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LETTER TO THE EDITOR

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A call to action for peripheral neuropathy research funding—Time to consolidate funding under one NIH initiative?

Peripheral neuropathies (PNs) pose a significant clinical challenge in the field of neurological disorders, with a prevalence of 2.4% in the general population that rises with age to over 8% in patients aged 55 years and older.[1] Symmetrical, distal-to-proximal axonal loss is the most common form of PN and accounts for most cases.[2,3] It is characterized by damage to the peripheral nerves that typically, especially for diabetes (the leading cause of PN), impacts small-diameter axons beginning in the feet and progresses proximally in a length-dependent manner. PN results in a range of debilitating symptoms such as numbness, tingling, weakness, as well as burning or shooting pain.[4] Along with these painful symptoms, patients may experience depression, anxiety, and sleep disturbances.[5] As PN progresses, individuals may present with diminished sensation to mechanical and thermal stimuli, making it challenging to perceive or effectively heal injuries or trauma, which increases the risk of non-healing ulcers. In severe cases, the cumulative effects of sensation loss and non-healing ulcers can necessitate lower limb amputations.[6] In fact, patients with PN are almost four times at greater risk of undergoing lower-limb amputation than those without.[7] Additionally, PN also leads to an increased risk of falls due to compromised balance and proprioception, further exacerbating the potential for injury and disability in affected individuals. PN likely impacts far more tissues and organs than previously appreciated.[8] Data now indicate diabetic PN exists in the muscle, liver, adipose tissue, pancreas, gastrointestinal tract, and heart.[9–17] PN profoundly impacts the lives of patients, with limited therapeutic options to mitigate pain symptoms, prevent progression, or regenerate lost axons.

While clinical presentations may appear similar, PN can result from a range of causes, including both inherited and acquired conditions. Hereditary neuropathies (HN), such as Charcot–Marie-Tooth (CMT) disease and hereditary sensory and autonomic neuropathies, comprise a diverse group of inherited PN disorders, with an overall prevalence of 1:2500.[18] These differ in their inheritance patterns (autosomal dominant, recessive, or X-linked), electrophysiological characteristics (demyelinating, axonal, or intermediate), and clinical features. While not as common as the other PN types, HN highlight the importance of genetic factors in neuropathic disorders.

Of the acquired neuropathies, diabetic peripheral neuropathy (DPN) is the most prevalent, accounting for 32%–53% of total cases.[2] As cases of diabetes are expected to rise from 537 to 783 million by 2045, DPN, which affects 50% or more of patients and increases in frequency with disease duration, will also increase.[19] Importantly, the Global Burden of Disease Study 2021 ranked DPN among the top 10 leading causes of ill health and disability worldwide.[20] Chemotherapy-induced neuropathy (CIPN) is a challenging side effect of chemotherapeutic agents, affecting roughly half of patients undergoing cancer treatments,[21] and may lead to dose reduction or premature cessation of chemotherapy, thus impeding treatment efficacy and worsening clinical outcomes.[22] Additionally, neuropathic symptoms may persist in about one-third of cancer survivors after treatment cessation, severely affecting the quality of life.[22] Inflammatory neuropathies, such as those observed in autoimmune conditions like Guillain-Barré syndrome, arise when the immune system directly attacks and damages nerve fibers, causing axonal degeneration, demyelination, and subsequent motor and sensory impairments.[23] Infectious neuropathies, on the other hand, can result from direct infection or inflammatory responses triggered by pathogens such as human immunodeficiency virus, leprosy, or COVID-19. These infections can lead to nerve damage through mechanisms like viral replication within peripheral nerves, immune-mediated attacks, or the production of neurotoxic substances. Of note, PN associated with long COVID represents a growing patient population with a wealth of data regarding autonomic dysfunction.[24] Finally, PN can be categorized as idiopathic, with no known underlying cause, and can manifest alongside the natural aging process.

Beyond its clinical implications, PN poses a significant economic and societal burden, encompassing direct medical and indirect social costs, in addition to decreased quality of life for affected individuals.[25] For example, in 2003, the estimated annual healthcare costs of DPN and its complications were between 4.6 and 13.7 billion USD, while the estimated annual cost of managing Guillain-Barré syndrome in 2004 was 1.7 billion USD.[26,27] Likewise, average healthcare costs for CIPN patients were $17 344 higher than those without.[28] These estimates have not been updated and underrepresent current costs. The financial implications of managing PN extend to increased medical visits, hospitalizations, and specialized care.[29] Moreover, PN, both inherited and acquired, can result in long-term disability, leading to reduced workforce participation. Employed individuals with neuropathic pain miss an average of 5.5 workdays per month[30] and have

TABLE 1 National Institutes of Health (NIH) agency funding for peripheral neuropathies between 2017 and 2022.

	Diabetic peripheral neuropathy		Chemotherapy-induced peripheral neuropathy		Hereditary neuropathy	
	Funding (USD)	Percentage of agency funding (%)	Funding (USD)	Percentage of agency funding (%)	Funding (USD)	Percentage of agency funding (%)
NINDS	89 200 000	0.76	58 000 000	0.50	207 000 000	1.76
NIDDK	380 000 000	3.10	4 760 000	0.04	30 600 000	0.25
NCI	9 700 000	0.04	90 300 000	0.37	7 650 000	0.03

Abbreviations: NCI, National Cancer Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NINDS, National Institute of Neurological Disorders and Stroke.

increased reliance on social support systems. Additionally, the emotional toll of living with chronic pain and disability can impact mental health and interpersonal relationships, further exacerbating the societal burden of the condition.[31] As the population ages and the prevalence of conditions associated with PN, such as diabetes and cancer, continues to rise, understanding the underlying mechanisms of PN and identifying effective treatment options remains an unmet public health need.

Inherited and acquired PN differ in their underlying etiology. They do, however, share similar patterns of peripheral nerve damage, including axonal degeneration, myelin abnormalities, and immune cell activation, which may point to overlapping molecular mechanisms or provide insights across PN etiologies. For example, NIH-funded studies have revealed that oxidative stress and inflammation are established key players in all PN conditions.[4,32,33] More recently, studies in HN have guided our understanding of the precise role of abnormal mitochondrial dynamics in DPN and CIPN.[34,35] Additionally, we now know that axon stability is regulated by non-cell autonomous mechanisms, which involve metabolic communication with Schwann cells.[4] Consequently, we believe that supporting basic and foundational research in the field of PN as a whole is crucial, as understanding pathogenic mechanisms in one subtype may provide valuable clues for understanding and treating other subtypes. For example, the development of gene therapies for transthyretin (TTR) neuropathies, the rapid evolvement from identifying sorbitol dehydrogenase (SORD) deficiency as an HN to clinical trials for this disease, and the development of targeted next-generation sequencing panels for improved CMT diagnosis each highlight how basic research discoveries can translate to tangible advancements in patient care. Moreover, the focus of the PN field has shifted from investigating single pathogenic factors to exploring biological systems using omics-based approaches such as genomics and single-cell transcriptomics. These approaches can potentially uncover previously unrecognized targets for PN therapies and thereby enhance our understanding of PN as a whole.[4] Therefore, we contend that prioritizing basic research and identifying shared pathogenic mechanisms, including via advanced techniques such as omics methodologies or advanced microscopy, will inform therapeutic approaches towards *all* neuropathies, underscoring the importance of PN investigations as a collaborative effort across institutes at the National Institutes of Health (NIH).

The economic and societal impacts of PN are difficult to overstate. However, in the United States, NIH allocates funding through specialized institutes, each dedicated to a specific area of health research. As a result, PN research as a whole is fragmented, with different types of PN receiving support from separate NIH institutes: DPN is primarily funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), CIPN by the National Cancer Institute (NCI), aging-related neuropathy at the National Institute on Aging (NIA), and HN and inflammatory neuropathies by the National Institute of Neurological Disorders and Stroke (NINDS; Table 1). While the current siloed approach has led to important scientific discoveries regarding disease pathogenesis and therapeutic intervention, as described above, it also hinders effective collaboration and information-sharing among researchers and under-values investigations that target peripheral nerve degeneration versus degeneration overall, making it difficult to consider PN as a distinct highly morbid disorder worthy of its own mechanistic and therapeutic investigations even beyond (or not restricted) to individual disease etiologies. The limitations of the current funding structure likely perpetuate the lack of mechanistic understanding of disease pathogenesis and the slow identification of effective disease-modifying therapies. By comparison, Europe's funding structure, led by the European Union through Horizon Europe (2021–2027),[36] adopts a more comprehensive, cross-disciplinary strategy. Horizon Europe emphasizes extensive, collaborative projects that engage various stakeholders and prioritize critical pathological areas based on parameters like public health impact, disease burden, and potential innovation, including PN. This structure offers numerous advantages for information sharing and treatment development across PN subtypes.

Centralizing the coordination of PN-related funding at NIH would streamline collaboration among researchers, allowing for the exchange of knowledge, data, and resources across various PN disciplines. Moreover, by pooling resources and expertise under a cross-institute funding initiative, NIH could foster the development of innovative therapies targeting common molecular pathways underlying the different PN subtypes. A successful example of this type of approach is the NIH Pain Consortium, led by NINDS, which has brought together researchers from multiple NIH institutes to address pain research comprehensively, encouraging multidisciplinary collaboration and resource sharing and increasing visibility for pain research. Similarly,

the collaboration between NINDS and NIA to focus on Alzheimer's Disease and Alzheimer's Disease–Related Dementias (AD/ADRD) highlights the effectiveness of an integrated approach in establishing research priorities and advancing our understanding and treatment of complex neurological disorders. Importantly, PN is even more prevalent than AD/ADRD,[20] highlighting the critical need for unified research efforts. These collaborative models can serve as valuable templates for our proposed cross-institute initiative. Overall, consolidating PN research funding as a partnership among numerous NIH institutes that is within a single overall NIH program represents a strategic and efficient approach to advancing scientific knowledge and improving outcomes for the many individuals affected by these debilitating neurological conditions. This letter proposes an operational model for the scientific community to share and promote among stakeholders and decision-makers.

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CONFLICT OF INTEREST STATEMENT

K.L.T. is a co-founder and CSO of Neuright, Inc. All other authors have no relevant conflicts to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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