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Bridging Imaging and Molecular Biomarkers in Trigeminal Neuralgia: Toward Precision Diagnosis and Prognostication in Neuropathic Pain

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ABSTRACT

Despite advances in imaging and clinical assessment, current diagnostic paradigms lack precision needed to subcategorize disease or predict therapeutic response with accuracy. This review proposes precision neuropathic pain diagnostics through the combination of artificial intelligence-guided imaging and molecular biomarker identification, using the use-case of Trigeminal neuralgia (TN), a refractory craniofacial pain disorder characterized by paroxysmal, one-sided facial pain and variable treatment response. We use trigeminal neuralgia as a case example to explore how deep learning, advanced imaging, and molecular profiling can work together to improve the diagnosis and treatment of neuropathic pain. First, the current paper reviews contemporary advances in deep learning for neuroimaging, particularly convolutional neural networks and U-Net architectures that have enabled automatic segmentation of the trigeminal nerve and paved the way for radiomic measurement of neurovascular compression. Such advances optimize the objectivity of surgery stratification and help to distinguish classical from idiopathic Trigeminal Neuralgia. In parallel, proteomic profiling of cerebrospinal fluid and plasma has revealed TN-specific molecular signatures, including upregulation of inflammatory, stress-related, and axonal damage markers that are different from those of similar disorders such as multiple sclerosis. Both markers not only have implications for disease pathobiology but also for identifying new therapeutic targets. The current study proposes a multimodal data integration platform combining imaging and molecular phenotypes using machine learning and multi-omics platforms. The integration permits mechanistic subtyping and predictive modeling of treatment response, with potential applications expanding to diabetic neuropathy and complex regional pain syndrome. Clinical deployment challenges, such as heterogeneity of data, ambiguity regarding regulation, and ethical risk, are addressed along with near-term solutions such as federated learning and interoperable biomarker registries. At the intersection of neurosurgery, radiology, and computational science, Trigeminal Neuralgia offers a scalable model for precision pain medicine, transforming care through mechanism-based classification and patient-stratified interventions.

Keywords: Trigeminal Neuralgia, Neuropathic Pain, Precision Medicine, Deep Learning, Biomarkers, Multimodal Integration

Introduction

Trigeminal neuralgia (TN) is a disabling, excruciating craniofacial pain syndrome that is an episodic, electric shock-like pain paroxysmally occurring in the distribution of one or more divisions of the trigeminal nerve (CN V)[1,2]. The pain is abrupt in onset and often precipitated by innocuous stimuli such as light touch, speaking, chewing, or even wind exposure[3,4]. Such characteristic triggering features are found in as many as 79% of cases, are an important diagnostic feature, and are most often located in the perioral and nasal regions, corresponding to the preferential involvement of the V2 (maxillary) and V3 (mandibular) divisions[5-7].

Spontaneous episodes of pain mayoccur but are less common. Pain is distributed into the weblike pattern of the areas of the skin elsewhere referred to as the dermatome (V1 [ophthalmic], V2 [maxillary], and V3 [mandibular]), with V2 and V3 being the most common presentations. Cases of V1-only involvement are uncommon (around 4%) and should prompt consideration of other diagnoses, including trigeminal autonomic cephalalgias[8-10]. Pain is usually unilateral, and the incidence of bilateral TN is low except for secondary causes such as multiple sclerosis. Around 50% of patients with TN experience background pain that is persistent, dull, or burning, interspersed with episodes of a band-like paroxysmal pain called TN with concomitant continuous pain[11,12]. This phenotype is more common in younger age groups and women, and it is characterized by greater therapeutic demand and reduced responsiveness to standard treatments[13-15]. However, such variability of clinical manifestations with both remitting and relapsing phases complicates the diagnostic process and calls for careful phenotyping.

Most patients with idiopathic or classical TN show no demonstrable deficit on neurological examination. Neurologic examination is characteristically normal, but minor sensory abnormalities (including mild cases of hypaesthesia or hyperaesthesia) may be present in 10-30% of cases[16]. The occurrence of severe or worsening sensory loss, however, might indicate secondary causes such as multiple sclerosis, neoplasms, and postherpetic neuropathy, leading to further diagnostic imaging and workup[17,18]. Magnetic resonance imaging (MRI) of the brainstem is the cornerstone of diagnostic investigation in TN, which allows clinicians to appreciate the neurovascular contact, generally observed between the transverse portion of the trigeminal nerve at the root entry zone and the superior cerebellar artery[19,20]. High-resolution sequences (3D T2, 3D T1 with gadolinium, time-of-flight angiography) are useful in confirming classical TN, defined by morphological changes of the nerve, including distortion or atrophy, in concordance with the clinical pattern observed[21,22].

Importantly, neurovascular contact does not always lead to the presentation of TN symptoms, as contact is also seen in asymptomatic subjects[23]. Therefore, the diagnosis is more confidently made when MRI findings and further imaging correspond to clinical laterality and pain distribution. Trigeminal reflex testing might offer ancillary diagnostic value when MRI is contraindicated or not available, particularly in differentiating TN from painful trigeminal neuropathy or demyelinating diseases. Yet, it is not specific enough to distinguish classical and idiopathic TN and should be reserved for atypical cases[24,25].

TN is characterized by overlapping symptomatology with other facial pain syndromes, including painful post-traumatic trigeminal neuropathy, glossopharyngeal neuralgia, persistent idiopathic facial pain, orofacial pain with dental or temporomandibular involvement[26]. Hence, a comprehensive clinical evaluation is crucial. Overdiagnosis of TN, especially in the setting of neurosurgery, may occur due to the over interpretation of imaging findings without sufficient clinical correlation[27,28]. This underscores the necessity of an extensive workup, which needs to include meticulous patient history, precise drawing of the sensory field on examination, and exclusion of dental pathologies.

Despite increasing awareness, TN still presents a diagnostic dilemma, particularly for dental and

primary care physicians. Insufficiently validated screening tools and many inappropriate online patient resources highlight the requirement for improved diagnostic algorithms and patient resources[29,30]. Early and accurate diagnosis is crucial since cases with both surgical and non-surgical indications vary dramatically according to the TN phenotype. Given that traditional clinical and radiological parameters are limited in terms of sensitivity and specificity, there is a developing interest in combining molecular biomarker research with advanced image acquisition techniques for improved diagnosis, prognostication, and treatment stratification of TN. New advances in nerve segmentation using deep learning machine learning techniques, together with cerebrospinal fluid and plasma-based proteomics, provide a roadmap for multimodal precision diagnostics[31-33]. Here we present TN as an exemplary use case, inviting further inspection of how artificial intelligence, high-resolution imaging, and molecular profiling might converge to address wider challenges of neuropathic pain syndromes.

Deep Learning in Neuropathic Pain Imaging: Current Landscape

Deep learning (DL) models have revolutionized the interpretation of medical images, notably in domains with the need for high-resolution anatomical precision, such as neuropathic pain syndromes. Methods based on convolutional neural networks (CNNs), U-Net architectures, as well as attention-based systems, have become essential for segmenting peripheral and central nervous system structures, detecting microstructural abnormalities, or extracting quantitative radiomic features that are related to the respective clinical phenotypes[32-36]. In the setting of TN, DL has held promise in automating the segmentation of the trigeminal nerve from high-resolution T2-weighted and diffusion tensor imaging (DTI) volumes in the past, which require extensive manual and time-consuming training tasks[32,35,36].

Over the last year, U-Net-based networks have been used for the delineation of the Root Entry Zone (REZ) of the trigeminal nerve and nearby vascular loops and volume calculation of the neurovascular contact and asymmetry metrics[34]. Such novel approaches may help in identifying objective biomarkers for the differential diagnosis of classical and idiopathic TN and of surgical indication. Besides TN, DL-based radiomics have also shown value in other neuropathic pain diseases. In sciatica, CNN-based classification models trained on lumbar MRI have been able to predict the compression of the nerve roots and the severity of the related pain[35.] Additionally, in the field of diabetic neuropathy, DL models fusing MRI and nerve conduction features have increased the diagnostic accuracy and risk stratification[37,38]. These findings highlight the promise of multimodal DL pipelines in capturing subtle structural and functional changes that may be missed by the human eye (Table 1).

However, various obstacles limit the extent of their clinical application. A significant limitation is the variability of imaging protocols within and across institutions, restricting the generalizability of the model. Small sample sizes and a lack of external validation are common problems, especially in rare diseases such as TN. Third, DL is not intuitively interpretable, which in turn reduces DL's potential for adoption into regulation and trust among clinicians[39].These challenges may be partially addressed by combining multi-center learning frameworks and explainable AI techniques. Insistence on multicenter harmonization of imaging protocols, substantial external validation cohorts, and prospective evaluation as part of clinical decision pathways will be needed before exhaustive deployment into the medical field.

Table 1. Deep Learning Applications in Neuropathic Pain Imaging. Table summarizes key insights demonstrating the role of DL models in imaging-based diagnosis and stratification of neuropathic pain conditions, along with clinical benefits and current limitations.

Neuropathic Pain Condition	Imaging Modality	DL Model Used	Clinical Value	Limitations
Trigeminal Neuralgia (TN)	High-res T2-weighted MRI, DTI	U-Net, CNNs	Automated segmentation of the trigeminal nerve; stratification of classical vs idiopathic TN	Small sample sizes, limited generalizability across centers, and interpretability concerns
Sciatica	Lumbar MRI	CNN-based classifiers	Prediction of nerve root compression and pain severity	Lack of standardization; model transferability issues
Diabetic Neuropathy	MRI + Nerve Conduction Studies	Fusion DL models (MRI + NCS)	Enhanced diagnostic accuracy and patient risk stratification	Integration challenges of multimodal inputs; need for large external datasets

DL = Deep Learning; MRI = Magnetic Resonance Imaging; DTI = Diffusion Tensor Imaging; CNN = Convolutional Neural Network; NCS = Nerve Conduction Studies.

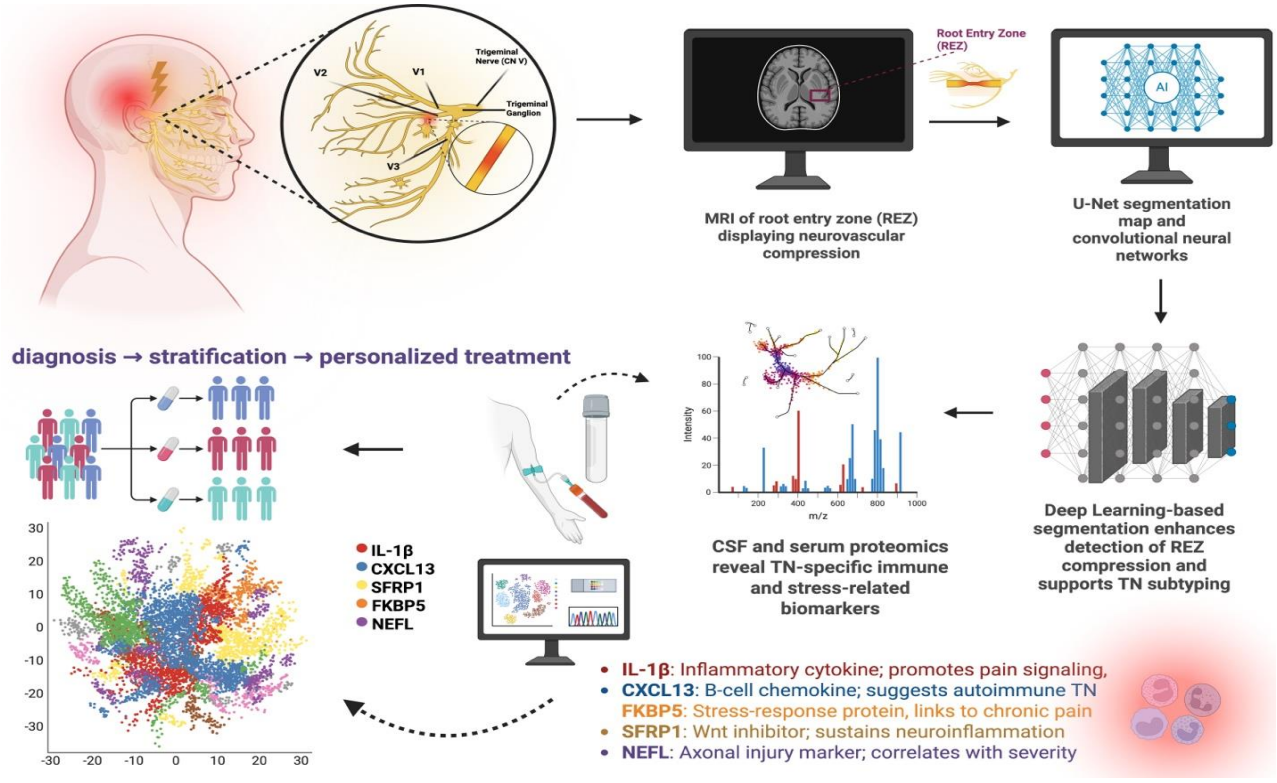
Molecular Biomarkers in Neuropathic Pain: Proteomics and Beyond

In tandem with imaging, molecular diagnostics for neuropathic pain have been progressing rapidly with the development of high-throughput proteomics, metabolomics, and transcriptomic technologies[40,41]. In TN, profiling of the proteome of cerebrospinal fluid (CSF) and serum has revealed different molecular signatures that distinguish TN from healthy controls and neuroinflammatory controls, such as individuals with multiple sclerosis (MS)[42]. A recent study from Lafta et al. used the proximity extension assay (PEA) technology to study 92 neurologically relevant proteins in TN, MS, and control individuals. Among the 19 TN patients analyzed, 15 exhibited upregulation of proteins linked to neuroinflammation (SFRP1), glucocorticoid signaling and stress induction (FKBP5), as well as cytoskeletal remodeling of cells (TBCB), reflecting mutual pathophysiologic factors involving immune activation, chronic stress, and axonal degeneration[42]. Interestingly, surgical treatment by microvascular decompression tended to normalize several of these protein levels, supporting their disease association rather than reflecting downstream effects of chronic pain behavior.

Furthermore, the very limited overlap of trigeminal neuralgia and multiple sclerosis proteomic signatures calls into question the conventional wisdom of common inflammatory etiologies, favoring the concept of biologic heterogeneity. In addition to TN, other neuropathic pain syndromes have shown proteomic and metabolomic abnormalities in both CSF and plasma. In complex regional pain syndrome (CRPS), there is increased pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and components of the complement cascade such as C3a, C5a, and C1q. In diabetic neuropathy, however, there is upregulation of the markers of oxidative stress (8-isoprostane, MDA), mitochondrial damage (cytochrome c, ATP synthase subunits), and deranged lipid metabolism (ceramides, acylcarnitines) [43-45].

These observations support a model in which distinct molecular cascades underlie divergent neuropathic pain phenotypes, ultimately converging on shared downstream effectors such as neuronal sensitization and glial activation. Therapeutic targets aligned with these mechanisms have been increasingly identified through molecular profiling and differential gene expression studies[46]. As an inhibitor of Wnt signaling and microglia–astrocyte crosstalk, SFRP1 may contribute to sustaining neuroinflammation in TN and might serve as a new therapeutic target[47]. FKBP5, previously associated with glucocorticoid resistance and stress-induced synaptic remodeling, has received much attention in both psychiatric and neurodegenerative disorders, and it may be similarly important, and under study, in chronic pain[48]. Furthermore, changes in inflammation-related molecules such as GRO-alpha and EGF have been shown to accompany symptom remission in late-life depression, further recapitulating the broader relevance of immune changes in treatment response across neurologic and neuropsychiatric conditions and neuropathic pain syndromes[49]. Such findings may be used to inform biomarker-based clinical trials, in which molecular genotyping guides the selection of patients, monitoring of response to treatment, and development of novel pain management therapeutics (Figure 1).

Figure 1. Precision Diagnostics in Trigeminal Neuralgia: Multimodal Integration of Imaging, Biomarkers, and Deep Learning. This figure illustrates a diagnostic pathway for accuracy in trigeminal neuralgia (TN) involving high-resolution imaging, deep learning analysis, and molecular biomarker profiling. Convolutional neural networks and U-Net segmentation improve automated REZ compression detection and support TN subtype classification. Simultaneously, proteomic analysis of cerebrospinal fluid and serum detects disease-specific biomarkers associated with neuroinflammation, stress signaling, and axonal injury. Machine learning integrates radiomic and molecular data to develop disease phenotypes that inform surgical candidacy and therapeutic response prediction. Figure created using BioRender.com.



Abbreviations – IL-1β: Interleukin-1 beta (inflammatory cytokine); CXCL13: C-X-C motif chemokine ligand 13 (B-cell chemokine); FKBP5: FK506-binding protein 5 (stress-response regulator); SFRP1: Secreted frizzled-related protein 1 (Wnt signaling inhibitor); NEFL: Neurofilament light chain (axonal damage marker); REZ: Root Entry Zone; CSF: Cerebrospinal Fluid; TN: Trigeminal Neuralgia; AI: Artificial Intelligence.

Integrating Imaging and Molecular Biomarkers: Toward Precision Neuropathic Pain Care

The whole picture of neuropathic pain demands an integration of structural, functional, and molecular dimensions. High-resolution imaging techniques, such as diffusion tensor imaging (DTI), magnetic resonance neurography (MRN), and high-resolution 3D MRI, enable the characterization of trigeminal nerve compression, demyelination, and central white matter changes[26]. Concurrently, proteomic and transcriptomic studies have identified molecular derangements in the neurovascular interface of TN patients undergoing microvascular decompression (MVD), such as upregulation of axonal injury markers (NEFL), endothelial signaling proteins (vWF, ICAM1), and inflammatory mediators such as CXCL13 and IL-1β[50].

This multimodal approach allows for the generation of disease phenotypes that link radiographic abnormalities with molecular states (Table 2). For instance, a patient with loss of DTI-derived fractional anisotropy in the trigeminal nerve root entry zone with an increase in markers of axonal degeneration in CSF or peripheral blood would be a mechanistic subtype that would be optimally treated by decompressive rather than ablative procedures, such as microvascular decompressions (MVD) through retrosigmoid craniotomy[51].

Table 2. Key Molecular Biomarkers in Trigeminal Neuralgia. Biomarkers were selected based on their relevance to neuroinflammation, immune dysregulation, stress signaling, and axonal injury in trigeminal neuralgia. These candidates may support subtype stratification and guide biomarker-informed treatment strategies.

Biomarker	Pathophysiologic Role	Clinical Implications
IL-1β	Pro-inflammatory cytokine; contributes to glial activation	Potential marker of inflammatory subtype; candidate for immunomodulatory treatment
CXCL13	B cell chemokine; involved in meningeal inflammation	Suggests autoimmune-like features; differentiator from idiopathic TN
FKBP5	Stress response mediator; linked to glucocorticoid signaling	May serve as a stress-related biomarker; possible psychiatric overlap
SFRP1	Wnt pathway inhibitor; modulates microglial/astrocyte interactions	Therapeutic target for sustaining neuroinflammation
TBCB	Cytoskeletal regulation; implicated in axonal degeneration	Supports the axonal degeneration mechanism in TN
NEFL	Marker of axonal injury; reflects white matter damage	Predictor of surgical response; correlates with imaging changes

IL-1β = Interleukin-1 beta; CXCL13 = C-X-C motif chemokine ligand 13; FKBP5 = FK506-binding protein 5; SFRP1 = Secreted frizzled-related protein 1; TBCB = Tubulin-folding cofactor B; NEFL = Neurofilament light chain.

Findings in TN may be generalizable to other neuropathic pain syndromes, such as diabetic peripheral neuropathy and complex regional pain syndrome (CRPS), that share molecular signatures, such as axonal degeneration, neuroinflammation, and aberrant glial signaling[43,44,52]. Radiomic features from high-resolution MR neurography or spinal imaging may unmask conserved structural patterns (such as dorsal root ganglia hypertrophy, white matter tract reorganization) among them. Moreover, proteomic markers identified in TN, such as S100B, PRDX1, and GFAP, may be universal biomarkers of neuropathic pain severity and therapeutic response[50]. Hence, the application of integrative machine learning methods to these datasets allows for elucidation of common pathogenic mechanisms, prediction of therapeutic response, and the development of unified biomarker panels for application across a spectrum of pain etiologies.

Graph-based and deep learning artificial intelligence (AI) models enable the integration of heterogeneous datasets spanning imaging, proteomics, genomics, and clinical variables. Autoencoders, CNNs, and attention-based transformers represent some of the models that can learn complex interactions between radiomic and molecular features, ending in exact stratification of patient subtypes[53-55]. Multi-omics platforms also strengthen such models by adding transcriptomic, proteomic, and epigenomic data layers, resulting in unprecedented granularity in the description of neuropathic pain biology[56]. In TN, for example, the fusion of pre-operative MRI radiomics and label-free quantification (LFQ) proteomics of CSF or blood samples was able to predict MVD responders from non-responders[50]. Such models can also be used to guide treatment in CRPS or diabetic neuropathy by identifying those patients most likely to respond to immune-modulating therapies or neuromodulation.

Clinical Translation: Challenges and Opportunities

Despite the potential of multimodal data fusion, clinical translation is held back by formidable barriers. These include a lack of standardization across imaging modalities, limited interoperability of electronic health records, batch effects of proteomic assays, and a shortage of validated thresholds for interpretation of radiomic or molecular biomarkers. Uncertainty regarding the regulation of AI-based diagnostic devices also prevents full implementation of such techqiques[57].

To address these issues, federated learning is a potential solution. This distributed machine learning framework allows institutions to collaboratively train models across locally retained data without sharing sensitive patient information[58,59]. Such strategies are particularly relevant in neuropathic pain research, in which cohort sizes at an individual center are generally small and heterogeneous. Federated learning can aid model generalizability while preserving privacy and embracing institutional variability in imaging and proteomic protocols. As AI and biomarker-guided decision tools become more widely adopted in clinical practice, it is essential to address ethical concerns in advance. Such concerns encompass potential algorithmic prejudice, underrepresentation of minority groups in training datasets, and low-specificity biomarker signatures leading to medical overdiagnosis. Clear model explainability and oversight frameworks are critical to the fair deployment of such technologies[57,60,61].

A sequential approach to using these tools in the clinic could be: (1) establishing the validity of combined imaging and molecular markers in real patients; (2) using these markers to guide treatment choices such as MVD surgery vs. radiation for trigeminal neuralgia, or immunotherapy vs. nerve ablation for complex regional pain syndrome; and (3) building shared databases that integrate imaging, laboratory results, and outcomes. This strategy could begin with patients who have severe, treatment-resistant, and medication-refractory neuropathic pain, where no alternative managements currently exist.

Future Directions in Neuropathic Pain Research

Achieving precision in pain medicine will require next-generation, large-scale trials that integrate imaging, proteomics, single-cell transcriptomics, and clinical outcomes across diverse patient cohorts. Improved single-cell proteomics and spatial transcriptomics will enable cell-type–specific mapping of neuropathic pain drivers in pain-affected nerves, DRG, and spinal cord segments[62]. Concurrently, radiogenomic models that link genotype, molecular phenotype, and imaging biomarkers are poised to enhance subtype-specific diagnosis and guide individualized treatment. Within TN specifically, they may elucidate unresolved biological heterogeneity, such as why some patients manifest exclusively paroxysmal pain and others develop continuous pain, or why just a proportion of patients respond therapeutically in a stable fashion to surgical decompression. Radiogenomic frameworks incorporating MRI-derived neurovascular contact patterns with transcriptomic and proteomic data could potentially delineate mechanistic TN subtypes to inform patient-stratified therapy.

More broadly, these radiogenomic approaches will be capable of enhancing subtype-specific diagnosis across neuropathic pain syndromes and identifying predictive biomarkers of treatment response[62,63]. Large-scale initiatives such as NIH's Bridge2AI and Pain Consortium[64] or the European IMI-PainCare platform[65] can form the foundation for data-sharing consortia, model training, and cross-validation across diverse institutions. Open-source, privacy-preserving repositories will be necessary to allow for equitable global participation and ensure TN and other focal neuropathic syndromes are represented.

Conclusion

The integration of high-resolution imaging with molecular and proteomic biomarkers offers an unprecedented chance to transform the treatment of neuropathic pain patients. By bridging molecular phenotypes to structural change, clinicians can move beyond symptom-based diagnosis to mechanism-based precision medicine. Instantiation of such precision-based prognostication of neuropathic pain can only be achieved through a combined team effort of neurology, neurosurgery, radiology, bioinformatics, and ethics in defining, validating, and implementing multimodal approaches for guiding diagnosis, predicting treatment effects, and personalizing care trajectories. By integrating high-level machine learning, inter-professional collaboration, and standardization of diagnostic data (e.g., MRI sequences), the practice of neuropathic pain medicine can provide substantial improvements in diagnostic precision, therapeutic efficacy, and long-term patient outcomes, with the hope of ultimately setting a new standard for personalized neurological care.

Conflict of Interest Disclosure:

No pertinent conflicts of interest relevant to this manuscript.

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