig. at 0.001, VD A = 0.88.
- 211. Fasting Glucose Level: As expected, IPN has a much lower Fasting Glucose level than DPN. Median IPN = 88, DPN = 104. Mann-Whitney U test sig. at 0.001, VD A = 0.83.
- 346. Marital status: Marital status differs sig. between IPN and DPN. Chi square test sig. at 0.001, Cramer's V = 0.25. E.g. IPN has more single, less married, and less widowed than DPN; however rather surprisingly more divorced. This difference is most likely artificial and caused by the lower age of IPN than DPN.
- 351. Hyperglycemia: As expected, IPN has a much lower ratio of Hyperglycemia than DPN (in fact all DPN patients have Hyperglycemia). Fisher's exact test sig. at 0.001, Cramer's V = 0.57.
- 453. Metabolic disease: As expected, IPN has a much lower ratio of Metabolic disease than DPN. Fisher's exact test sig. at 0.001, Cramer's V = 0.28.
- 455. Patient with Diabetes Mellitus: As expected, IPN has a much lower ratio of positive Diabetes Mellitus than DPN. Fisher's exact test sig. at 0.001, Cramer's V = 0.52.

8.2.2 Analysis 2: LFN diabetic vs idiopathic

- 69. Vibration sense: toes right: This is sig. more reduced in IPN than in DPN. This interesting.
- 83. Monofilament: Ankle - right. Assessment for loss of protective sensation: This is sig. more reduced in IPN than in DPN. This interesting.
- 121. Ulnar - MNCV - Wrist to elbow - Right. This is sig. more frequently abnormal in DPN than in IPN. This is interesting.
- 122. Ulnar - MNCV (m/s) - Around elbow - Right: Median Motor Nerve Conduction Velocity between wrist and elbow AND 127. Unar - Distal CMAP - Right (Action Potential): DPN are more likely to have carpal tunnel and ulnar entrapment around the elbow than IPN. This is interesting.
- 205. Chemistry (Chem 12-18). High Creatinine level: DPN are sig. more likely to have kidney disease than IPN. This is a known side effect of DM and an interesting fact to report.

- 221. 8. Erythrocyte Sedimentation Rate (ESR): ESR is more likely to be sig. abnormal in DPN than in IPN, i.e. DPN are more likely to have inflammation going on in their body than IPN. This is an interesting finding. ESR is an unspecific marker for overall health.

- 224. 10. Lipid Profile: This is sig. more likely to be abnormal in DPN than in IPN. This was expected.

- 226. Triglycerides AND 227. HDL-cholesterol levels: High triglycerides and low HDL levels are associated with making neuropathy symptoms worse. Both variable are sig. worse in DPN than in IPN. This is an interesting fact to report.

- 286. Do you have pain?: DPN are sig. more likely to have pain than IPN. This was anticipated and interesting to report.

- 290. How sharp does your pain feel?: DPN are sig. more likely to experience sharp pain than IPN. This is an interesting fact.

- 300. Allodynia: DPN are sig. more likely to experience allodynia than IPN. This is an interesting finding.

- 366. Diagnosis of hypertension: DPN have sig. more frequently a diagnosis of hypertension than IPN. This is expected and worth reporting.

- 374. Diagnosis of dyslipidemia: DPN have sig. more frequently a diagnosis of dyslipidemia than IPN. This is expected and worth reporting.

- 375. Does patient exercise?: DPN patients are sig. less likely to exercise than IPN. This is interesting.

- 453. Does patient have metabolic disease?: DPN patients are sig. more likely to have a metabolic disease than IPN. This is expected and interesting to report.

- 471. Calculated METS: This is a compound measure that shows how often and how intensive activities and exercises a person does. IPN patients have a sig. higher METS value than DPN. This behavior for lower METS was anticipated.

8.2.3 Analysis 3: SFN vs LFN

- 8. Type of DM: SFN has a higher occurrence of pre-diabetes than LFN.

- 48. Patellar - right reflex: In SFN patellar reflex is sig. more likely to me normal than in LFN. This is expected.

- 50. Achilles - Right reflex. In SFN achilles reflex is sig. more likely to me normal than in LFN. This is expected.

- 52. Gait AND 54. Toe walk AND 55. Heel walk: These variables to assess balance are sig. more likely to be abnormal in LFN than in SFN. This is expected.

- 56. Romberg. Can patient keep the balance with closed eyes? Romberg is sig. more likely to be abnormal in LFN than in SFN. This is expected.

- 57. Pinprick at Toes right: Pinprick is sig. more likely to be normal in SFN than in LFN.
- 63. Cold sense at Toes right: This is sig. more likely to be normal in SFN than in LFN.
- 69: Vibration sense: This is sig. more likely to be normal in SFN than in LFN.
- 75: Join position sense - Toes right: This is sig. more likely to be normal in SFN than in LFN.
- 81. Touch sense in toes right: This is sig. more likely to be normal in SFN than in LFN.
- 143. Peroneal - MNCV - Ankle to knee - Right. Peroneal Motor nerve conduction velocity is sig. more likely to be abnormal in LFN than in SFN.
- 148. Peroneal - Distal CMAP (millivolts) - Right: This action potential is sig. different between SFN and LFN. The mean is below threshold of 2 with 1.7 for LFN and normal in SFN with mean of 4.45.
- 160. Peroneal - Distal CMAP - Left: This action potential is sig. more frequently abnormal in LFN than in SFN. As expected.
- 166. Sural SNAP (microvolts) - Right. AND 170. Sural SNAP (microvolts) - Left: This action potentials are sig. higher in SFN than in LFN. As expected.
- 229: 11. C-reactive protein. This unspecific inflammatory marker is sig. more frequently abnormal in LFN than in SFN. This is expected because SFN often progresses further into LFN with time.
- 300. Allodynia: SFN experience sig. more frequently allodynia than LFN.
- 303. Do you have numbness?: LFN experience sig. more frequently allodynia than SFN.
- 311: BALANCE: Do you have trouble with your balance of difficulties walking because of poor balance?: LFN experience sig. more frequently balance issues than SFN.
- 349: Do you have any family members with autoimmune disease?: SFN have sig. more frequently family members with autoimmune disease than LFN. This means that SFN patients will have more often a undiagnosed AI disease or than LFN.
- 374. Dyslipidemia diagnosis: LFN have sig. more frequently Dyslipidemia. This is associated with metabolic syndrome.
- 375. Does the patient exercise?: SFN patients do sig. more frequently exercise than LFN patients.
- 434: Total Neuropathy Score (TNS). Severity score: LFN have a sig. worse TNS score than LFN. This is in line with disease progression.

Chapter 9

Discussion

In analysis 1 (SFN: diabetic vs. idiopathic), there are only 7 variables with sig. differences (2.1% of tests) and 6 of them are DM-related variables. Not surprisingly, the two etiologies are well discernible by DM-related variables such as HgA1C, Fasting glucose level, dyslipidemia or metabolic disease. The variable unrelated to DM was Marital status that showed a small effect strength of Cramer's V. This might be due to the age difference even though this difference was not sig. between DPN and IPN. No sig. differences were found in other variables, which means that DPN and IPN is barely discernible by means of physical exam or blood values.

In analysis 2 (LFN: diabetic vs. idiopathic), the two etiologies showed sig. differences in 19.5% of tests. It must be noted that the sample size of LFN is much larger (N=1238) than that of SFN (N=307), which may be add to the reason why there are so much more variables with sig. differences in LFN. IPN has a sig. higher share of males, a sig. higher mean age, and also a sig. longer disease duration than DPN, though we have difficulties to explain these differences. DM is associated with obesity and this is confirmed in the sig. heigher BMI and weight for DPN as opposed to IPN. DM-related variables show as anticipated clear-cut different results, such as HgA1C levels, Triglycerids, or HDL-cholesterol levels.

In analysis 2 some interesting observations of sig. differences were found. DPN are more likely to have carpal tunnel and ulnar entrapment around the elbow than IPN. Erythrocyte Sedimentation Rate (ESR) is more likely to be sig. abnormal in DPN than in IPN. This indicates that DPN have more inflammation occurring in the body than IPN. Furthermore, DPN are sig. more likely to have pain, experience sharp pain and allodynia than IPN. Also DPN are sig. more likely to have a metabolic disease and have sig. lower METS values (meaning they do less and less intensive activities) than IPN.

In analysis 3 (SFN vs LFN), the two neuropathy types showed sig. different results in 63.4% of tests. Clearly, neuropathy types are more differentiable than etiologies. LFN has a share of 70.7% males whereas SFN almost an even share with 51.5%. This however does not mean that men are more prone to get PN than women, no this is an artificial difference and the clinic attributes this bias to "aggressive", demanding behavior of men to get a second opinion and at a renowned hospital. On the other hand in SFN, share of males (51.1%) is only slightly higher than that of females, and it may be attributed to the fact that pain is the hallmark symptom of SFN and patients typically go see a neurologist when they have pain (women just as urgently than men), rather than in the case of numbness (which is more prevalent in LFN than

in SFN) for what symptom patients would not immediately seek neurological examination. An important difference between LFN and SFN is that SFN can progress into an LFN meaning that LFN is a more advanced stage of neuropathy, rather than LFN and SFN simply being two distinct types of neuropathy. This is seen e.g. in the sig. longer duration since disease begin or in the sig. worse total Neuropathy Score (TNS) in LFN as opposed to SFN. This fact influences many other health parameters that indicate general health status, such as Creatine Kinase or C-reactive protein. In terms of symptoms SFN and LFN differ sig. in multiple variables. For example, a sig. higher share of SFN patients undergo pain or have allodynia than LFN patients. Numbness is sig. more often an issue in LFN, and rather seldom in SFN, which is kind of the counter-player of pain. When a large sensory nerve fiber is damaged, it means that its attached (damaged) small fibers can less easily transfer their pain signal through the large fiber to the brain. Further variables of symptom differences are example balance-related ones such as gait, toe walk or Romberg. Or reflexes, vibration sense, pinprick, proprioception, nerve conduction velocities, action potentials, which all are sig. more frequently abnormal in LFN than in SFN.

Chapter 10

Conclusion and Outlook

10.1 Conclusion

PN, and SFN even more, are poorly understood and lack research. Public awareness for PN is little compared to its prevalence. PN is a condition that is very difficult to diagnose but also to treat. Therefore, over 30% of PN patients are idiopathic and cannot initiate a therapy to tackle the cause. The aim of this thesis was to make a step towards developing better diagnosis methods. Perhaps in the future, it will be possible to separate different PN etiologies by symptoms, clinical and neurological evaluation, blood work and disease development. The PNRR is the largest cohort for DPN and IPN and offers the basis for statistical evaluations in PN.

This research project has performed the first encompassing analyses on the PNRR. In systematic bivariate statistical comparisons on over 300 variables in three study populations. This research sought for sig. differences among all testable variables and for shortlisted variables of our interest we interpreted our findings. We looked at clearly DM-related variables and quantified the anticipated differences between DPN and IPN. Also we identified some variables with sig. differences (in analysis 2 and 3) that gave us previously rather unknown observations.

10.2 Outlook

Despite the large number of affected PN patients, large pharmaceutical companies have little interest in developing solutions for PN and SFN. To date, only few treatments exist for neuropathy and only for few causes. Current medical solutions focus mainly on pain management, as no solutions for nerve regeneration have been developed until today (even though very few clinical trials are underway). Clinical studies focus usually on the two most frequent causes diabetic PN (DPN) and chemotherapy induced PN (CIPN), while neglecting the other causes.

The previous lack of scientific interest in PN/SFN is also reflected in the small number of publications in comparison to diseases with more public awareness and larger lobbies. Figure 10.1 shows the count of publications for SFN (blue line) and related

conditions per year on PubMed from 1970 until 2022 [1]. The scientific interest in Multiple Sclerosis (MS) has been similar to that of PN until the mid 90ies, and thereafter doubled its publication numbers until to date. The scientific interest in SFN has been very low over the years, though has gained more interest recently. Fibromyalgia and Dysautonomia got more scientific interest and feature a similar growth rate. Only ME/CFS (red line) has gotten a lower medical interest than SFN. It becomes obvious that PN and SFN in particular has gotten very limited attention despite its large prevalence and impact on society. With the outbreak of the Covid-19 pandemic, SFN has received more attention. The Covid-19 infection seems triggering vast numbers of new SFN cases.

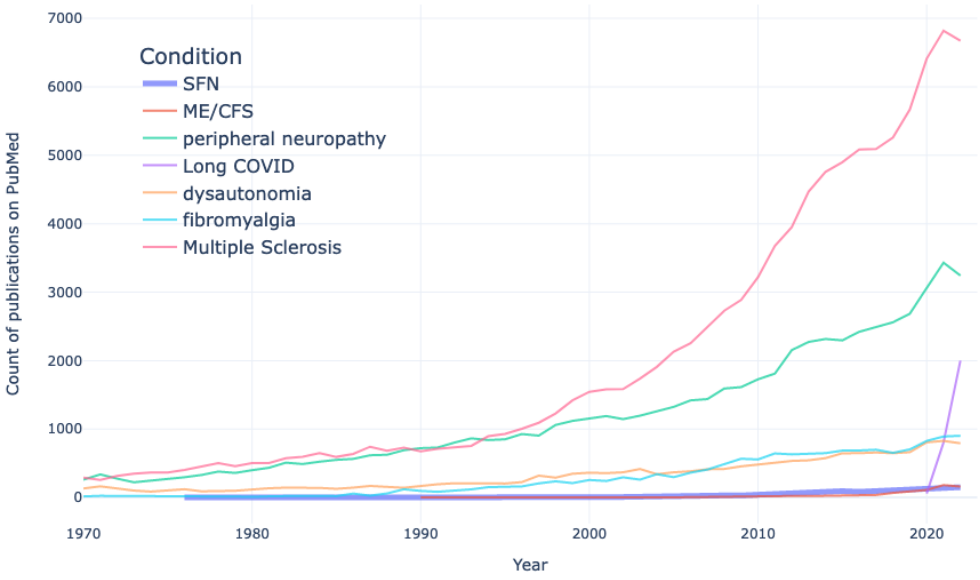

FIGURE 10.1: . Data source: PubMed. [10].

[1] Search on PubMed was carried out on 14 May 2023 with the following key word searches: “small fiber neuropathy" OR "small fibre neuropathy”, "ME/CFS" or "chronic fatigue syndrom", "peripheral neuropathy" OR polyneuropathy, "long COVID" or "long haul COVID" or "post-COVID-19 syndrome", dysautonomia, fibromyalgia.

Appendix A

The PNRR data and its preprocessing

A.1 PNRR data and metadata

Data was provided in a data file and a data dictionary file in csv format. The data dictionary contains metadata for all 917 PNRR variables. In the following, the most important columns of the data dictionary are introduced:

Variable / Field Name holds the variable codes.

Form Name indicates a variable's visit information form.

Field Type indicates the variable's interrogation type, i.e. how the question was posed in the questionnaire resp. RedCap system: a) Radio button (only one choice possible). b) Yes or No question. c) Checkbox (multiple boxes can be ticked). d) Dropdown (only one choice possible). e) Calculation (formula of how a variable (such as BMI) was computed by the system based on input variables). f) Text (manual data input by the PERSONNEL, e.g. a number, text, date or other. Example data input could be HbA1C, blood pressure, or a nerve conduction value). g) Notes (patient answers to open questions, such as "Which symptoms bother you the most?").

Field Label contains the designation of the variable.

Choices, Calculations, OR Slider Labels. For the Field Types radio button, yes or no question, checkbox, and dropdown, this column contains the mapping for the available choices (integer value with corresponding label) in a |-separated format. E.g. for the variable skinbiopsydistal it denotes as: 2, Normal Density | 1, Reduced Density | 0, Absent | ND, Not Done. For the Field Type Calculation, the formula of the by the system applied calculation is presented; e.g. for BMI it is ([pef]_weight]/([pef_height] x [pef_height])) x 703.

Field Note gives directions for the PERSONNEL on how to evaluate a parameter or how to enter a value.

Text Validation Type signifies the variable's data format (e.g. integer, date_mdy, number, etc).

Text Validation Min and Text Validation Max contain the range of the - by the system - allowed input values.

Branching Logic. Certain questions apply and thus surface only if a certain previous branching logic is met. This column indicates the condition under which the question (variable) occurs, e.g. [pnw_1] = '2'.

A.2 Data Preprocessing

Data cleaning, manipulation, visualization, and modeling was done with Python 3.9.

A.2.1 Preprocessing of the Data Dictionary

Column names were renamed and simplified. Variable that were not provided in the PNRR data were deleted from the data dictionary. A new column *Data_Type* was added to the data dictionary and filled in for all variables of Field_Type 'Calculation'. This info has not been (correctly) provided. Additional helpful variables were introduced: ID (patient ID), *patID_year* (combination of ID and examination year), *first_visit* (boolean; whether an observation was a patient's first enrolment), Site_ID (ID of hospital in charge), and Hospital (hospital name).

A.2.2 Preprocessing of the PNRR Data

PNRR raw data (provided as separate csv file for each FORM) were concatenated to one table. From the contents of the data dictionary variable *Choices, Calculations, OR Slider Labels*, a dictionary mapping was created that maps for each categorical variable the integer values to the corresponding levels. Then, the newly introduced variables patID_year, first_visit, Site_ID, and Hospital were populated. Where necessary column data types were converted to correct format and data values representing NA were converted to the data type NaN. Observations of missing diagnosis were filtered out. Observations of diagnosis DPN and IPN were filtered. Some patients are reevaluated in the registry after some years. In order not to bias the analysis, only observations of first hospital enrolments were kept for the study population. Variables of Field Type *Checkbox* are represented in the PNRR data in a one-hot-encoding manner (e.g. Var1_a, Var1_b, Var1_c), i.e. each variable level figures as an own variable in the data. These variables were converted into one variable (Var1) of data type *list*. In this way, each observation holds all ticked checkbox answers in a list (e.g. [a, c] or []).

Appendix B

Statistically significant results per analysis

B.1 Analysis 1: SFN: diabetic vs idiopathic

B.2 Analysis 2: LFN: diabetic vs idiopathic

B.3 Analysis 3: SFN vs. LFN

Index	Variable	Field_Label	available obs	obs pct	obs DPN	obs IPN	Median DPN	Median IPN	Cramers V	Strength of Cramer's V	Vargha Delaney's A	Applied test	p	Sig. (BH)
208	**pnw_tier1_5**	(HgA1C)	266	87	50	216	Normal 34.0 Abnormal 66.0	Normal 80.6 Abnormal 19.4	0.39	M		Fishers exact	4E-10	TRUE
209	**pnw_hga1c_lvl**	HgA1C Level	256	83	48	208	6.05	5.45			0.88	Mann-Whitney U	0	TRUE
211	**pnw_bld_gluc_fast_lvl**	Fasting Glucose Level	126	41	15	111	104	88			0.83	Mann-Whitney U	0	TRUE
346	**phq1_marital**	21. What is your marital status?	307	100	51	256	Married 80.4 Widowed 11.8	Married 71.5 Widowed 2.0	0.25	S		Chi square	0.0007	TRUE
351	**hyperglycemia**	The HgA1C level reported on	192	63	35	157	No 0.0 Yes 100.0	No 73.9 Yes 26.1	0.57	L		Fishers exact	2E-17	TRUE
453	**xtra_metabolicdisease**	Does patient have metabolic disease?	203	66	33	170	Yes 63.6 No 36.4	Yes 25.9 No 74.1	0.28	S		Fishers exact	6E-05	TRUE
455	**doessubjhavedm**	Does patient have Diabetes Mellitus?	238	78	40	198	Yes 2, No 45.0 2 0 55.0	Yes 2, No 2.5 2 0 97.5	0.52	L		Fishers exact	5E-12	TRUE

FIGURE B.1: Statistically significant results for Analysis 1.

Index	Variable	Field_Label	total rows	available obs	obs pct	obs DPN	obs IPN	Median DPN	Median IPN	Cramers V	Strength of Cramer's V	Vargha & Delaney's A	Applied test	p	Sig. (BH)
2	**pef_sex**	Sex	1238	1238	100	436	802	Male 64.9 Female 35.1	Male 73.8 Female 26.2	0.09	_		Chi square	0.001	TRUE
3	**pef_age**	Estimated Age at Visit:	1238	1238	100	436	802	64.5	68.5			0.4	Mann-Whitney U	0	TRUE
4	**pef_weight_kg**	Weight (kg)	1238	1233	100	433	800	98.07	90.13			0.6	Mann-Whitney U	0	TRUE
5	**pef_height_cm**	Height (cm)	1238	1236	100	435	801	175.77	177.8			0.42	Mann-Whitney U	0	TRUE
6	**pef_bmi**	BMI:	1238	1233	100	433	800	31.46	28.22			0.66	Mann-Whitney U	0	TRUE
7	**pef_pn_type**	Type of PN:	1238	1238	100	436	802	Painful 78.0 Non-Painful 22.0	Painful 65.2 Non-Painful 34.8	0.13	S		Chi square	4E-06	TRUE
69	**pef_vib_toes_right**	Toes - Right	1238	1205	97	425	780	1 (reduced) 22.1 2 (normal) 17.4	1 (reduced) 14.9 2 (normal) 15.8	0.1	_		Chi square	0.002	TRUE
70	**pef_vib_toes_left**	Toes - Left	1238	1208	98	425	783	1 (reduced) 22.1 2 (normal) 18.4	1 (reduced) 14.8 2 (normal) 15.6	0.11	S		Chi square	9E-04	TRUE
83	**pef_touch_ankle_right**	Ankle - Right	1238	442	36	165	277	1 (reduced) 37.0 2 (normal) 40.0	1 (reduced) 43.3 2 (normal) 23.1	0.18	S		Chi square	6E-04	TRUE
84	**pef_touch_ankle_left**	Ankle - Left	1238	442	36	166	276	1 (reduced) 37.3 2 (normal) 38.6	1 (reduced) 42.8 2 (normal) 22.8	0.17	S		Chi square	0.001	TRUE
87	**pef_abs_vibr_toes_right**	Vibration, Toes - Right	1238	1193	96	421	772	0	0			0.54	Mann-Whitney U	0.004	TRUE
88	**pef_abs_vibr_toes_left**	Vibration, Toes - Left	1238	1195	97	420	775	0	0			0.55	Mann-Whitney U	0.001	TRUE
96	**pef_abs_touch_ankle_right**	Touch, Ankle - Right	1238	429	35	160	269	0.4 19.4 1.0 18.1	0.4 17.1 1.0 17.1	0.21	S		Chi square	0.008	TRUE
100	**ncs_sex**	Sex:	1238	1238	100	436	802	Male 65.6 Female 34.4	Male 73.8 Female 26.2	0.09	_		Chi square	0.003	TRUE
102	**ncs_med_mncv_r_val**	Median - MNCV (m/s) - Right	1238	746	60	245	501	50	51			0.41	Mann-Whitney U	0	TRUE
103	**ncs_med_mncv_r**	Median - MNCV - Right	1238	754	61	250	504	Abnormal (ABNL) 36.4 NR 1.6	Abnormal (ABNL) 21.0 NR 0.8	0.17	S		Chi square	2E-05	TRUE
104	**ncs_med_laten_r_val**	Median - Distal motor latency (msec) - Right	1238	753	61	245	508	4.199999809	3.900000095			0.59	Mann-Whitney U	0	TRUE
105	**ncs_med_laten_r**	Median - Distal motor latency - Right	1238	761	62	250	511	Abnormal (ABNL) 44.0 NR 1.6	Abnormal (ABNL) 29.2 NR 0.6	0.16	S		Chi square	7E-05	TRUE
111	**ncs_med_mncv_l_val**	Median - MNCV (m/s) - Left	1238	394	32	135	259	50	51			0.41	Mann-Whitney U	0.003	TRUE
113	**ncs_med_laten_l_val**	Median - Distal motor latency (msec) - Left	1238	406	33	139	267	4.17	3.9			0.59	Mann-Whitney U	0.003	TRUE
120	**ncs_uln_mncv_r_val**	Ulnar - MNCV (m/s) - Wrist to elbow - Right	1238	720	58	233	487	51	53.20000076			0.39	Mann-Whitney U	0	TRUE
121	**ncs_uln_mncv_r**	Ulnar - MNCV - Wrist to elbow - Right	1238	727	59	238	489	Abnormal (ABNL) 30.3 NR 0.4	Abnormal (ABNL) 15.5 NR 0.2	0.17	S		Chi square	2E-05	TRUE
122	**ncs_uln_aroun_r_val**	Ulnar - MNCV (m/s) - Around elbow - Right	1238	704	57	225	479	47	48.79999924			0.44	Mann-Whitney U	0.007	TRUE
127	**ncs_uln_cmap_r**	Ulnar - Distal CMAP - Right	1238	730	59	239	491	Abnormal (ABNL) 14.6 NR 0.4	Abnormal (ABNL) 7.5 NR 0.2	0.11	S		Chi square	0.009	TRUE
131	**ncs_uln_mncv_l_val**	Ulnar - MNCV (m/s) - Wrist to elbow - Left	1238	345	28	119	226	50	53.90000153			0.36	Mann-Whitney U	0	TRUE
133	**ncs_uln_aroun_l_val**	Ulnar - MNCV (m/s) - Around elbow - Left	1238	341	28	117	224	47.59999847	50			0.39	Mann-Whitney U	0.001	TRUE
141	**ncs_prnl_rt_collapse**	testing performed on the RIGHT side?	1238	1238	100	436	802	1	1			0.44	Mann-Whitney U	0	TRUE
144	**ncs_pero_aroun_r_val**	Peroneal - MNCV (m/s) - Around knee - Right	1238	690	56	217	473	42	45			0.42	Mann-Whitney U	0.001	TRUE
163	**ncs_sural_sns_desc**	Was sural sensory nerve testing performed?	1238	1237	100	435	802	1	1			0.46	Mann-Whitney U	0	TRUE
172	**ncs_mdn_sns_desc**	Was median sensory nerve testing performed?	1238	1237	100	436	801	1	1			0.46	Mann-Whitney U	0.004	TRUE
181	**ncs_uln_sns_desc**	Was ulnar sensory nerve testing performed?	1238	1238	100	436	802	1	1			0.46	Mann-Whitney U	0.002	TRUE
190	**ncs_rad_sns_desc**	Was radial sensory nerve testing performed?	1238	1237	100	435	802	1	1			0.46	Mann-Whitney U	0.002	TRUE
199	**pnw_sex**	Sex	1238	1238	100	436	802	Male 65.6 Female 34.4	Male 74.1 Female 25.9	0.09	_		Chi square	0.002	TRUE
202	**pnw_1_b**	-----> If NCS/EMG was Abnormal, select one:	1238	1222	99	427	795	Demyelinating 2.6 Mixed 26.5	Demyelinating 2.4 Mixed 16.2	0.12	S		Chi square	9E-05	TRUE
205	**pnw_tier1_4**	3. Chemistry (Chem 12-18)	1238	1190	96	414	776	Normal 74.6 Abnormal 25.4	Normal 84.5 Abnormal 15.5	0.12	S		Chi square	5E-05	TRUE
207	**pnw_gluc_switch**	Was glucose testing done?	1238	1238	100	436	802	No 2.1 Yes 97.9	No 5.5 Yes 94.5	0.08	_		Chi square	0.007	TRUE
208	**pnw_tier1_5**	(HgA1C)	1238	1100	89	418	682	Normal 14.6 Abnormal 85.4	Normal 73.9 Abnormal 26.1	0.57	L		Chi square	8E-81	TRUE

FIGURE B.2: Statistically significant results for Analysis 2. Part 1.

209	**pnw_hga1c_lvl**	HgA1C Level	1238	1018	82	393	625	6.6	5.5			0.9	Mann-Whitney U	0	TRUE
210	**pnw_bld_gluc_fast**	4. b. Blood Glucose (fasting)	1238	335	27	81	254	Normal 39.5 Abnormal 60.5	Normal 83.1 Abnormal 16.9	0.41	M		Fishers exact	3E-13	TRUE
211	**pnw_bld_gluc_fast_lvl**	Fasting Glucose Level	1238	333	27	80	253	106.5	92			0.74	Mann-Whitney U	0	TRUE
212	**pnw_tier2_10**	4. c. Oral Glucose Tolerance test	1238	165	13	32	133	Normal 43.8 Abnormal 56.2	Normal 82.7 Abnormal 17.3	0.34	M		Fishers exact	2E-05	TRUE
213	**pnw_glucose_lvl**	Glucose level	1238	129	10	26	103	128.5	102			0.71	Mann-Whitney U	0.001	TRUE
221	**pnw_tier1_6**	Rate (ESR)	1238	712	58	239	473	Normal 71.5 Abnormal 28.5	Normal 82.2 Abnormal 17.8	0.12	S		Fishers exact	0.001	TRUE
224	**pnw_tier2_11**	10. Lipid Profile	1238	808	65	306	502	Normal 34.6 Abnormal (report if	Normal 45.6 Abnormal (report if	0.11	S		Fishers exact	0.003	TRUE
225	**pnw_cholest_value**	Cholesterol	1238	733	59	274	459	163	175			0.44	Mann-Whitney U	0.004	TRUE
226	**pnw_triglyc_value**	Triglycerides	1238	737	60	277	460	149	109			0.63	Mann-Whitney U	0	TRUE
227	**pnw_hdl_value**	HDL	1238	732	59	277	455	44	49			0.4	Mann-Whitney U	0	TRUE
228	**pnw_ldl_value**	LDL	1238	724	59	274	450	86	99			0.42	Mann-Whitney U	0	TRUE
235	**pnw_inflam_test**	autoimmune testing been performed on this patient?	1238	1238	100	436	802	0	1			0.4	Mann-Whitney U	0	TRUE
251	**pnw_infectious_test**	Has infectious testing been performed on this patient?	1238	1238	100	436	802	0	1			0.44	Mann-Whitney U	0	TRUE
257	**pnw_genetic_test**	Has genetic testing been performed on this patient?	1238	1238	100	436	802	0	0			0.44	Mann-Whitney U	0	TRUE
260	**pnw_paraneoplastic_test**	been performed on this patient?	1238	1238	100	436	802	0	0			0.46	Mann-Whitney U	0	TRUE
265	**pnw_other_test**	performed on this patient (incl. CK, homocysteine,	1238	1238	100	436	802	0	1			0.45	Mann-Whitney U	0.001	TRUE
283	**phq1_sex**	What is your sex?	1238	1237	100	436	801	Male 65.4 Female 34.6	Male 73.7 Female 26.3	0.09	_		Chi square	0.003	TRUE
284	**phq1_hispanic**	Are you Hispanic or Latino?	1238	1230	99	432	798	0	0			0.52	Mann-Whitney U	0	TRUE
285	**phq1_race**	What is your race?	1238	1233	100	434	799	Alaska Native 0.5 Asian 2.3	Alaska Native 0.1 Asian 0.1	0.19	S		Chi square	4E-09	TRUE
286	**phq_pain**	1. PAIN: Do you have pain?	1238	1237	100	436	801	No 21.1 Yes 78.9	No 34.3 Yes 65.7	0.14	S		Chi square	2E-06	TRUE
290	**phq_pain_sharp**	us how SHARP your pain feels.	1238	867	70	344	523	1 0.9 2 7.0	1 5.7 2 8.4	0.21	S		Chi square	4E-05	TRUE
300	**phq_n**	abnormal perceptions of pain or discomfort from a	1238	814	66	322	492	No 43.2 Yes 56.8	No 53.9 Yes 46.1	0.1	S		Fishers exact	0.003	TRUE
305	**phq_numbness_c**	numbness (loss of sensation) start?	1238	1134	92	396	738	0.5 2 to 4 weeks ago	0.0 2 to 4 weeks ago	0.14	S		Chi square	0.003	TRUE
310	**phq_contractions_a1**	contractions of your muscles controlled with medications?	1238	683	55	222	461	medication does not work 16.7	medication does not work 8.9	0.13	S		Chi square	0.003	TRUE
317	**phq_sleep**	experienced sleeping difficulties?	1238	1236	100	435	801	No 36.1 Yes 63.9	No 44.4 Yes 55.6	0.08	_		Chi square	0.005	TRUE
322	**phq_symptoms**	9. Which symptom bothers you the most?	1238	1224	99	430	794	47.9 Numbness (loss of	36.4 Numbness (loss of	0.14	S		Chi square	8E-05	TRUE
326	**phq1_diabetes**	You selected Diabetes. Please specify.	1238	433	35	340	93	Type II 82.4 Pre-diabetic 9.7	Type II 32.3 Pre-diabetic 66.7	0.57	L		Chi square	7E-31	TRUE
339	**phq1_drink**	19. Have you ever drunk alcohol?	1238	1237	100	436	801	No 28.2	No 14.6	0.19	S		Chi square	1E-10	TRUE
346	**phq1_marital**	21. What is your marital status?	1238	1235	100	434	801	Married 67.5 Widowed 7.4	Married 73.4 Widowed 8.0	0.12	S		Chi square	0.001	TRUE
350	**phq1_family_diab**	members with the following diseases or conditions:	1238	1056	85	387	669	No 20.9 Yes 79.1	No 38.6 Yes 61.4	0.18	S		Chi square	5E-09	TRUE
351	**hyperglycemia**	The HgA1C level reported on	1238	644	52	227	417	No 4.0 Yes 96.0	No 69.8 Yes 30.2	0.63	L		Fishers exact	4E-67	TRUE
352	**severityhyperglycemia**	Type/severity of hyperglycemia	1238	344	28	218	126	DM Type 2 72.5 DM Type 1 6.4	DM Type 2 17.5 DM Type 1 0.0	0.6	L		Chi square	2E-27	TRUE
356	**yearsdiabetes**	Time elapsed since patient was diagnosed with diabetes	1238	182	15	162	20	10	3			0.71	Mann-Whitney U	0.002	TRUE
360	**hba1cvalue_1**	1. Past HbA1C value	1238	214	17	134	80	6.8	5.9			0.79	Mann-Whitney U	0	TRUE
362	**hba1cvalue_2**	2. Past HbA1C value	1238	115	9.3	78	37	7.3	6			0.76	Mann-Whitney U	0	TRUE
363	**hba1cyear_2**	2. a. Year of HbA1C test	1238	114	9.2	77	37	2015	2018			0.32	Mann-Whitney U	0.002	TRUE
364	**hba1cvalue_3**	3. Past HbA1C value	1238	65	5.3	42	23	7.25	6.1			0.73	Mann-Whitney U	0.003	TRUE
365	**hba1cyear_3**	3. a. Year of HbA1C test	1238	64	5.2	42	22	2016	2018.5			0.28	Mann-Whitney U	0.004	TRUE
366	**hypertension**	Diagnosis of hypertension	1238	630	51	214	416	No 25.2 Yes 74.8	No 40.4 Yes 59.6	0.15	S		Fishers exact	2E-04	TRUE
373	**current_bmi**	Calculated BMI	1238	287	23	98	189	31.8	28.5			0.63	Mann-Whitney U	0	TRUE
374	**dyslipidemiadiagnosis**	label"><p>Diagnosis of dyslipidemia <br	1238	542	44	184	358	No 32.1 Yes 67.9	No 57.8 Yes 42.2	0.24	S		Fishers exact	1E-08	TRUE
375	**exercise_reported**	Does the patient exercise?	1238	483	39	139	344	No 56.1 Yes 43.9	No 35.5 Yes 64.5	0.19	S		Fishers exact	4E-05	TRUE
452	**yearspnsymptoms**	Years since onset of PN	1238	737	60	228	509	5	6			0.43	Mann-Whitney U	0.003	TRUE
453	**xtra_metabolicdisease**	Does patient have metabolic disease?	1238	616	50	188	428	Yes 77.1 No 22.9	Yes 34.8 No 65.2	0.39	M		Fishers exact	1E-22	TRUE
455	**doessubjhavedm**	Does patient have Diabetes Mellitus?	1238	744	60	229	515	Yes 2, No 73.8 2.0 26.2	Yes 2, No 5.0 2.0 95.0	0.72	L		Fishers exact	2E-85	TRUE
456	**yearsdmdiagnosis**	Years since diagnosis of Diabetes Mellitus	1238	161	13	143	18	10	2			0.77	Mann-Whitney U	0	TRUE
468	**doessubjexercise**	Does patient exercise regularly?	1238	488	39	134	354	Yes 49.3 No 50.7	Yes 68.1 No 31.9	0.17	S		Fishers exact	2E-04	TRUE
471	**calculatedmets**	Calculated METS	1238	425	34	115	310	0	51.13			0.38	Mann-Whitney U	0	TRUE

FIGURE B.3: Statistically significant results for Analysis 2. Part 2.

2	**pef_sex**	Sex	1545	**1545**	100			Male 51.5 Female 48.5	Male 70.7 Female 29.3	0.161	S		Chi square	2E-10	TRUE
3	**pef_age**	Estimated Age at Visit:	1545	1545	100			57	67			0.29	Mann-Whitney U	0	TRUE
4	**pef_weight_kg**	Weight (kg)	1545	1540	99.7			84.82	92.53			0.37	Mann-Whitney U	0	TRUE
5	**pef_height_cm**	Height (cm)	1545	1543	99.9			172.72	177.8			0.39	Mann-Whitney U	0	TRUE
6	**pef_bmi**	BMI:	1545	1540	99.7			27.52	29.41			0.41	Mann-Whitney U	0	TRUE
7	**pef_pn_type**	Type of PN:	1545	1545	100			Painful 83.7 Non-Painful 16.3	Painful 69.7 Non-Painful 30.3	0.123	S		Chi square	1E-06	TRUE
8	**pef_diab_type**	Type of diabetes mellitus	1545	418	27.1			Type2 42.9 Pre-diabetic 55.1	Type2 69.4 Pre-diabetic 24.4	0.221	S		Chi square	4E-05	TRUE
11	**pef_hearing**	Hearing (to finger rubbing):	1545	1541	99.7			Abnormal 2.6 Normal 97.4	Abnormal 7.5 Normal 92.5	0.075	_		Chi square	0.0031	TRUE
22	**pef_finger_ext_right**	Finger extension - Right	1545	1545	100			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 2.5 2 (normal) 97.5	0.065	_		Chi square	0.0101	TRUE
23	**pef_finger_ext_left**	Finger extension - Left	1545	1544	99.9			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 2.3 2 (normal) 97.6	0.07	_		Chi square	0.0224	TRUE
24	**pef_finger_flex_right**	Finger flexion - Right	1545	1545	100			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 1.9 2 (normal) 98.1	0.056	_		Chi square	0.0277	TRUE
26	**pef_inter_right**	Interossei and ADM - Right	1545	1543	99.9			1 (reduced) 2.6 2 (normal) 97.4	1 (reduced) 9.7 2 (normal) 90.3	0.1	_		Chi square	9E-05	TRUE
27	**pef_inter_left**	Interossei and ADM - Left	1545	1542	99.8			1 (reduced) 2.6 2 (normal) 97.4	1 (reduced) 9.7 2 (normal) 90.3	0.1	_		Chi square	9E-05	TRUE
28	**pef_abduct_right**	Abductor pollicis brevis - Right	1545	1541	99.7			1 (reduced) 3.3 2 (normal) 96.7	1 (reduced) 9.8 2 (normal) 90.0	0.096	_		Chi square	0.0009	TRUE
29	**pef_abduct_left**	Abductor pollicis brevis - Left	1545	1540	99.7			1 (reduced) 2.6 2 (normal) 97.4	1 (reduced) 9.3 2 (normal) 90.6	0.1	_		Chi square	0.0005	TRUE
30	**pef_hip_right**	Hip flexion - Right	1545	1545	100			1 (reduced) 1.6 2 (normal) 98.4	1 (reduced) 6.4 2 (normal) 93.6	0.08	_		Chi square	0.0017	TRUE
31	**pef_hip_left**	Hip flexion - Left	1545	1545	100			1 (reduced) 2.6 2 (normal) 97.4	1 (reduced) 6.7 2 (normal) 93.3	0.066	_		Chi square	0.0095	TRUE
34	**pef_knee_flex_right**	Knee flexion - Right	1545	1544	99.9			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 2.2 2 (normal) 97.8	0.06	_		Chi square	0.0179	TRUE
36	**pef_ankle_dorsi_right**	Ankle dorsiflexion - Right	1545	1544	99.9			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 13.6 2 (normal) 85.8	0.179	S		Chi square	2E-11	TRUE
37	**pef_ankle_dorsi_left**	Ankle dorsiflexion - Left	1545	1545	100			1 (reduced) 0.0 2 (normal) 100.0	1 (reduced) 13.5 2 (normal) 85.1	0.184	S		Chi square	5E-12	TRUE
38	**pef_toe_dorsi_right**	Great toe dorsiflexion - Right	1545	1539	99.6			1 (reduced) 2.9 2 (normal) 97.1	1 (reduced) 26.4 2 (normal) 71.3	0.242	S		Chi square	2E-20	TRUE
39	**pef_toe_dorsi_left**	Great toe dorsiflexion - Left	1545	1539	99.6			1 (reduced) 2.6 2 (normal) 97.4	1 (reduced) 25.9 2 (normal) 71.5	0.245	S		Chi square	1E-20	TRUE
40	**pef_toe_plantar_right**	Great toe plantar - Right	1545	1537	99.5			1 (reduced) 3.6 2 (normal) 96.4	1 (reduced) 21.5 2 (normal) 77.2	0.197	S		Chi square	1E-13	TRUE
41	**pef_toe_plantar_left**	Great toe plantar - Left	1545	1537	99.5			1 (reduced) 4.2 2 (normal) 95.8	1 (reduced) 22.0 2 (normal) 76.3	0.196	S		Chi square	2E-13	TRUE
42	**pef_bicep_right**	Biceps - Right	1545	1542	99.8			1 (reduced) 4.9 2 (normal) 88.9	1 (reduced) 19.3 2 (normal) 68.7	0.211	S		Chi square	8E-15	TRUE
43	**pef_bicep_left**	Biceps - Left	1545	1541	99.7			1 (reduced) 4.6 2 (normal) 88.6	1 (reduced) 18.8 2 (normal) 69.0	0.214	S		Chi square	4E-15	TRUE
44	**pef_triceps_right**	Triceps - Right	1545	1541	99.7			1 (reduced) 2.3 2 (normal) 91.8	1 (reduced) 17.2 2 (normal) 69.6	0.213	S		Chi square	5E-15	TRUE
45	**pef_triceps_left**	Triceps - Left	1545	1540	99.7			1 (reduced) 2.6 2 (normal) 91.5	1 (reduced) 17.2 2 (normal) 69.8	0.213	S		Chi square	4E-15	TRUE
46	**pef_brach_right**	Brachioradialis - Right	1545	1542	99.8			1 (reduced) 4.6 2 (normal) 89.9	1 (reduced) 17.6 2 (normal) 67.2	0.211	S		Chi square	9E-15	TRUE
47	**pef_brach_left**	Brachioradialis - Left	1545	1541	99.7			1 (reduced) 4.6 2 (normal) 89.5	1 (reduced) 17.3 2 (normal) 67.4	0.211	S		Chi square	9E-15	TRUE
48	**pef_patellar_right**	Patellar - Right	1545	1540	99.7			1 (reduced) 3.9 2 (normal) 86.3	1 (reduced) 22.3 2 (normal) 52.4	0.304	M		Chi square	1E-30	TRUE
49	**pef_patellar_left**	Patellar - Left	1545	1542	99.8			1 (reduced) 5.2 2 (normal) 85.6	1 (reduced) 22.2 2 (normal) 52.3	0.297	S		Chi square	3E-29	TRUE
50	**pef_achilles_right**	Achilles - Right	1545	1539	99.6			1 (reduced) 14.4 2 (normal) 67.6	1 (reduced) 13.3 2 (normal) 21.1	0.427	M		Chi square	1E-60	TRUE
51	**pef_achilles_left**	Achilles - Left	1545	1540	99.7			1 (reduced) 14.1 2 (normal) 68.3	1 (reduced) 13.4 2 (normal) 21.4	0.429	M		Chi square	5E-61	TRUE
52	**pef_gait**	Gait:	1545	1543	99.9			Abnormal 7.8 Normal 92.2	Abnormal 35.4 Normal 64.6	0.239	S		Chi square	6E-21	TRUE
53	**pef_tandem**	Tandem gait:	1545	1518	98.3			Able 89.9 Not Able 10.1	Able 57.3 Not Able 42.7	0.271	S		Chi square	6E-26	TRUE
54	**pef_toe_walk**	Toe walk:	1545	1528	98.9			Able 95.1 Not Able 4.9	Able 72.7 Not Able 27.3	0.211	S		Chi square	1E-16	TRUE
55	**pef_heel_walk**	Heel walk:	1545	1528	98.9			Able 94.8 Not Able 5.2	Able 71.7 Not Able 28.3	0.215	S		Chi square	4E-17	TRUE
56	**pef_romberg**	Romberg:	1545	1522	98.5			Present/Positive 4.9 Absent/Negative 95.1	Present/Positive 29.6 Absent/Negative 70.4	0.227	S		Chi square	8E-19	TRUE
57	**pef_pin_toes_right**	Toes - Right	1545	1541	99.7			1 (reduced) 47.1 2 (normal) 40.2	1 (reduced) 52.8 2 (normal) 17.7	0.234	S		Chi square	5E-19	TRUE
58	**pef_pin_toes_left**	Toes - Left	1545	1544	99.9			1 (reduced) 47.4 2 (normal) 39.9	1 (reduced) 51.9 2 (normal) 17.9	0.23	S		Chi square	2E-18	TRUE
59	**pef_pin_ankle_right**	Ankle - Right	1545	1519	98.3			1 (reduced) 36.9 2 (normal) 58.6	1 (reduced) 49.1 2 (normal) 34.9	0.206	S		Chi square	9E-15	TRUE
60	**pef_pin_ankle_left**	Ankle - Left	1545	1522	98.5			1 (reduced) 37.6 2 (normal) 57.6	1 (reduced) 49.7 2 (normal) 34.2	0.203	S		Chi square	2E-14	TRUE
61	**pef_pin_finger_right**	Fingers - Right	1545	1535	99.4			1 (reduced) 18.3 2 (normal) 80.7	1 (reduced) 26.6 2 (normal) 70.5	0.095	_		Chi square	0.0009	TRUE
62	**pef_pin_finger_left**	Fingers - Left	1545	1534	99.3			1 (reduced) 18.0 2 (normal) 81.4	1 (reduced) 25.7 2 (normal) 71.5	0.096	_		Chi square	0.0009	TRUE
63	**pef_cold_toes_right**	Toes - Right	1545	756	48.9			1 (reduced) 53.7 2 (normal) 33.3	1 (reduced) 57.0 2 (normal) 18.8	0.167	S		Chi square	3E-05	TRUE
64	**pef_cold_toes_left**	Toes - Left	1545	759	49.1			1 (reduced) 53.1 2 (normal) 33.3	1 (reduced) 57.4 2 (normal) 18.2	0.17	S		Chi square	2E-05	TRUE
65	**pef_cold_ankle_right**	Ankle - Right	1545	744	48.2			1 (reduced) 43.9 2 (normal) 53.2	1 (reduced) 51.7 2 (normal) 34.2	0.196	S		Chi square	6E-07	TRUE
66	**pef_cold_ankle_left**	Ankle - Left	1545	747	48.3			1 (reduced) 42.8 2 (normal) 53.8	1 (reduced) 52.3 2 (normal) 33.1	0.204	S		Chi square	2E-07	TRUE
67	**pef_cold_finger_right**	Fingers - Right	1545	759	49.1			1 (reduced) 15.9 2 (normal) 83.5	1 (reduced) 24.4 2 (normal) 73.4	0.104	S		Chi square	0.017	TRUE

FIGURE B.4: Statistically significant results for Analysis 3. Part 1.

68	**pef_cold_finger_left**	Fingers - Left	1545	758	49.1			1 (reduced) 15.3 2 (normal) 84.7	1 (reduced) 24.6 2 (normal) 73.2	0.123	S		Chi square	0.0033	TRUE
69	**pef_vib_toes_right**	Toes - Right	1545	1508	97.6			1 (reduced) 16.5 2 (normal) 63.0	1 (reduced) 17.4 2 (normal) 16.3	0.442	M		Chi square	1E-64	TRUE
70	**pef_vib_toes_left**	Toes - Left	1545	1510	97.7			1 (reduced) 17.5 2 (normal) 61.3	1 (reduced) 17.4 2 (normal) 16.8	0.426	M		Chi square	2E-60	TRUE
71	**pef_vib_ankle_right**	Ankle - Right	1545	1386	89.7			1 (reduced) 10.2 2 (normal) 84.7	1 (reduced) 26.2 2 (normal) 45.7	0.296	S		Chi square	4E-27	TRUE
72	**pef_vib_ankle_left**	Ankle - Left	1545	1391	90			1 (reduced) 10.2 2 (normal) 85.6	1 (reduced) 24.8 2 (normal) 46.8	0.295	S		Chi square	6E-27	TRUE
73	**pef_vib_finger_right**	Fingers - Right	1545	1500	97.1			1 (reduced) 6.6 2 (normal) 93.4	1 (reduced) 16.9 2 (normal) 81.3	0.134	S		Chi square	2E-06	TRUE
74	**pef_vib_finger_left**	Fingers - Left	1545	1499	97			1 (reduced) 5.6 2 (normal) 94.4	1 (reduced) 16.2 2 (normal) 82.8	0.139	S		Chi square	6E-07	TRUE
75	**pef_joint_toes_right**	Toes - Right	1545	1528	98.9			1 (reduced) 5.6 2 (normal) 93.1	1 (reduced) 29.8 2 (normal) 56.4	0.305	M		Chi square	1E-31	TRUE
76	**pef_joint_toes_left**	Toes - Left	1545	1529	99			1 (reduced) 5.2 2 (normal) 93.1	1 (reduced) 30.5 2 (normal) 56.8	0.308	M		Chi square	4E-32	TRUE
77	**pef_joint_ankle_right**	Ankle - Right	1545	1226	79.4			1 (reduced) 1.0 2 (normal) 99.0	1 (reduced) 8.8 2 (normal) 89.5	0.127	S		Chi square	5E-05	TRUE
78	**pef_joint_ankle_left**	Ankle - Left	1545	1227	79.4			1 (reduced) 1.0 2 (normal) 99.0	1 (reduced) 8.8 2 (normal) 89.5	0.127	S		Chi square	5E-05	TRUE
79	**pef_joint_finger_right**	Fingers - Right	1545	1525	98.7			1 (reduced) 0.7 2 (normal) 99.3	1 (reduced) 3.9 2 (normal) 95.9	0.076	_		Chi square	0.0122	TRUE
80	**pef_joint_finger_left**	Fingers - Left	1545	1525	98.7			1 (reduced) 0.7 2 (normal) 99.3	1 (reduced) 3.9 2 (normal) 95.7	0.078	_		Chi square	0.0094	TRUE
81	**pef_touch_toes_right**	Toes - Right	1545	796	51.5			1 (reduced) 22.7 2 (normal) 70.6	1 (reduced) 43.8 2 (normal) 21.8	0.438	M		Chi square	7E-34	TRUE
82	**pef_touch_toes_left**	Toes - Left	1545	792	51.3			1 (reduced) 19.0 2 (normal) 73.6	1 (reduced) 41.2 2 (normal) 21.9	0.45	M		Chi square	2E-35	TRUE
83	**pef_touch_ankle_right**	Ankle - Right	1545	531	34.4			1 (reduced) 30.3 2 (normal) 65.2	1 (reduced) 41.8 2 (normal) 29.4	0.298	S		Chi square	5E-11	TRUE
84	**pef_touch_ankle_left**	Ankle - Left	1545	532	34.4			1 (reduced) 30.0 2 (normal) 64.4	1 (reduced) 40.7 2 (normal) 28.7	0.298	S		Chi square	5E-11	TRUE
85	**pef_touch_finger_right**	Fingers - Right	1545	788	51			1 (reduced) 30.9 2 (normal) 68.5	1 (reduced) 47.3 2 (normal) 48.7	0.167	S		Chi square	2E-05	TRUE
86	**pef_touch_finger_left**	Fingers - Left	1545	785	50.8			1 (reduced) 32.1 2 (normal) 67.9	1 (reduced) 47.8 2 (normal) 49.6	0.16	S		Chi square	4E-05	TRUE
87	**pef_abs_vibr_toes_right**	Vibration, Toes - Right	1545	1495	96.8			4.5	0			0.78	Mann-Whitney U	0	TRUE
88	**pef_abs_vibr_toes_left**	Vibration, Toes - Left	1545	1496	96.8			4.5	0			0.78	Mann-Whitney U	0	TRUE
89	**pef_abs_vibr_ankle_right**	Vibration, Ankle - Right	1545	1351	87.4			5	3			0.73	Mann-Whitney U	0	TRUE
90	**pef_abs_vibr_ankle_left**	Vibration, Ankle - Left	1545	1356	87.8			5	3			0.74	Mann-Whitney U	0	TRUE
91	**pef_abs_vibr_finger_right**	Vibration, Fingers - Right	1545	1482	95.9			7	7			0.61	Mann-Whitney U	0	TRUE
92	**pef_abs_vibr_finger_left**	Vibration, Fingers - Left	1545	1481	95.9			7	7			0.61	Mann-Whitney U	0	TRUE
94	**pef_abs_touch_toes_right**	Touch, Toes - Right	1545	784	50.7			0.4 44.7 1.0 4.3	0.4 21.8 1.0 5.3	0.423	M		Chi square	5E-27	TRUE
95	**pef_abs_touch_toes_left**	Touch, Toes - Left	1545	780	50.5			0.4 44.7 1.0 4.3	0.4 21.0 1.0 5.3	0.436	M		Chi square	1E-28	TRUE
96	**pef_abs_touch_ankle_right**	Touch, Ankle - Right	1545	517	33.5			0.4 38.6 1.0 10.2	0.4 17.5 1.0 17.5	0.338	M		Chi square	2E-10	TRUE
97	**pef_abs_touch_ankle_left**	Touch, Ankle - Left	1545	518	33.5			0.4 35.2 1.0 11.4	0.4 17.8 1.0 18.4	0.342	M		Chi square	1E-10	TRUE
98	**pef_abs_touch_finger_right**	Touch, Fingers - Right	1545	774	50.1			0.4 25.3 1.0 1.9	0.4 39.4 1.0 2.3	0.211	S		Chi square	1E-05	TRUE
99	**pef_abs_touch_finger_left**	Touch, Fingers - Left	1545	769	49.8			0.4 27.8 1.0 1.9	0.4 39.8 1.0 2.5	0.199	S		Chi square	8E-05	TRUE
100	**ncs_sex**	Sex:	1545	1545	100			Male 51.5 Female 48.5	Male 70.9 Female 29.1	0.163	S		Chi square	1E-10	TRUE
101	**ncs_med_rt_collapse**	Was median motor nerve testing performed on the RIGHT side?	1545	1545	100			0	1			0.35	Mann-Whitney U	0	TRUE
102	**ncs_med_mncv_r_val**	Median - MNCV (m/s) - Right	1545	845	54.7			53.20000076	50.5			0.75	Mann-Whitney U	0	TRUE
103	**ncs_med_mncv_r**	Median - MNCV - Right	1545	853	55.2			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 26.1 NR 1.1	0.204	S		Chi square	2E-08	TRUE
104	**ncs_med_laten_r_val**	Median - Distal motor latency (msec) - Right	1545	853	55.2			3.5	4			0.31	Mann-Whitney U	0	TRUE
105	**ncs_med_laten_r**	Median - Distal motor latency - Right	1545	861	55.7			Abnormal (ABNL) 13.0 NR 0.0	Abnormal (ABNL) 34.0 NR 0.9	0.151	S		Chi square	6E-05	TRUE
106	**ncs_med_cmap_r_val**	Median - Distal CMAP (millivolts) - Right	1545	853	55.2			10.14999962	8.399999619			0.66	Mann-Whitney U	0	TRUE
107	**ncs_med_cmap_r**	Median - Distal CMAP - Right	1545	860	55.7			Abnormal (ABNL) 1.0 NR 0.0	Abnormal (ABNL) 10.3 NR 0.9	0.109	S		Chi square	0.0061	TRUE
108	**ncs_med_fwave_r_val**	Median - F-wave latency (msec) - Right	1545	705	45.6			29.89999962	32.59999847			0.24	Mann-Whitney U	0	TRUE
109	**ncs_med_fwave_r**	Median - F-wave latency - Right	1545	713	46.1			Abnormal (ABNL) 15.6 NR 0.0	Abnormal (ABNL) 57.9 NR 1.6	0.274	S		Chi square	3E-12	TRUE
110	**ncs_med_lft_collapse**	Was median motor nerve testing performed on the LEFT side?	1545	1545	100			0	0			0.44	Mann-Whitney U	0	TRUE
111	**ncs_med_mncv_l_val**	Median - MNCV (m/s) - Left	1545	461	29.8			54.5	51			0.78	Mann-Whitney U	0	TRUE
112	**ncs_med_mncv_l**	Median - MNCV - Left	1545	462	29.9			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 28.4 NR 0.5	0.236	S		Chi square	3E-06	TRUE
113	**ncs_med_laten_l_val**	Median - Distal motor latency (msec) - Left	1545	473	30.6			3.33	4			0.29	Mann-Whitney U	0	TRUE
114	**ncs_med_laten_l**	Median - Distal motor latency - Left	1545	474	30.7			Abnormal (ABNL) 14.9 NR 0.0	Abnormal (ABNL) 35.9 NR 0.5	0.159	S		Chi square	0.0025	TRUE
115	**ncs_med_cmap_l_val**	Median - Distal CMAP (millivolts) - Left	1545	473	30.6			10.2	8.2				Student t	0	TRUE
116	**ncs_med_cmap_l**	Median - Distal CMAP - Left	1545	473	30.6			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 12.1 NR 0.5	0.141	S		Chi square	0.0089	TRUE
117	**ncs_med_fwave_l_val**	Median - F-wave latency (msec) - Left	1545	378	24.5			28.35000038	31.95000076			0.23	Mann-Whitney U	0	TRUE
118	**ncs_med_fwave_l**	Median - F-wave latency - Left	1545	383	24.8			Abnormal (ABNL) 14.8 NR 0.0	Abnormal (ABNL) 52.3 NR 1.5	0.272	S		Chi square	7E-07	TRUE

FIGURE B.5: Statistically significant results for Analysis 3. Part 2.

119	**ncs_uln_rt_collapse**	Was ulnar motor nerve testing performed on the RIGHT side?	1545	1545	100			0	1			0.36	Mann-Whitney U	0	TRUE
120	**ncs_uln_mncv_r_val**	Ulnar - MNCV (m/s) - Wrist to elbow - Right	1545	814	52.7			56	52.70000076			0.72	Mann-Whitney U	0	TRUE
121	**ncs_uln_mncv_r**	Ulnar - MNCV - Wrist to elbow - Right	1545	821	53.1			Abnormal (ABNL) 2.1 NR 0.0	Abnormal (ABNL) 20.4 NR 0.3	0.152	S		Chi square	8E-05	TRUE
122	**ncs_uln_aroun_r_val**	Ulnar - MNCV (m/s) - Around elbow - Right	1545	798	51.7			53.65000153	48			0.65	Mann-Whitney U	0	TRUE
123	**ncs_uln_aroun_r**	Ulnar - MNCV - Around elbow - Right	1545	805	52.1			Abnormal (ABNL) 35.1 NR 0.0	Abnormal (ABNL) 53.2 NR 0.3	0.118	S		Chi square	0.0035	TRUE
124	**ncs_uln_laten_r_val**	Ulnar - Distal motor latency (msec) - Right	1545	817	52.9			2.700000048	2.900000095			0.34	Mann-Whitney U	0	TRUE
125	**ncs_uln_laten_r**	Ulnar - Distal motor latency - Right	1545	824	53.3			Abnormal (ABNL) 3.2 NR 0.0	Abnormal (ABNL) 16.8 NR 0.3	0.122	S		Chi square	0.0021	TRUE
126	**ncs_uln_cmap_r_val**	Ulnar - Distal CMAP (millivolts) - Right	1545	817	52.9			10.25	8.300000191			0.71	Mann-Whitney U	0	TRUE
127	**ncs_uln_cmap_r**	Ulnar - Distal CMAP - Right	1545	824	53.3			Abnormal (ABNL) 1.1 NR 0.0	Abnormal (ABNL) 9.9 NR 0.3	0.1	S		Chi square	0.0158	TRUE
128	**ncs_uln_fwave_r_val**	Ulnar - F-wave latency (msec) - Right	1545	668	43.2			29.60000038	32.40000153			0.25	Mann-Whitney U	0	TRUE
129	**ncs_uln_fwave_r**	Ulnar - F-wave latency - Right	1545	680	44			Abnormal (ABNL) 9.9 NR 0.0	Abnormal (ABNL) 45.0 NR 1.3	0.226	S		Chi square	3E-08	TRUE
130	**ncs_uln_lft_collapse**	Was ulnar motor nerve testing performed on the LEFT side?	1545	1545	100			0	0			0.45	Mann-Whitney U	0	TRUE
131	**ncs_uln_mncv_l_val**	Ulnar - MNCV (m/s) - Wrist to elbow - Left	1545	402	26			58	52			0.75	Mann-Whitney U	0	TRUE
132	**ncs_uln_mncv_l**	Ulnar - MNCV - Wrist to elbow - Left	1545	404	26.1			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 19.3 NR 0.6	0.184	S		Chi square	0.0011	TRUE
133	**ncs_uln_aroun_l_val**	Ulnar - MNCV (m/s) - Around elbow - Left	1545	397	25.7			52.5	50			0.65	Mann-Whitney U	0	TRUE
135	**ncs_uln_laten_l_val**	Ulnar - Distal motor latency (msec) - Left	1545	409	26.5			2.650000095	2.930000067			0.32	Mann-Whitney U	0	TRUE
136	**ncs_uln_laten_l**	Ulnar - Distal motor latency - Left	1545	413	26.7			Abnormal (ABNL) 3.5 NR 0.0	Abnormal (ABNL) 19.4 NR 0.6	0.149	S		Chi square	0.0104	TRUE
137	**ncs_uln_cmap_lval**	Ulnar - Distal CMAP (millivolts) - Left	1545	408	26.4			10	8.399999619			0.7	Mann-Whitney U	0	TRUE
138	**ncs_uln_cmap_l**	Ulnar - Distal CMAP - Left	1545	412	26.7			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 13.0 NR 0.6	0.146	S		Chi square	0.0128	TRUE
139	**ncs_uln_fwave_l_val**	Ulnar - F-wave latency (msec) - Left	1545	325	21			29.10000038	32.34999847			0.21	Mann-Whitney U	0	TRUE
140	**ncs_uln_fwave_l**	Ulnar - F-wave latency - Left	1545	331	21.4			Abnormal (ABNL) 6.1 NR 0.0	Abnormal (ABNL) 43.3 NR 1.8	0.283	S		Chi square	2E-06	TRUE
142	**ncs_pero_mncv_r_val**	Peroneal - MNCV (m/s) - Ankle to knee - Right	1545	993	64.3			43	39			0.8	Mann-Whitney U	0	TRUE
143	**ncs_pero_mncv_r**	Peroneal - MNCV - Ankle to knee - Right	1545	1114	72.1			Abnormal (ABNL) 5.2 NR 0.5	Abnormal (ABNL) 37.6 NR 23.8	0.438	M		Chi square	3E-47	TRUE
144	**ncs_pero_aroun_r_val**	Peroneal - MNCV (m/s) - Around knee - Right	1545	885	57.3			53	43.40000153			0.77	Mann-Whitney U	0	TRUE
145	**ncs_pero_aroun_r**	Peroneal - MNCV - Around knee - Right	1545	1001	64.8			Abnormal (ABNL) 0.0 NR 0.5	Abnormal (ABNL) 19.6 NR 26.1	0.371	M		Chi square	1E-30	TRUE
146	**ncs_pero_laten_r_val**	Peroneal - Distal motor latency (msec) - Right	1545	1023	66.2			4.199999809	4.599999905			0.4	Mann-Whitney U	0	TRUE
147	**ncs_pero_laten_r**	Peroneal - Distal motor latency - Right	1545	1133	73.3			Abnormal (ABNL) 5.6 NR 0.5	Abnormal (ABNL) 18.2 NR 22.5	0.288	S		Chi square	3E-21	TRUE
148	**ncs_pero_cmap_r_val**	Peroneal - Distal CMAP (millivolts) - Right	1545	1028	66.5			4.449999809	1.700000048			0.83	Mann-Whitney U	0	TRUE
149	**ncs_pero_cmap_r**	Peroneal - Distal CMAP - Right	1545	1139	73.7			Abnormal (ABNL) 7.0 NR 0.5	Abnormal (ABNL) 39.5 NR 22.5	0.427	M		Chi square	9E-46	TRUE
151	**ncs_pero_fwave_r**	Peroneal - F-wave latency - Right	1545	816	52.8			Abnormal (ABNL) 37.7 NR 0.6	Abnormal (ABNL) 42.3 NR 37.9	0.427	M		Chi square	5E-33	TRUE
152	**ncs_prnl_lft_collapse**	Was peroneal motor nerve testing performed on the LEFT side?	1545	1545	100			0	1			0.42	Mann-Whitney U	0	TRUE
153	**ncs_pero_mncv_l_val**	Peroneal - MNCV (m/s) - Ankle to knee - Left	1545	791	51.2			44	39			0.81	Mann-Whitney U	0	TRUE
154	**ncs_pero_mncv_l**	Peroneal - MNCV - Ankle to knee - Left	1545	883	57.2			Abnormal (ABNL) 5.5 NR 0.0	Abnormal (ABNL) 37.9 NR 24.3	0.422	M		Chi square	6E-35	TRUE
155	**ncs_pero_aroun_l_val**	Peroneal - MNCV (m/s) - Around knee - Left	1545	718	46.5			53	43			0.77	Mann-Whitney U	0	TRUE
156	**ncs_pero_aroun_l**	Peroneal - MNCV - Around knee - Left	1545	804	52			Abnormal (ABNL) 3.6 NR 0.0	Abnormal (ABNL) 22.0 NR 25.9	0.341	M		Chi square	5E-21	TRUE
158	**ncs_pero_laten_l**	Peroneal - Distal motor latency - Left	1545	920	59.5			Abnormal (ABNL) 4.7 NR 0.0	Abnormal (ABNL) 18.1 NR 23.1	0.283	S		Chi square	1E-16	TRUE
159	**ncs_pero_cmap_l_val**	Peroneal - Distal CMAP (millivolts) - Left	1545	829	53.7			4.5	1.600000024			0.82	Mann-Whitney U	0	TRUE
160	**ncs_pero_cmap_l**	Peroneal - Distal CMAP - Left	1545	923	59.7			Abnormal (ABNL) 9.4 NR 0.0	Abnormal (ABNL) 40.3 NR 23.6	0.406	M		Chi square	1E-33	TRUE
162	**ncs_pero_fwave_l**	Peroneal - F-wave latency - Left	1545	648	41.9			Abnormal (ABNL) 29.5 NR 1.8	Abnormal (ABNL) 41.2 NR 38.4	0.426	M		Chi square	3E-26	TRUE
164	**ncs_sural_r_val**	Sural SNCV (m/s) - Right	1545	829	53.7			46	34			0.84	Mann-Whitney U	0	TRUE
165	**ncs_sural_r**	Sural SNCV - Right	1545	1143	74			Abnormal (ABNL) 2.6 NR 0.4	Abnormal (ABNL) 16.6 NR 57.8	0.583	L		Chi square	4E-85	TRUE
166	**ncs_sural_snap_r_val**	Sural SNAP (microvolts) - Right	1545	898	58.1			12.19999981	2.700000048			0.96	Mann-Whitney U	0	TRUE
167	**ncs_sural_snap_r**	Sural SNAP - Right	1545	1262	81.7			Abnormal (ABNL) 4.5 NR 0.4	Abnormal (ABNL) 33.4 NR 56.1	0.754	L		Chi square	2E-156	TRUE
168	**ncs_sural_l_val**	Sural SNCV (m/s) - Left	1545	740	47.9			45.79999924	32			0.84	Mann-Whitney U	0	TRUE
169	**ncs_sural_l**	Sural SNCV - Left	1545	1042	67.4			Abnormal (ABNL) 2.2 NR 0.6	Abnormal (ABNL) 16.5 NR 58.4	0.563	L		Chi square	2E-72	TRUE
170	**ncs_sural_snap_l_val**	Sural SNAP (microvolts) - Left	1545	802	51.9			11.69999981	2.5			0.95	Mann-Whitney U	0	TRUE
171	**ncs_sural_snap_l**	Sural SNAP - Left	1545	1149	74.4			Abnormal (ABNL) 4.7 NR 0.5	Abnormal (ABNL) 34.5 NR 56.4	0.754	L		Chi square	1E-142	TRUE
172	**ncs_mdn_sns_desc**	Was median sensory nerve testing performed?	1545	1544	99.9			0	1			0.34	Mann-Whitney U	0	TRUE
173	**ncs_med_r_val**	Median SNCV (m/s) - Right	1545	724	46.9			52.5	46.40000153			0.71	Mann-Whitney U	0	TRUE
174	**ncs_med_r**	Median SNCV - Right	1545	794	51.4			Abnormal (ABNL) 19.8 NR 2.2	Abnormal (ABNL) 42.1 NR 17.8	0.247	S		Chi square	3E-11	TRUE

FIGURE B.6: Statistically significant results for Analysis 3. Part 3.

175	**ncs_med_snap_r_val**	Median SNAP (microvolts) - Right	1545	779	50.4			19.20000076	8.399999619			0.81	Mann-Whitney U	0	TRUE
176	**ncs_med_snap_r**	Median SNAP - Right	1545	854	55.3			Abnormal (ABNL) 13.1 NR 2.0	Abnormal (ABNL) 46.9 NR 17.2	0.319	M		Chi square	1E-19	TRUE
177	**ncs_med_l_val**	Median SNCV (m/s) - Left	1545	383	24.8			52.20000076	44.5			0.7	Mann-Whitney U	0	TRUE
178	**ncs_med_l**	Median SNCV - Left	1545	436	28.2			Abnormal (ABNL) 28.4 NR 3.0	Abnormal (ABNL) 46.6 NR 20.1	0.271	S		Chi square	1E-07	TRUE
179	**ncs_med_snap_l_val**	Median SNAP (microvolts) - Left	1545	414	26.8			22.95000076	8			0.82	Mann-Whitney U	0	TRUE
180	**ncs_med_snap_l**	Median SNAP - Left	1545	468	30.3			Abnormal (ABNL) 16.2 NR 2.9	Abnormal (ABNL) 47.2 NR 19.2	0.342	M		Chi square	1E-12	TRUE
181	**ncs_uln_sns_desc**	Was ulnar sensory nerve testing performed?	1545	1545	100			0	1			0.31	Mann-Whitney U	0	TRUE
182	**ncs_ulnar_r_val**	Ulnar SNCV (m/s) - Right	1545	657	42.5			53	50			0.68	Mann-Whitney U	0	TRUE
183	**ncs_ulnar_r**	Ulnar SNCV - Right	1545	752	48.7			Abnormal (ABNL) 5.2 NR 1.3	Abnormal (ABNL) 22.4 NR 23.6	0.243	S		Chi square	2E-10	TRUE
184	**ncs_ulnar_snap_r_val**	Ulnar SNAP (microvolts) - Right	1545	726	47			13.30000019	6.650000095			0.77	Mann-Whitney U	0	TRUE
185	**ncs_ulnar_snap_r**	Ulnar SNAP- Right	1545	807	52.2			Abnormal (ABNL) 22.4 NR 1.2	Abnormal (ABNL) 45.2 NR 22.0	0.283	S		Chi square	9E-15	TRUE
186	**ncs_ulnar_l_val**	Ulnar SNCV (m/s) - Left	1545	315	20.4			52.20000076	50			0.75	Mann-Whitney U	0	TRUE
187	**ncs_ulnar_l**	Ulnar SNCV - Left	1545	377	24.4			Abnormal (ABNL) 5.5 NR 1.8	Abnormal (ABNL) 24.8 NR 27.6	0.321	M		Chi square	4E-09	TRUE
188	**ncs_ulnar_snap_l_val**	Ulnar SNAP (microvolts) - Left	1545	347	22.5			14	6.400000095			0.79	Mann-Whitney U	0	TRUE
189	**ncs_ulnar_snap_l**	Ulnar SNAP- Left	1545	399	25.8			Abnormal (ABNL) 18.5 NR 1.9	Abnormal (ABNL) 44.1 NR 27.0	0.366	M		Chi square	3E-12	TRUE
190	**ncs_rad_sns_desc**	Was radial sensory nerve testing performed?	1545	1544	99.9			0	1			0.29	Mann-Whitney U	0	TRUE
191	**ncs_radial_r_val**	Radial SNCV (m/s) - Right	1545	632	40.9			58	54			0.69	Mann-Whitney U	0	TRUE
192	**ncs_radial_r**	Radial SNCV - Right	1545	658	42.6			Abnormal (ABNL) 1.9 NR 0.0	Abnormal (ABNL) 14.7 NR 7.8	0.14	S		Chi square	0.0016	TRUE
193	**ncs_radial_snap_r_val**	Radial SNAP (microvolts) - Right	1545	668	43.2			25.10000038	15.19999981			0.76	Mann-Whitney U	0	TRUE
194	**ncs_radial_snap_r**	Radial SNAP- Right	1545	698	45.2			Abnormal (ABNL) 1.7 NR 0.0	Abnormal (ABNL) 22.8 NR 7.4	0.177	S		Chi square	2E-05	TRUE
195	**ncs_radial_l_val**	Radial SNCV (m/s) - Left	1545	284	18.4			59	53.90000153			0.73	Mann-Whitney U	0	TRUE
196	**ncs_radial_l**	Radial SNCV - Left	1545	303	19.6			Abnormal (ABNL) 0.0 NR 0.0	Abnormal (ABNL) 16.9 NR 10.4	0.174	S		Chi square	0.0104	TRUE
197	**ncs_radial_snap_l_val**	Radial SNAP (microvolts) - Left	1545	303	19.6			34.59999847	14			0.88	Mann-Whitney U	0	TRUE
198	**ncs_radial_snap_l**	Radial SNAP- Left	1545	322	20.8			Abnormal (ABNL) 3.8 NR 0.0	Abnormal (ABNL) 35.1 NR 9.1	0.224	S		Chi square	0.0003	TRUE
199	**pnw_sex**	Sex	1545	1545	100			Male 52.1 Female 47.9	Male 71.1 Female 28.9	0.16	S		Chi square	4E-10	TRUE
200	**pnw_1**	1. Nerve Conduction Study / Electromyography (NCS/EMG) diagnosis	1545	1545	100			Normal 100.0 Abnormal 0.0	Normal 0.0 Abnormal 100.0	0.998	L		Chi square	0	TRUE
203	**pnw_2**	2. Skin biopsy (if NCS/EMG is normal)	1545	491	31.8			Normal 0.0 Abnormal 100.0	Normal 17.9 Abnormal 82.1	0.338	M		Fishers exact	1E-15	TRUE
204	**pnw_2_a**	-----> If Skin biopsy was Abnormal, select one:	1545	454	29.4			Non-length-dependent 22.4	Length-dependent 94.0 Non-length-dependent 6.0	0.199	S		Fishers exact	4E-06	TRUE
205	**pnw_tier1_4**	3. Chemistry (Chem 12-18)	1545	1489	96.4			Normal 93.0 Abnormal 7.0	Normal 81.1 Abnormal 18.9	0.126	S		Chi square	1E-06	TRUE
206	**pnw_creatinine**	Creatinine level: enter measured creatinine value in milligram per deciliter (mg/dL)	1545	1359	88			0.9	0.97			0.41	Mann-Whitney U	0	TRUE
208	**pnw_tier1_5**	4. a. Glycated Hemoglobin (HgA1C)	1545	1366	88.4			Normal 71.8 Abnormal 28.2	Normal 51.4 Abnormal 48.6	0.161	S		Chi square	3E-09	TRUE
209	**pnw_hga1c_lvl**	HgA1C Level	1545	1274	82.5			5.5	5.7			0.38	Mann-Whitney U	0	TRUE
210	**pnw_bld_gluc_fast**	4. b. Blood Glucose (fasting)	1545	462	29.9			Normal 83.5 Abnormal 16.5	Normal 72.5 Abnormal 27.5	0.108	S		Fishers exact	0.0153	TRUE
211	**pnw_bld_gluc_fast_lvl**	Fasting Glucose Level	1545	459	29.7			89	94			0.38	Mann-Whitney U	0	TRUE
218	**pnw_tier1_9**	6. Vitamin B12	1545	1449	93.8			Normal 99.0 Abnormal 1.0	Normal 95.2 Abnormal 4.8	0.072	_		Chi square	0.006	TRUE
220	**pnw_tier1_3**	Differential	1545	1329	86			Normal 67.0 Abnormal 33.0	Normal 58.8 Abnormal 41.2	0.066	_		Chi square	0.0169	TRUE
221	**pnw_tier1_6**	8. Erythrocyte Sedimentation Rate (ESR)	1545	918	59.4			Normal 88.8 Abnormal 11.2	Normal 78.7 Abnormal 21.3	0.105	S		Fishers exact	0.0008	TRUE
225	**pnw_cholest_value**	Cholesterol	1545	911	59			183	171			0.59	Mann-Whitney U	0	TRUE
227	**pnw_hdl_value**	HDL	1545	907	58.7			51	48			0.56	Mann-Whitney U	0.012	TRUE
228	**pnw_ldl_value**	LDL	1545	901	58.3			107	92			0.6	Mann-Whitney U	0	TRUE
229	**pnw_tier2_12**	11. C-reactive protein	1545	475	30.7			Normal 85.6 Abnormal 14.4	Normal 74.0 Abnormal 26.0	0.116	S		Fishers exact	0.009	TRUE
233	**pnw_urine_upep**	13. b. Urine Electrophoresis (UPEP)	1545	304	19.7			Normal 90.8 Abnormal 9.2	Normal 78.5 Abnormal 21.5	0.127	S		Fishers exact	0.0166	TRUE
234	**pnw_tier2_15**	14. Methyl malonic acid (MMA)	1545	620	40.1			Normal 99.3 Abnormal 0.7	Normal 94.1 Abnormal 5.9	0.095	_		Fishers exact	0.0061	TRUE
235	**pnw_inflam_test**	Has inflammatory and/or autoimmune testing been performed on this patient?	1545	1545	100			1	1			0.62	Mann-Whitney U	0	TRUE
236	**pnw_kllc**	15. Kappa / Lambda Light Chains	1545	426	27.6			Normal 72.5 Abnormal 27.5	Normal 54.9 Abnormal 45.1	0.151	S		Fishers exact	0.0015	TRUE
251	**pnw_infectious_test**	Has infectious testing been performed on this patient?	1545	1545	100			1	0			0.56	Mann-Whitney U	0	TRUE
260	**pnw_paraneoplastic_test**	Has paraneoplastic testing been performed on this patient?	1545	1545	100			0	0			0.57	Mann-Whitney U	0	TRUE
265	**pnw_other_test**	patient (incl. CK, homocysteine, urine heavy metals, vitamins E and B)?	1545	1545	100			1	1			0.6	Mann-Whitney U	0	TRUE
266	**pnw_other_41**	41. Creatine Kinase (CK)	1545	431	27.9			Normal 89.8 Abnormal 10.2	Normal 79.2 Abnormal 20.8	0.117	S		Fishers exact	0.0108	TRUE
275	**pnw_autonomic_test**	Has autonomic testing been performed on this patient?	1545	1545	100			0	0			0.51	Mann-Whitney U	0.016	TRUE

FIGURE B.7: Statistically significant results for Analysis 3. Part 4.

283	**phq1_sex**	What is your sex?	1545	1544	99.9			Male 51.1 Female 48.9	Male 70.7 Female 29.3	0.164	S		Chi square	1E-10	TRUE
286	**phq_pain**	1. PAIN: Do you have pain?	1545	1544	99.9			No 16.6 Yes 83.4	No 29.7 Yes 70.3	0.115	S		Chi square	6E-06	TRUE
288	**phq_pain_c**	c. How long ago did your pain start?	1545	1124	72.8			2 to 4 weeks ago 0.4 1 to 6 months ago 4.3	2 to 4 weeks ago 0.6 1 to 6 months ago 5.4	0.145	S		Chi square	0.0013	TRUE
290	**phq_pain_sharp**	e. Please us the scale to tell us how SHARP your pain feels.	1545	1123	72.7			1 6.2 2 6.2	1 3.8 2 7.8	0.134	S		Chi square	0.0285	TRUE
296	**phq_pain_quality**	k. Which of the following best describes the time quality of your pain?	1545	1125	72.8			the time and occasional flare ups (break-through pain)	the time and occasional flare ups (break-through pain)	0.099	_		Chi square	0.0043	TRUE
300	**phq_n**	pain or discomfort from a normally non-painful stimulus? For example, do you experience	1545	1057	68.4			No 38.7 Yes 61.3	No 49.6 Yes 50.4	0.09	_		Chi square	0.0034	TRUE
303	**phq_numbness**	2. NUMBNESS: Do you have numbness (loss of sensation)?	1545	1544	99.9			No 17.9 Yes 82.1	No 8.2 Yes 91.8	0.125	S		Chi square	9E-07	TRUE
304	**phq_numbness_b**	2 b. Is your numbness (loss of sensation):	1545	1376	89.1			Sometimes present 34.3 Rarely present 6.0	Sometimes present 17.5 Rarely present 1.2	0.212	S		Chi square	3E-14	TRUE
305	**phq_numbness_c**	2 c. How long ago did your numbness (loss of sensation) start?	1545	1385	89.6			2 to 4 weeks ago 0.8 1 to 6 months ago 4.0	2 to 4 weeks ago 0.2 1 to 6 months ago 3.8	0.195	S		Chi square	5E-09	TRUE
306	**phq_sensation**	sensations (with or without loss of sensation)? Some people might describe these as "pins and	1545	1534	99.3			Yes, all the time 39.7 Yes, occasionally 51.5	Yes, all the time 36.6 Yes, occasionally 48.3	0.073	_		Chi square	0.0176	TRUE
307	**phq_weakness**	4. WEAKNESS: Do you have weakness (loss of strength or power)?	1545	1544	99.9			No 57.7 Yes 42.3	No 41.1 Yes 58.9	0.132	S		Chi square	2E-07	TRUE
311	**phq_balance**	balance of difficulties walking because of poor balance?	1545	1544	99.9			No 54.4 Yes 45.6	No 27.0 Yes 73.0	0.232	S		Chi square	8E-20	TRUE
312	**phq_balance_a**	6 a. Is your trouble with balance:	1545	1034	66.9			Sometimes present 56.4 Rarely present 19.3	Sometimes present 37.8 Rarely present 8.1	0.215	S		Chi square	4E-11	TRUE
317	**phq_sleep**	8. SLEEP: Have you experienced sleeping difficulties?	1545	1543	99.9			No 33.9 Yes 66.1	No 41.5 Yes 58.5	0.061	_		Chi square	0.0175	TRUE
318	**phq_sleep_a**	staying asleep at night from pain due to your peripheral neuropathy?	1545	926	59.9			No 16.3 Yes 83.7	No 26.8 Yes 73.2	0.099	_		Fishers exact	0.0017	TRUE
322	**phq_symptoms**	9. Which symptom bothers you the most?	1545	1531	99.1			Numbness (loss of sensation) 27.4	Numbness (loss of sensation) 31.3	0.217	S		Chi square	8E-15	TRUE
326	**phq1_diabetes**	You selected Diabetes. Please specify.	1545	490	31.7			Type II 42.1 Pre-diabetic 56.1	Type II 71.6 Pre-diabetic 21.9	0.252	S		Chi square	2E-07	TRUE
331	**phq1_3month**	or the flu 1 to 3 months before the onset of your neuropathy?	1545	1099	71.1			No 78.1 Yes 21.9	No 85.4 Yes 14.6	0.076	_		Chi square	0.0114	TRUE
335	**phq1_smoke**	18. Have you ever smoked?	1545	1544	99.9			No 64.8 Yes, I	No 52.5 Yes, I	0.11	S		Chi square	9E-05	TRUE
336	**phq1_18_smoke_packs**	If Yes, how many packs per day?	1545	677	43.8			Less than 1 pack 76.2 More than 1 pack 23.8	Less than 1 pack 63.8 More than 1 pack 36.2	0.09	_		Fishers exact	0.0139	TRUE
338	**phq1_stopped_smoking**	At what age did you stop smoking?	1545	581	37.6			35	39			0.41	Mann-Whitney U	0.008	TRUE
340	**phq1_drink_number**	If Yes, how many drinks per day?	1545	1231	79.7			Less than 2 drinks 89.6 More than 2 drinks 10.4	Less than 2 drinks 82.3 More than 2 drinks 17.7	0.077	_		Chi square	0.0067	TRUE
341	**phq1_drink_years**	For how many years?	1545	1213	78.5			Less than 10 years 23.6 More than 10 years 76.4	Less than 10 years 15.8 More than 10 years 84.2	0.081	_		Chi square	0.0049	TRUE
342	**phq1_stopped_drinking**	At what age did you stop drinking?	1545	296	19.2			39	48			0.39	Mann-Whitney U	0.007	TRUE
344	**phq1_drugs_years**	For how many years?	1545	284	18.4			Less than 10 years 86.4 More than 10 years 13.6	Less than 10 years 66.5 More than 10 years 33.5	0.176	S		Fishers exact	0.0018	TRUE
345	**phq1_stopped_drugs**	At what age did you stop using recreational drugs?	1545	180	11.7			24	30			0.35	Mann-Whitney U	0.002	TRUE
346	**phq1_marital**	21. What is your marital status?	1545	1542	99.8			Married 73.0 Widowed 3.6	Married 71.3 Widowed 7.8	0.089	_		Chi square	0.0166	TRUE
347	**phq1_living_sit**	22. Which best describes your living situation?	1545	1538	99.5			I live with my spouse/partner. 76.3	I live with my spouse/partner. 75.1	0.104	S		Chi square	0.0022	TRUE
349	**phq1_family_auto**	24. Do you have any family members with autoimmune disease?	1545	1305	84.5			No 55.8 Yes 44.2	No 76.2 Yes 23.8	0.182	S		Chi square	5E-11	TRUE
351	**hyperglycemia**	The HgA1C level reported on the PNW is	1545	836	54.1			No 60.4 Yes 39.6	No 46.6 Yes 53.4	0.114	S		Fishers exact	0.001	TRUE
352	**severityhyperglycemia**	Type/severity of hyperglycemia	1545	420	27.2			DM Type2 25.0 DM Type1 1.3	DM Type2 52.3 DM Type1 4.1	0.232	S		Chi square	1E-05	TRUE
366	**hypertension**	Diagnosis of hypertension	1545	821	53.1			No 50.8 Yes 49.2	No 35.2 Yes 64.8	0.132	S		Fishers exact	0.0001	TRUE
368	**mets_systolic**	Systolic BP on day of PNRR visit	1545	833	53.9			130	132			0.43	Mann-Whitney U	0.004	TRUE
372	**current_weight**	BMI Calculator - Weight (in kg)	1545	341	22.1			82.55	94.8			0.32	Mann-Whitney U	0	TRUE
373	**current_bmi**	Calculated BMI	1545	341	22.1			25.95	29.7			0.36	Mann-Whitney U	0.001	TRUE
374	**dyslipidemiadiagnosis**	of dyslipidemia Triglyceride value on PNW is	1545	698	45.2			No 59.6 Yes 40.4	No 49.1 Yes 50.9	0.084	_		Fishers exact	0.023	TRUE
375	**exercise_reported**	Does the patient exercise?	1545	640	41.4			No 30.6 Yes 69.4	No 41.4 Yes 58.6	0.092	_		Fishers exact	0.0183	TRUE
395	**mrcfingerextensionright**	Finger extension [Right]	1545	905	58.6			resistance) 0.0 4 (Reduced movement	resistance) 0.3 4 (Reduced movement	0.091	_		Chi square	0.023	TRUE
396	**mrcfingerextensionleft**	Finger extension [Left]	1545	904	58.5			resistance) 0.0 4 (Reduced movement	resistance) 0.3 4 (Reduced movement	0.091	_		Chi square	0.0229	TRUE
399	**mrcinterosseiadmright**	Interossei and ADM [Right]	1545	900	58.3			0.0 2 (No movement	0.2 2 (No movement	0.137	S		Chi square	0.0021	TRUE
400	**mrcinterosseiadmleft**	Interossei and ADM [Left]	1545	899	58.2			0.0 2 (No movement	0.2 2 (No movement	0.128	S		Chi square	0.0053	TRUE
402	**mrcapbleft**	APB [Left]	1545	901	58.3			0.0 1 (Flicker only)	0.2 1 (Flicker only)	0.131	S		Chi square	0.0086	TRUE
409	**mrcankledorsiright**	Ankle Dorsiflexion [Right]	1545	906	58.6			0.0 1 (Flicker only)	1.5 1 (Flicker only)	0.217	S		Chi square	4E-08	TRUE
410	**mrcankledorsileft**	Ankle Dorsiflexion [Left]	1545	906	58.6			0.0 1 (Flicker only)	2.4 1 (Flicker only)	0.226	S		Chi square	8E-09	TRUE
411	**mrcankleplantarright**	Ankle Plantarflexion [Right]	1545	905	58.6			0.0 1 (Flicker only)	1.2 1 (Flicker only)	0.16	S		Chi square	0.0003	TRUE
412	**mrcankleplantarleft**	Ankle Plantarflexion [Left]	1545	905	58.6			0.0 1 (Flicker only)	1.3 1 (Flicker only)	0.157	S		Chi square	0.0005	TRUE
413	**mrctoedorsiright**	Toe Dorsiflexion [Right]	1545	902	58.4			0.0 1 (Flicker only)	3.8 1 (Flicker only)	0.318	M		Chi square	4E-18	TRUE
414	**mrctoedorsileft**	Toe Dorsiflexion [Left]	1545	902	58.4			0.0 1 (Flicker only)	4.1 1 (Flicker only)	0.314	M		Chi square	1E-17	TRUE
415	**mrctoeplantarright**	Toe Plantarflexion [Right]	1545	898	58.1			0.0 1 (Flicker only)	2.0 1 (Flicker only)	0.264	S		Chi square	4E-12	TRUE
416	**mrctoeplantarleft**	Toe Plantarflexion [Left]	1545	898	58.1			0.0 1 (Flicker only)	2.4 1 (Flicker only)	0.258	S		Chi square	1E-11	TRUE

FIGURE B.8: Statistically significant results for Analysis 3. Part 5.

417	**pinprickkneeright**	Pinprick: Knee [Right]	1545	843	54.6			1 (Reduced) 2.2 2 (Normal) 97.0	1 (Reduced) 9.6 2 (Normal) 86.1	0.155	S		Chi square	4E-05	TRUE
418	**pinprickkneeleft**	Pinprick: Knee [Left]	1545	844	54.6			1 (Reduced) 2.2 2 (Normal) 97.0	1 (Reduced) 10.4 2 (Normal) 85.5	0.161	S		Chi square	2E-05	TRUE
419	**pinprickwristright**	Pinprick: Wrist [Right]	1545	828	53.6			1 (Reduced) 5.7 2 (Normal) 93.9	1 (Reduced) 11.8 2 (Normal) 86.1	0.107	S		Chi square	0.0091	TRUE
420	**pinprickwristleft**	Pinprick: Wrist [Left]	1545	827	53.5			1 (Reduced) 5.7 2 (Normal) 93.9	1 (Reduced) 11.7 2 (Normal) 86.5	0.105	S		Chi square	0.0104	TRUE
421	**prinprickborderlegright**	Pinprick: Border Right Leg	1545	854	55.3			1 (mid foot) 13.4 2 (below ankle) 9.1	1 (mid foot) 9.3 2 (below ankle) 6.6	0.258	S		Chi square	6E-10	TRUE
422	**prinprickborderlegleft**	Pinprick: Border Left Leg	1545	854	55.3			1 (mid foot) 12.9 2 (below ankle) 8.6	1 (mid foot) 8.3 2 (below ankle) 6.9	0.261	S		Chi square	4E-10	TRUE
425	**vibrationkneeright**	Vibration Sense: Knee [Right]	1545	441	28.5			6	5			0.62	Mann-Whitney U	0.002	TRUE
426	**vibrationkneeleft**	Vibration Sense: Knee [Left]	1545	440	28.5			6	5			0.64	Mann-Whitney U	0	TRUE
427	**vibrationwristright**	Vibration Sense: Wrist [Right]	1545	103	6.7			7	6.5			0.65	Mann-Whitney U	0.023	TRUE
428	**vibrationwristleft**	Vibration Sense: Wrist [Left]	1545	104	6.7			7	6.5			0.66	Mann-Whitney U	0.019	TRUE
429	**tns_symptomextension**	0 - normal	1545	847	54.8			1 27.6 2 22.4	1 28.9 2 31.9	0.163	S		Chi square	0.0002	TRUE
430	**tns_pinsensibility**	0 - normal	1545	852	55.1			1 20.2 2 15.5	1 12.1 2 15.5	0.258	S		Chi square	2E-11	TRUE
431	**tns_vibrationsensibility**	0 - normal	1545	850	55			1 32.8 2 8.2	1 38.5 2 32.8	0.473	M		Chi square	5E-40	TRUE
432	**tns_strength**	0 - normal	1545	854	55.3			1 14.6 2 0.0	1 34.8 2 4.3	0.322	M		Chi square	2E-18	TRUE
433	**tns_tendonreflexes**	0 - ankle reflex normal	1545	852	55.1			1 13.7 2 9.0	1 9.9 2 21.3	0.462	M		Chi square	3E-38	TRUE
434	**totalneuropathyscore**	Total Neuropathy Score (TNS)	1545	857	55.5			5	9			0.2	Mann-Whitney U	0	TRUE
435	**skinbiopsyyesno**	Was skin biopsy performed?	1545	926	59.9			Yes 99.1 No 0.9	Yes 21.9 No 78.1	0.678	L		Fishers exact	2E-110	TRUE
436	**skinbiopsydistal**	Nerve fiber density skin biopsy distal punch site	1545	373	24.1			Reduced Density 79.2 Normal Density 5.8	Reduced Density 42.9 Normal Density 23.1	0.379	M		Chi square	2E-12	TRUE
437	**skinbiopsyproximal**	Nerve fiber density skin biopsy proximal punch site	1545	367	23.8			Reduced Density 33.3 Normal Density 66.7	Reduced Density 21.4 Normal Density 78.6	0.123	S		Fishers exact	0.0134	TRUE
441	**igmabsolutevalue**	Absolute value of Immunoglobulin M	1545	734	47.5			86.5	76			0.57	Mann-Whitney U	0.006	TRUE
442	**kappaabsolutevalue**	Absolute value of kappa light chain	1545	394	25.5			15.3	18.6			0.38	Mann-Whitney U	0	TRUE
443	**lambdaabsolutevalue**	Absolute value of lambda light chain	1545	393	25.4			13.80000019	14.5			0.41	Mann-Whitney U	0.005	TRUE
452	**yearspnsymptoms**	Years since onset of PN	1545	975	63.1			3	6			0.34	Mann-Whitney U	0	TRUE
453	**xtra_metabolicdisease**	Does patient have metabolic disease?	1545	819	53			Yes 32.0 No 68.0	Yes 47.7 No 52.3	0.134	S		Fishers exact	9E-05	TRUE
454	**xtra_smallfiber**	Does patient have small fiber neuropathy?	1545	912	59			Yes 96.6 No 3.4	Yes 8.9 No 91.1	0.824	L		Fishers exact	2E-145	TRUE
455	**doessubjhavedm**	Does patient have Diabetes Mellitus?	1545	982	63.6			Yes 2, No 9.7 2.0 90.3	Yes 2, No 26.2 2.0 73.8	0.168	S		Fishers exact	2E-08	TRUE
472	**supp_systolic**	Systolic Blood Pressure	1545	672	43.5			127	133			0.42	Mann-Whitney U	0.001	TRUE

FIGURE B.9: Statistically significant results for Analysis 3. Part 6.

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20.10.2023

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