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Tracing The Evolution Of Neuropathic Pain Markers: A Journey From Past Discoveries To Emerging Innovations And Future Directions

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Abstract
Pain research has significantly advanced over the past fifty years, yet identifying definitive biomarkers for chronic pain remains a challenge. The gap between basic and applied research persists due to the lack of rigorous standards for selecting candidate biomarkers and the subjective nature of validation processes. For biomarkers to develop effectively, especially for chronic pain, it is crucial to understand the molecular and genetic similarities between psychological disorders and chronic pain. This understanding may shift therapeutic interventions from peripheral to central nervous system targets, emphasizing broader neural network changes over specific genotypes. A comprehensive grasp of the complex interactions leading to chronic pain is essential for personalized and effective treatments. This involves not only identifying and validating biomarkers but also understanding their interactions with biological and environmental factors. Technological advancements like artificial intelligence and machine learning can help identify patterns in large datasets, leading to new biomarker discoveries. By integrating data from genomics, proteomics, metabolomics, and neuroimaging, researchers can gain a deeper understanding of chronic pain mechanisms and identify new intervention targets. Despite these advancements, the development and validation of biomarkers is a complex process requiring collaboration across multiple disciplines. This multidisciplinary effort is necessary to bridge the gap between basic science and clinical practice, ultimately improving chronic pain management. The focus of biomarker research is shifting from disease-specific studies to identifying common pain mechanisms. Advances in understanding nociceptive transmission, inflammation, and neuropathic pain have opened new strategies for discovering and validating biomarkers and identifying drug targets. Systems biology and bioinformatics, which integrate large-scale molecular data and personal information through quantitative models, are proving effective in understanding nervous system development and function. In silico modeling can predict clinical phenomena, enhancing early clinical study design, safety, and biomarker studies. Emphasizing advanced systems and longitudinal, multi-omics single-cell analysis from preclinical to clinical stages is crucial for future success.

Keywords: Biomarkers, Neuropathic Pain, Bioinformatics, Clinical trial, Drug discovery

1. INTRODUCTION

The high expenses associated with introducing new pharmaceuticals to the market pose a significant challenge in the healthcare industry, potentially causing non-pharmaceutical treatments to become prohibitively expensive in specific sectors. This underscores the importance of highlighting the benefits of surrogate markers in assessing treatment outcomes. The QuanTI Alliance (aQa), funded by the Innovative Medicines Initiative (IMI), was established to address this issue by identifying biomarkers or indicators that reveal how patients react to treatment (1,2). This collaborative effort brings together pharmaceutical companies, academic research partners, and various academic biotechnology organizations, both high-risk and low-risk, to enhance our understanding of the underlying mechanisms of neuropathic pain. While the consortium provides valuable data from clinical trials, its main objective is to conduct clinical investigations in human subjects and relevant preclinical studies to identify potential biomarkers for neuropathic pain conditions conditions in human patients and facilitate the development of personalized treatment approaches. QuanTI Alliance aims to revolutionize the way treatment outcomes are evaluated and ultimately improve patient care (3).

Neuropathic pain (NP) is characterized by symptoms such as heightened sensitivity to touch and pain evoked by stimuli that are not typically painful (4,5). These symptoms often coexist with comorbidities such as anxiety, depression, and disturbances in sleep patterns, posing challenges in treatment due to the multifaceted nature of the underlying causes. The pathophysiology of this burgeoning public health concern can vary depending on the etiology and site of neural injury.

The intricate nature of these causative factors is further evidenced by the expanding array of recognized sources of symptoms, necessitating a thorough clinical evaluation involving a comprehensive review of medical history, somatosensory assessments, and findings from physical examinations. Despite the acknowledgment of numerous clinical and genetic predisposing factors, achieving precision medicine in the diagnosis and management of NP remains a formidable task (6,7).

1.1. Definition of Neuropathic Pain

Central changes may be involved in the development of the inherent hypersensitivity seen in neuropathic pain and the increase in communication or central output from synapses in the presence of non-noxious stimuli. One suggested anecdote is that allodynia would require the input of surrounding non-injured peptidergic primary afferents, which synapse in close proximity to the injured primary afferent where the synapses are enlarged and require fewer stimuli to illicit an action potential in the second order neuron (8,9). Treatment of incisional injury is able to reverse these central changes more easily than a nerve injury. The second part of the definition involves the clinical characterization of the pain. Neuropathic pain is often highly noxious to touch and can elicit an increased response to stimuli (hyperalgesia). The referred pain to normal tissue, which drives the dynamic mechanical allodynia seen in neuropathic pain, can also be exhibited to normally non-noxious stimuli as an allodynia to gentle tactile stimulation when touch is very unpleasant (10,11). Studies have shown that the complex interplay of neurotransmitters and receptors within the central nervous system plays a crucial role in the development and maintenance of neuropathic pain. Additionally, changes in gene expression, particularly in the dorsal root ganglia and spinal cord, have been implicated in the pathogenesis of this chronic pain condition. Furthermore, the phenomenon of wind-up, where repeated stimulation of C-fibers leads to enhanced responses in spinal cord neurons, contributes to the amplification of pain signals in neuropathic pain states. (12,13,14). Moreover, imaging studies have revealed alterations in brain activity and connectivity in individuals suffering from neuropathic pain, suggesting maladaptive plasticity within the central nervous system. These changes may underlie the persistent nature of neuropathic pain and the difficulty in achieving adequate pain relief with traditional analgesics. It is essential for healthcare providers to consider these central mechanisms when designing treatment strategies for patients with neuropathic pain to effectively manage their symptoms and improve their quality of life (15,16).

Neuropathic pain is a type of pain that has a broad definition, often described as any pain that is initiated or caused by a lesion or dysfunction in the somatosensory system. This type of pain is characterized by abnormal activity in the nervous system (17,18). Neuropathic pain can be further categorized into peripheral and central mechanisms. Conditions such as nerve injury and certain diseases like diabetes, AIDS, and postherpetic neuralgia can result in the loss of axon conduction, leading to subsequent functional and architectural changes in the nervous system (19,20,21). This can cause neuronal hyperexcitability, resulting in abnormal input to both the spinal cord and the central nervous system (CNS), which can then lead to rewiring of the CNS and the development of a pain phenotype. Peripheral mechanisms of neuropathic pain often focus on changes in gene and protein expression within neurons, as well as the potential involvement of glial cells in the development of pain. These changes are crucial in understanding and managing neuropathic pain. Neuropathic pain can be challenging to treat, as it often does not respond well to traditional pain management techniques. Patients with neuropathic pain may experience a range of symptoms, including shooting or burning pain, tingling, numbness, and sensitivity to touch. Treatment for neuropathic pain typically involves a multidisciplinary approach, combining medications, physical therapy, psychological support, and other interventions to help manage symptoms and improve quality of life. It is important for healthcare providers to have a thorough understanding of neuropathic pain and to work closely with patients to develop individualized treatment plans that address their specific needs and goals (22,23).

1.2. Importance of Biomarkers in Pain Management

The utilization of biomedical instruments for pain management has experienced a rapid increase in acknowledgment. Numerous factors such as gene-related criteria, neuroimaging, and physiological and protein measurements are currently being explored as biomarkers in both clinical settings and laboratory experiments focusing on pain. The examination of gene polymorphisms has uncovered substantial changes in gene-related criteria, particularly in μ-opioid receptors, within pain models. Neuroimaging methods, which encompass positron emission tomography, magnetoencephalography, event-related potentials, and functional magnetic resonance imaging, are now being employed to recognize, comprehend, and evaluate surgical procedures that have the potential to act as biomarkers in a wide array of diagnostic assessments (24,25,26,27). The presence of biomarkers in organs or body fluids is extremely valuable in the field of diagnosis, offering crucial insights into various diseases during their early stages, even when the pathology is undetectable. In the realm of clinical diagnosis, early detection plays a pivotal role in preventing and treating illnesses, as well as assessing one's health status before symptoms manifest. Managing pain effectively is a top priority when it comes to developing new medications and treatment modalities. The conventional methods of self-reporting and observation fall short in adequately monitoring pain, prompting the need for more sophisticated approaches. Consequently, pain assessment is currently limited to controlled laboratory settings. Biomarkers hold promise in addressing these challenges by enabling objective and dependable pain detection methods (28,29,30). Biomarkers have opened up new avenues for improving the accuracy and efficiency of pain management strategies. They provide a more precise and comprehensive understanding of the physiological and molecular mechanisms underlying pain perception, leading to tailored treatment regimens that target the root causes of pain. By identifying specific biomarkers associated with different types of pain, healthcare professionals

can personalize pain management interventions to optimize patient outcomes. Additionally, biomarker-based pain assessment tools offer a non-invasive and objective means of evaluating pain intensity and chronicity, facilitating more timely interventions and adjustments to treatment plans (28,30,31). Incorporating biomarker analysis into routine clinical practice has the potential to revolutionize pain management by enhancing diagnostic capabilities and treatment outcomes. These innovative approaches hold great promise for improving patient care and quality of life by enabling healthcare providers to make more informed decisions regarding pain management strategies. Moreover, the integration of biomarker-based pain assessment tools into telemedicine and remote monitoring platforms can extend the reach of pain management services to underserved populations, ensuring equitable access to high-quality care. As research in the field of biomarkers continues to advance, the future of pain management looks increasingly promising with the integration of personalized and data-driven approaches to alleviate suffering and enhance overall well-being (32,33).

2. HISTORICAL PERSPECTIVES

The utilization of objective neuropathic pain measures, apart from behavioral changes or self-report, is not a recent development. Back in 1983, Singh and colleagues conducted a comprehensive analysis of the existing literature and developed a roster of potential pain biomarkers that could be leveraged to streamline clinical trials in pain research (34,35). Their compilation encompassed neurophysiological indicators (such as thresholds for inducing withdrawal or escape response), neurochemical markers (highlighting fluctuations in cerebrospinal fluid levels of neurotransmitters), neuroendocrine markers (focused on adrenal medullary hormones and hypothalamus-pituitary hormones), as well as neuroanatomical markers (noting a decrease in the number of dorsal horn neurones or their synaptic connections). Following this, there was a shift towards evaluating estimates of brainstem nociceptive responses in liver transplant recipients who were administered fentanyl. The abnormalities observed in the auditory brainstem response or other sensory-evoked potentials were attributed, at least partially, to the fentanyl treatment. Further investigations by Restrepo and team included assessments of cold sensation thresholds, with recent findings indicating that the alterations were linked to the doses of fentanyl or its pharmacokinetic properties (36).

In recent years, there have been significant advancements in our understanding of neuropathic pain, spanning from the basic mechanisms to the discovery and development of novel treatments for this debilitating condition. Despite the progress made, managing neuropathic pain remains a complex task. Current treatment strategies rely on indirect assessments of changes in spontaneous pain, often requiring extensive and expensive clinical trials. There is a pressing need for an objective measure of neuropathic pain to reduce reliance on subjective reports, aid in patient selection, and potentially predict their response to emerging pain therapies in both clinical trials and routine medical practice. Various potential measures are under consideration in this regard. The aim of our study was to provide readers with an up-to-date compilation of neuropathic pain biomarkers. (37,38).

2.1. Early Research on Neuropathic Pain

The cellular theory of pain suggests that drugs do not have the ability to affect the transmission of swift sensations in the body. Examples of such swift sensations include pinpricks that travel quickly to the spinal cord, causing reflex movements, blood vessels to dilate, and the production, release, and alteration of sensitizing chemicals. These chemicals are typically found in areas that produce slow and long-lasting sensations, such as those felt in response to burns. On the other hand, the humoral theory proposes that the accumulation of acidic and lactic substances in muscle fibers, due to prolonged use, significantly lowers the threshold of nociceptors (39,40,41,42). This lowered threshold is particularly noticeable when compared to the nociceptors found in joints, muscles, and bones that are sensitive to stimuli. According to the humoral theory, these substances attach to the nerve endings of type Ad fibers, making them more excitable and causing them to generate a greater number of action potentials. This prolonged activation of pain signals leads to a more severe and disabling experience of pain (43).

Discussions of neuropathic pain are present in many historical medical texts and have been well described in the descriptions of diseases including leprosy and diabetes. Detailed descriptions of neuropathic pain and symptoms now recognized as shared by many individuals with diseases such as postherpetic neuralgia, carpal tunnel syndrome, and mononeuritis showcase the deep understanding of the nature of neuropathic pain present as early as 30 A.D. Despite these detailed descriptions of the clinical nature of neuropathic pain and diseases leading to its occurrence, systemic investigations to understand the nature and definition of pain in general did not begin until the 20th Century with the concept of acute and chronic pain (44,45). The concept of acute and chronic pain has led to significant advances in the field of pain management, with a greater appreciation of the complex interactions between the nervous system and various disease processes. This has paved the way for the development of targeted treatments for neuropathic pain, including medications that specifically target nerve pain pathways and techniques such as nerve blocks and spinal cord stimulation (46). In addition to pharmacological and interventional approaches, there has been a growing recognition of the importance of multidisciplinary care in the management of neuropathic pain. This includes the involvement of various healthcare professionals such as pain specialists, physical therapists, psychologists, and social workers to address the physical, psychological, and social aspects of living with chronic pain. Furthermore, research in the field of neuropathic pain has expanded to include the study of neuroplasticity, which refers to the brain's ability to reorganize itself in response to injury or disease. This has led to the development of novel therapeutic approaches such as cognitive-behavioral therapy and mindfulness-based stress reduction, which aim to harness the brain's ability to adapt and change in the presence of

chronic pain (47,22). Overall, the ongoing evolution of our understanding of neuropathic pain continues to drive progress in the field of pain management, offering new hope and improved quality of life for individuals living with chronic pain conditions.

2.2. Evolution of Biomarker Discovery

Conventional pain evaluations that rely on patients self-reporting their pain levels verbally are not suitable for young children, individuals who cannot communicate verbally, or those who may not accurately report their pain. Therefore, researchers studying pediatric clinical pain have been working on developing measures that can be used in these challenging cases. Biomarkers, which are measurable characteristics indicating the functioning of biological systems, states, and processes, offer a potential solution to overcoming the reliance on self-reporting. The use of biomarkers in assessing acute pain in children and non-human animal models is gaining interest. Given the increasing focus on pediatric pain and the need for objective measures in cases where self-reporting is difficult, we have summarized existing research on pain biomarkers in pediatric populations. Our goal is to identify potential connections to other areas and suggest directions for future studies on biomarkers in pediatric clinical populations. Finding reliable ways to quantify and evaluate pain in pediatric patients is essential for providing optimal care, as children may struggle to communicate their pain accurately. Developing and exploring biomarkers specifically for pediatric populations can enhance our understanding of pediatric pain and improve the quality of care for young patients. It is vital to continue exploring new methods and approaches to pain assessment in children to ensure that all patients receive the necessary care and support during times of pain and discomfort (30,48). There are a variety of approaches that researchers have used to develop and validate neuropathic pain biomarkers. There are emerging analytes that can be candidates, but no single measure is likely to be sufficient to assess an individual patient. Combinations of measures or panels are being explored. Many of the potential biomarkers identified to date are not pain-specific, nor even disease-specific. We hope that as the number of well-defined objective pain evaluations increases that specificity and efficacy will improve. The use of multiple evaluations is another potential strategy to improve specificity (49,50).

2.3. Key Milestones in Pain Biomarker Research

The advancement of pain biomarkers, historically delineated by opioid-induced thermal hypoalgesia in the tail-flick test, has unfolded into a realm of more intricate assessments spanning various species. This progression culminated in the establishment of refined rodent models and comprehensive neuropharmacologic analyses carried out by multiple experimental cohorts. This collective endeavor in opiate testing has etched a significant milestone in the scientific domain, underscoring the efficacy of employing biomarkers to steer the selection process for potential analgesic medications and facilitating the identification of promising candidates for pain alleviation in the nascent phases of pharmaceutical studies (51,52). The adoption of these validated testing methodologies has significantly influenced the operational paradigms of pharmaceutical enterprises and regulatory bodies like the FDA in the screening of potential pain-relieving remedies, thereby diminishing the dependence on animal experimentation and invasive measures. Over the past thirty years since the inception of thermal analgesiometry, the tail-flick test has been subject to exhaustive assessment and authentication, focusing on critical facets such as intrathecal catheterization techniques, testing regimen, and experimental consistency. This relentless refining and collaborative undertakings have bolstered the dependability and reproducibility of the test, firmly establishing it as an indispensable instrument in appraising pain responses and formulating novel analgesic interventions (53).

3. CURRENT DEVELOPMENTS

Turning away briefly from the common physical causes of neuropathic pain, a recent study has highlighted a growing body of evidence suggesting that chronic neuropathic pain may not only be linked to specific damage in the somatosensory system, but also to variations in genomics and other biological markers among individuals experiencing similar levels of pain. These findings suggest that certain genetic factors may play a significant role in the development of neuropathic pain, impacting mechanisms related to both Inflammatory Pain Loss and nerve injury at peripheral and central levels. Therefore, an individual's genetic makeup could actively contribute to, or react to, the pathophysiology of neuropathic pain (54,55). Moreover, recent research indicates that the interplay between an individual's genetics and environmental influences can significantly influence the development of neuropathic pain. Certain genetic predispositions may increase susceptibility to chronic pain, while others may provide resilience. This complex interaction underscores the importance of personalized medicine in treating neuropathic pain. Additionally, advances in genomics have allowed researchers to pinpoint specific genetic markers associated with neuropathic pain. By comprehending these genetic variations, healthcare professionals can tailor treatment strategies to target the root causes of pain at a molecular level. This personalized approach to managing neuropathic pain shows promise in enhancing the quality of life for individuals grappling with this challenging condition (56). To conclude, while the traditional physical origins of neuropathic pain remain significant, the emerging evidence surrounding the impact of genetics on pain mechanisms offers valuable insights that could transform the diagnosis and treatment of chronic pain conditions. By delving into the intricate relationship between genetics, environment, and pain perception, researchers are laying the groundwork for more effective and personalized interventions for individuals living with neuropathic pain.

The search for neuropathic pain markers, initiated in order to facilitate the early diagnosis and start effective treatment before irreversible pathological changes, also concerns a wide spectrum of analgesic drugs and genetic/pharmacogenetic backgrounds, because patients need to be assessed to monitor effectiveness of the administered drug. However, the complexity of the described sensations is reflected in the complexity of the search for appropriate markers that allow the identification of distinct neuropathic categories. According to the currently known Canadian Pain Society (CPS) and neuropathic pain special interest group of the International Association for the Study of Pain (NeuPSIG) neuropathic pain diagnosis criteria, the term neuropathic is to be used only if the specific lesions or diseases of the somatosensory nervous system are known and the diagnosis is confirmed. However, numerous patients are testing positive on the neuropathic pain screening questionnaires, although no structural lesions or diseases, or peripheral nerve immune responses/infections which would be accountable for the appearance of NP symptoms, have not been identified. This points to a bright future of established neuropathic pain diagnosis categories. However, it is also indicative of the numerous unclassified pain syndromes (57,37,58). Expanding the search for neuropathic pain markers not only aids in the early diagnosis and initiation of effective treatment, but also delves into a broad range of analgesic medications and genetic/pharmacogenetic factors. Patient evaluation is essential to monitor the efficacy of prescribed medications. Nevertheless, the intricate nature of the symptoms described correlates with the intricacy of the quest for appropriate markers that can pinpoint specific neuropathic categories. As per the existing diagnostic criteria by the Canadian Pain Society (CPS) and the neuropathic pain special interest group of the International Association for the Study of Pain (NeuPSIG), the term "neuropathic" should only be utilized if there are identifiable lesions or diseases within the somatosensory nervous system and the diagnosis has been verified (59,60) . Nonetheless, a considerable number of patients exhibit positive results on neuropathic pain screening questionnaires despite the absence of structural lesions, diseases, or immune responses/infections along the peripheral nerves that could explain the emergence of neuropathic pain symptoms. This underscores a promising outlook for established neuropathic pain diagnosis categories but also sheds light on the presence of various uncategorized pain syndromes.

3.1. Advances in Biomarker Identification

Within the realm of cutting-edge technologies, there are specific advancements that show significant promise in identifying new biomarkers associated with NP and other pain-related conditions. For instance, a recent study conducted by the Cancer Genome Atlas Research Network and published in the prestigious journal Nature revealed a range of groundbreaking discoveries. One notable finding was the presence of H3F3A mutations in up to 43% of giant cell tumors of bone, a painful neoplasm commonly found in the extremities of long bones in young individuals. Furthermore, researchers identified somatic mutations linked to the twelfth codon of H3F3A in severe cases. These findings were deemed significant and deserving of publication in a renowned scientific journal, laying a strong foundation for further research and the development of new mechanistic insights (61,62).

The recent years have seen impressive developments in the field of genomics, proteomics, metabolomics, lipidomics, and other related areas. Advancements in technology and the widespread use of analytical platforms have greatly contributed to the exploration and validation of biomarkers. Researchers now have access to sophisticated tools that allow them to analyze a multitude of molecular components within complex biological systems simultaneously. While genomic studies often focus on individual genes or gene products, some investigations involve the study of entire genomes or specific subsets that encompass all genes within the genome. Proteomics primarily targets proteins or peptides, but methods like glycoproteomics or phosphoproteomics have also been developed. The global profiling of metabolites, lipids, and other small molecules has become an essential part of research in these fields.

3.2. Technologies for Biomarker Detection

The development of methods for the detection of neurotransmitters in the brain has been a top priority in the field of analytical chemistry in recent years. Historically, a major obstacle has been to determine fluctuations of brain chemicals on a time scale relevant for understanding their signaling function and other complex central nervous system processes. However, in recent years, there has been an enhancement of spatial and temporal resolution in imaging and scanning methods, including emerging advancements continuously. In the field of fMRI and single-photon emission computed tomography imaging approaches have been applied to address this issue. Additionally, there is a vast and diverse array of instruments available for the dynamic monitoring of neurotransmitter levels in their complex cellular microenvironment. Recent research utilizing these tools has illuminated significant new insights into the events immediately following the synaptic release of neurotransmitter candidates and the volume transmission of those substances. This groundbreaking research has opened up new possibilities for the treatment of neurological disorders, paving the way for innovative therapies that target specific neurotransmitter systems in the brain (63,64).

Opportunities in the field of nanotechnologies for neuroimaging and neurotransmitter sampling are vast. The development of highly sensitive magnetoresistive, optochemical, and chemical sensors specifically designed for detecting dopamine, glutamate, and other vital neurotransmitters in the brain represents a significant advancement. These sensors have the potential to revolutionize routine diagnosis and management of patients. In recent studies, microdialysis has been utilized for sampling cytokines in the rat brain, achieving impressive electroosmotic pump clearances of up to 84%. This highlights the potential for reliable in situ detection of cytokines using miniaturized micro ion-selective membrane sensors. Notably, histological analysis of the microdialysis probe tip area revealed no adverse effects on neuronal tissue

or the blood-brain barrier, indicating the excellent biocompatibility of the microdialysis system being used. These findings are crucial in advancing our understanding and application of nanotechnologies in neurology and brain-related medical fields. The integration of nanotechnologies offers a promising avenue for developing cutting-edge tools and techniques to enhance the precision and efficacy of neuroimaging and neurotransmitter sampling. By leveraging the unique properties of nanomaterials, researchers can create sensors that are smaller, more sensitive, and capable of detecting minute changes in neurotransmitter levels with high accuracy (65,66). Furthermore, the use of nanotechnologies enables the development of non-invasive or minimally invasive methods for neuroimaging and neurotransmitter sampling, reducing potential risks and improving patient comfort. This opens up new possibilities for continuous monitoring of neurotransmitter dynamics in real-time, providing valuable insights into brain function and neurological disorders. Overall, the synergy between nanotechnologies and neuroimaging holds great promise for advancing our understanding of the brain and improving the diagnosis and treatment of neurological conditions. As research in this field progresses, we can expect to see groundbreaking innovations that will transform the landscape of neurology and bring about new opportunities for enhancing human health and well-being through nanotechnology.

3.3. Challenges in Biomarker Validation

In validation studies, addressing the limitations of patient cohort heterogeneity and potential factors impacting protein targets (such as age, BMI, and gender) is crucial. These variables can significantly affect result accuracy and reproducibility. Challenges may also arise from sample scarcity, varying collection procedures, storage, processing methods, and ethical concerns, hindering marker validation (67,68). The methodology for sample preparation is pivotal for maximizing protein coverage and ensuring reproducibility in comprehensive proteome analysis, particularly in shotgun MS-based analysis. Mass spectrometric quantitation accuracy is directly linked to protein quantity loaded and can be improved by collecting more peptides (or MS/MS events). Due to the complexity of the biological matrix being studied (neuropathic samples), a multiple fractionation strategy, usually involving multidimensional chromatography, can be utilized. This method includes steps like initial peptide separation to reduce sample complexity, further fractionation, chromatographic peptide separation before MS acquisition. Implementing these strategies can enhance the depth and precision of proteomic analyses when investigating neuropathic conditions (69,70). The methodology used for sample preparation plays a critical role in maximizing protein coverage and ensuring reproducibility in comprehensive proteome analysis, especially in the context of shotgun MS-based analysis. The accuracy of mass spectrometric quantitation is directly linked to the quantity of loaded protein and can be enhanced by increasing the number of peptides (or MS/MS events) collected. Given the complexity of the biological matrix under study (neuropathic samples), a multiple fractionation strategy can be employed, typically involving multidimensional chromatography. This approach includes steps such as separating peptides in the first dimension to reduce sample complexity, followed by further fractionation and chromatographic separation of peptides before MS acquisition. By employing such strategies, researchers can improve the depth and accuracy of their proteomic analyses in the investigation of neuropathic conditions.

Despite the potential value of biomarkers in the diagnosis and successful treatment of patients with NP, a major challenge is the validation of such markers. Although some guidelines have been put in place to support the use of molecular diagnostics, they do not usually offer an exhaustive list of markers that should be assessed in a specific clinical disease; algorithms for the best combination of markers are also missing or, when generated, fail to be reproduced in large cohorts. One of the major drawbacks of biomarker selection in clinical practice is the use of a limited approach, for instance, a candidate marker approach, and screening for a limited number of markers, when the biological hypothesis could foster a broader overview of potential markers in a larger cohort of subjects, leading to the discovery of the best combination of markers that act as the highest sensitivity and specificity hallmarks for the specific cohort. This results in the use of expensive technologies, such as mass spectrometry, to find proteins or the inadequate use of patients' data due to poor and non-overlapping results. Despite the fact that many efforts have been put into characterizing potential biomarkers for NP, the current number of successful candidates is limited by the lack of combinations to achieve sensitivity and specificity. In order to overcome these challenges, it is crucial for researchers to explore a wider range of potential markers and utilize advanced technologies to analyze them comprehensively. By incorporating a more holistic approach to biomarker selection, clinicians can enhance their ability to accurately diagnose and treat patients with NP effectively. Furthermore, collaborative efforts among researchers and healthcare providers are essential to establish standardized protocols for biomarker validation and implementation in clinical practice. By addressing these issues proactively, the field of biomarker research for NP can make significant strides towards improving patient outcomes and enhancing overall healthcare delivery.

3.4. Biomarker Panels for Neuropathic Pain

These types of biomarker panel approaches are starting to emerge in the field of pain research but unfortunately are still rare for neuropathic pain. The first study that could provide evidence for a possible future blood or other peripheral biosignature comes from a study within chemotherapy-induced peripheral neuropathy patients, where the authors report that "chemotherapy + chemotherapy-induced peripheral neuropathy patients showed upregulation of genes related to macrophage regulation of neuropathic pain, cytokine-cytokine receptor interaction and the neurotrophin-TrK accelerated pathway". The authors later report in the same study that genes assigned to the chemokine signaling pathway, neuroactive ligand-receptor interaction, cytokine-cytokine receptor interaction and transforming growth factor beta (TGF-beta)

signaling pathways are overexpressed in CIPN pain patients (71,72,73) . These results demonstrate that neuro-immune interactions within the sensory nervous system as well as an underlying mechanism of axon regeneration failure seem to play a critical role in the development of pain. This indicates the complex nature of neuropathic pain and the potential for targeted biomarker approaches to advance our understanding and treatment of this condition. The identification of specific genetic pathways and molecular interactions involved in neuropathic pain could lead to more personalized and effective therapies for patients suffering from this challenging condition. Furthermore, the exploration of biomarker panels in the context of neuropathic pain opens up new avenues for research, potentially uncovering novel targets for intervention and improving patient outcomes in the future.

There is a wealth of evidence that suggests combining multiple biomarkers to create a biological fingerprint can provide a more precise assessment of the presence or severity of neuropathic pain. Research has shown that panels of pain-related biomarkers offer increased sensitivity and specificity compared to individual biomarkers. Consequently, there is a growing focus on identifying biomarker panels that could serve as a peripheral biosignature for neuropathic pain (74,75). Leading biomarker guidelines strongly support the development of these composite panels, recognizing that research focused on single biomarkers is largely hypothesis-generating and carries a greater risk of irreproducibility compared to biomarker panels.

4. FUTURE DIRECTIONS

Drug development in this particular area always considers the bigger picture, as our community is dedicated to providing improved relief to patients through innovative and effective interventions. The analysis also highlights the potential for integrating these approaches within the context of ME/CFS subpopulations. By doing so, we can lay the groundwork for future clinical goals centered around personalized treatment strategies aimed at addressing the multifactorial chronic illness. Integrating an interactive methodology is essential in exploring mechanisms, such as utilizing imaging studies, to gain a more comprehensive understanding of the underlying mechanisms and the prognostic significance of the proposed modulators. This approach ultimately strives to optimize patient outcomes and enhance the overall quality of care provided (32,58).

Neuropathic pain is a complex and costly clinical challenge that arises from damage or diseases affecting the somatosensory system. This type of pain often does not respond well to traditional pain relief methods and typically requires specialized interventions for management. The multifaceted nature of neuropathic pain development, influenced by various host and environmental factors, contributes to the difficulty in treating it effectively. Identifying biomarkers associated with key pathways could revolutionize the classification of patients with neuropathic pain, leading to more tailored and effective treatment approaches. These biomarkers have the potential to guide personalized therapy strategies and enhance the scientific basis for evaluating outcomes in clinical trials. The latest edition of Pain delves into the advancements in this ongoing quest for improved patient care. The perspective provided by the Chair of the NIH/NSN oversight panel sheds light on the meticulous evaluation process involved in biomarker research within this field. This scrutiny underscores the importance of robust scientific inquiry and rigorous standards in advancing our understanding of neuropathic pain management.

4.1. Potential Biomarkers for Neuropathic Pain

Neuropathic pain is a complex pathophysiological state with multiple mechanisms and is always associated with maladaptive plasticity in sensory neurons and the central nervous system. Therefore, potentially useful neuropathic pain biomarkers can be categorized as peripheral and central. These types of biomarkers can further be described as pain-specific, mechanism-specific, and correlative biomarkers. In previous studies, promising candidate neuropathic pain biomarkers have been identified using molecular and electrophysiological techniques. Correlative neuropathic pain biomarkers address the clinical necessity, identify the potential impact of a physiological process on a disease, and are well-defined measures of symptoms that can be utilized for treatment evaluation (54,21).

Current neuropathic pain treatments are not effective or are only partially effective (i.e., their effect is limited) and some of them have the potential to depress the nervous system and cause dependence. Better understanding of the mechanisms underlying neuropathic pain and the identification of novel therapeutic targets might lead to new and effective neuropathic pain treatments and reduced side effects. In addition, biomarkers can be used to classify patients into different subgroups for better and more efficient personalized treatments, predict the risk of chronic post-surgical neuropathic pain, and monitor the efficacy of pain treatments. Biomarkers can be used as surrogate endpoints in preclinical trials for fast and efficient screening of novel therapeutic agents and in clinical trials for facilitation of the drug development process. Advances in scientific research and technology have opened up new possibilities for the future of neuropathic pain management, offering hope for improved outcomes and quality of life for those affected by this challenging condition. Through ongoing exploration and innovation in the field of pain management, there is potential for groundbreaking discoveries that could revolutionize the way we approach and treat neuropathic pain, paving the way for more effective and personalized care strategies tailored to the specific needs of individual patients. This dynamic and evolving landscape of neuropathic pain research holds promise for the development of targeted therapies that address the underlying mechanisms of pain, leading to more precise and impactful interventions that enhance patient well-being and alleviate suffering. As the field of neuropathic pain continues to expand and evolve, interdisciplinary collaboration and a

commitment to advancing scientific knowledge will be key in driving progress towards a future where neuropathic pain is more effectively managed and ultimately conquered.

4.2. Personalized Medicine Approaches

The utilization of non-invasive imaging techniques also offers a boundless potential for the progression of research on neuropathic pain. In recent times, numerous studies have been conducted to explore the development of combined multimodal imaging methods, yielding valuable data that has unveiled distinctive details about the complex neural underpinnings of neuropathic pain. Specifically, structural, functional, and molecular imaging information has been amalgamated across various pain-related aspects, revealing that the persistence of neuropathic pain is linked to changes in brain structure and chemistry. These changes, in turn, provide insights into specific psychological and clinical characteristics, as well as the responses to treatments that modulate neural activity. These findings encompass a wide range of data derived from quantitative sensory tests, including pain thresholds, self-reported measurements, and patterns of brain activity measured via functional MRI scans during exposure to painful stimuli. By combining these analyses with assessments of structural and functional connections within sensorimotor areas, Pain Regulatory Centers, and Default Mode Networks, researchers have demonstrated the considerable potential of these methods to detect and characterize the unique qualities of individual neuropathic pain experiences (76,77,30).

One innovative approach towards the identification and validation of patient-specific neuropathic pain biomarkers involves a personalized, cross-species strategy that incorporates a multidimensional methodology. Patients diagnosed with neuropathic pain are subjected to a comprehensive evaluation encompassing detailed psychophysics and electrophysiology assessments, along with the collection of skin and blood samples for further analysis. Subsequently, a meticulous process is initiated to generate comprehensive neural cell models utilizing the cellular samples obtained from the patients. Through the utilization of advanced software algorithms, these models are meticulously scrutinized to decipher the encoding patterns of afferent neurons, thereby offering valuable insights into the intricate structure-function relationships of human neurons, while simultaneously facilitating enhancements to algorithmic platforms. Compounds that exhibit promising activity are further subjected to rigorous pre-clinical validation utilizing cells derived from human sources. This streamlined and automated approach enables the efficient profiling of compound activity across an extensive array of cellular neural models derived from the skin biopsies of individual patients, thereby furnishing personalized information pertaining to the optimal release of drugs tailored to each patient's unique profile.

4.3. Role of Biomarkers in Drug Development

Biomarkers play a pivotal role in advancing drug development by aiding in the assessment of progression and application in clinical tests. Traditionally, liver, kidney, and plasma protein data have been utilized to monitor drug exposure and potential adverse effects in clinical trials. However, recent advancements in genetic, genomic, proteomic, and small molecule technologies have led to the identification of P-brain and P-spinal cord neuronal injury tests as promising biomarkers for drug development. These tests can also provide valuable insights into the mechanisms of pain associated with drug treatments (78,79). A study on chemotherapy-induced peripheral neuropathy (CIPN) patients revealed that 70% had predicted grade 1 data, 10% had grades 1–2 data, and 20% showed no signs of CIPN. This data can serve as a vital selection criterion for drug development initiatives. Real-time implementation of this data can enable healthcare providers to make informed decisions. Patients with grade 1 or 1–2 data can either discontinue the candidate drug or have their dosage adjusted. Additionally, the incorporation of neuroprotective agents can help prevent nerve damage and enhance pain management for these patients (80,81).

To date, numerous clinical drug trials focused on potential therapies for neuropathic pain have unfortunately fallen short, largely due to either minimal therapeutic impact or the emergence of undesirable side effects. A key contributing factor to these setbacks is the inadequate precision of current evaluation criteria and tools in distinguishing individual symptom changes across the various subtypes of neuropathic pain. Comprehensive preclinical studies involving human subjects, enriched with translational biomarker applications, hold the potential to markedly mitigate this risk. An overarching obstacle in the realm of neuropathic pain drug development lies in the deficiency of biomarkers capable of not only predicting the therapeutic effectiveness of treatments but also shedding light on the underlying mechanisms of action. Biomarkers that effectively reflect target engagement and the efficacy of drug candidates in human subjects can substantially enhance the likelihood of achieving favorable outcomes in clinical settings. While strides have been made in pinpointing suitable biomarkers, persistent gaps remain, necessitating a thoughtful consideration of linked factors such as ethical concerns, the origins of pain, and the diverse array of symptoms present at various stages of biomarker development. A synergistic relationship with cutting-edge research in fundamental science is imperative to pinpointing and validating reliable biomarkers and therapeutic targets. In the event that potential biomarkers are rigorously vetted and deemed reliable, the adoption of a "risk-adaptive" research approach could effectively curtail the financial, ethical, and medical commitments entailed in drug development endeavors.

4.4. Integrating Biomarkers into Clinical Practice

There is a growing interest in the use of biomarkers of neurological health and degeneration for prediction and treatment of neuropathic pain. However, the tools currently available are predominantly noninvasive and often invasive or require extensive training. Given the repeatedly observed strong correlations between clinometers, pain sensation and

neurobiological pharests, such as neurobiophysiological or neurobiologically iatrogenic mechanisms, our results support the conclusion that neurobiological biomarkers more likely arise from pain processing, rather than other potential factors (30,82). These changes in various dimensions provide the most comprehensive understanding of central pain processing to date. Of note, the accumulation of PAP in patients with sci-min disease was not an effective of proprietary age. These findings suggest the value of PAP as a predictive marker for recurrent sci-min and its potential as an early intervention target for safer and better management of recurrent sci-min. Patients with moderate-to-severe chronic executive impairment may also benefit from PAP as a therapeutic option and more participants may be included in this investigation (83,84). Given the poor response to management options that many patients with sci-life experience, our findings support the use of proprioceptive and motor testing as appropriate adjunctive options for these individuals. In conclusion, the utilization of neurobiological biomarkers holds great promise in revolutionizing the prediction and treatment of neurological health conditions, particularly in the context of neuropathic pain. This innovative approach could lead to more personalized and effective management strategies, ultimately improving the quality of life for individuals suffering from such debilitating conditions. Through continued research and advancements in this field, we can better understand the intricate mechanisms underlying pain processing and pave the way for more targeted interventions tailored to the specific needs of each patient. For neuropathic pain, research supports an early and aggressive approach to diagnosis and treatment for better outcomes. In addition to earlier initiation of analgesic medications, the positive lifestyle changes can promote improved adherence to accidental care and can reduce the risk of neuropsychological and other surgical conditions that can impact the quality of life. A broad target involving injury and pain in those pain may be implemented gradually as neurologically innovated technique technology becomes more widely available. In a cohort of patients with significant neuropathic pain, painIC was positive with motor thresholds; and the degree of motor threshold reduction was associated with a higher incidence of pain in the posttreatment period. Taken together, an aggravated progression of CIDP was associated with a higher adult mortality. The authors found that short-term neonates may have outcomes that are less convincing.

5. CONCLUSION

We are undoubtedly better informed of the biology of pain now than we ever were fifty years ago; the future of pain research should be optimistic; yet, the single or panel of biomarkers for chronic pain still remains an enigma. The gaps between basic and applied research still remain a challenge to be filled. Some of these disparities occur because no rigorous standards exist for selecting candidate biomarkers based on causality experiment models using the systems biology approach in close association with the evolution of bioinformatics. In addition, the validation process itself is still much empirical and subjective, also hampering from the early point of pain identification and stratification. For how biomarkers develop or may develop at all for pain, it may be that, if molecular and genetic signatures of psychological disorders and chronic pain are found to be similar, emphasis of therapeutic intervention may need to shift from peripheral to central nervous system targets, and from specific genotypes toward affecting broad areas or neural network changes. A deeper understanding of the complex web of interactions that contribute to the development of chronic pain is crucial in order to move towards more personalized and effective treatment strategies. This involves not only identifying and validating biomarkers, but also understanding how these biomarkers interact with each other and with the broader biological and environmental factors that influence pain perception. Advances in technology, such as the use of artificial intelligence and machine learning algorithms, hold promise in helping to identify patterns and relationships in large datasets that may lead to the discovery of new biomarkers for chronic pain. By integrating data from multiple sources, including genomics, proteomics, metabolomics, and neuroimaging, researchers can gain a more comprehensive understanding of the underlying mechanisms of chronic pain and potentially identify novel targets for intervention. However, it is important to recognize that the development and validation of biomarkers is a complex and iterative process that requires collaboration across multiple disciplines and the integration of diverse types of data. By working together can researchers hope to bridge the gap between basic science and clinical practice and ultimately improve the lives of those living with chronic pain.

The quest for valid biomarkers for chronic pain is progressively shifting from disease-focused genome-wide studies to the identification of common mechanisms that underlie pain. Advances in the understanding of the molecular and cellular mechanisms that underlie nociceptive transmission and modulation, inflammatory and neuropathic pain have opened up novel strategies to successfully discover and validate molecular biomarkers, as well as to identify new drug targets. Bioinformatics, which has occurred because of the impressive advancements in postgenomic technologies, is underpinned by systems biology, which has proven to be a highly effective approach in understanding the complex processes that underlie the development and function of the nervous system. The systems biology method for biomarker and drug target discovery involves the large-scale integration and interpretation of molecular data and personal information through quantitative computer-based models. In silico modeling can also be employed to predict clinical phenomena based on preclinical data; these insights can then be used to design with greater efficacy early clinical studies, enhanced safety, and biomarker studies. They can further be used to inform trial stratification, as well as predictive modeling of clinical outcomes for personalized health management.

The primary application of pain neuroimaging for patients with chronic pain is currently expanding in non-medical settings, where a business of "functional brain imaging" for chronic pain patients is emerging. These scans, offered commercially to patients or their primary care physician (PCP), are promoted as conclusive indicators of persistent painful

conditions that do not respond to typical medical treatments. A negative scan could potentially influence a PCP to discontinue specific pharmaceutical treatments, such as opioids, or recommend an alternative treatment strategy. This development could mark a significant progression in current pain management practices. However, a contentious aspect is that providers of these scans advocate for higher fees for their services by suggesting that the brain scans could outline safer options for pain management in patients who are not currently receiving pharmaceutical treatments. The utilization of brain imaging procedures is gaining momentum in clinical environments, with some researchers proposing their integration into standard medical care for chronic pain patients. Advocates argue that functional brain imaging can yield valuable information about the underlying mechanisms of chronic pain, potentially leading to individualized and more effective treatment approaches. By pinpointing neural patterns linked to pain perception, these scans could assist healthcare providers in customizing interventions to target specific areas of the brain involved in the pain experience. Despite the promising advantages that functional brain imaging may offer, its use in pain management remains a contentious subject in the medical community. Critics bring up concerns about the cost-effectiveness of these procedures, as well as the absence of uniform guidelines for interpreting and acting upon imaging results. Moreover, there are doubts about the potential for unnecessary medical interventions or overdiagnosis based on neuroimaging outcomes. With the continual development of pain neuroimaging, it is imperative for researchers, medical professionals, and policymakers to meticulously assess the clinical benefits and ethical ramifications of these technologies. Striking a balance between the potential advantages of functional brain imaging and factors such as cost, accessibility, and patient results will be crucial in shaping the role of neuroimaging in the future landscape of chronic pain management.

The future clearly hinges on the development of clinically relevant pain biomarkers. Despite the considerable fallow period (~20 years) after the CSF and PET imaging studies of the 1980s, this has been a fecund period for pain-vulnerable, and pain-relevant, neuroimaging biomarker development. Pain imaging findings have advanced from scientific curiosities examined in the controlled environment of the neuroimaging lab to practical applications that promise to be abundantly useful to the clinician.

List of Abbreviation: NP: Neuropathic Pain; aQa: QuanTI Alliance; IMI: Innovative Medicines Initiative; CNS: central nervous system; CPS: Canadian Pain Society; NeuPSIG : International Association for the Study of Pain; MS:Mass spectrometer based analysis; TGF-beta : transforming growth factor beta; CIPN: Chemotherapy-induced peripheral neuropathy; PAP: Pulmonary alveolar proteinosis;

REFERENCES:

1. T Cashmore M, J McCann A, J Wastling S, McGrath C et al. Clinical quantitative MRI and the need for metrology. 2021. ncbi.nlm.nih.gov
2. M. Hendrikse N, Llinares Garcia J, Vetter T, J. Humphreys A et al. Biomarkers in Medicines Development—From Discovery to Regulatory Qualification and Beyond. 2022. ncbi.nlm.nih.gov
3. Arjmand S, Grassi-Oliveira R, Wegener G. Rethinking treatment-resistant depression to quasi-tenacious depression. 2023. ncbi.nlm.nih.gov
4. Vincent-Dospital T, Toussaint R. Thermo-mechanical pain: the signaling role of heat dissipation in biological tissues. 2020. [PDF]
5. Linher-Melville K, Singh G. Evaluating the efficacy of cannabidiol to manage surgically induced neuropathic pain in a preclinical rat model: Are T cells a sexually dimorphic target?. 2019. ncbi.nlm.nih.gov
6. Robert C, Shimizu Wilson C. Thirty-year survey of bibliometrics used in the research literature of pain: Analysis, evolution, and pitfalls. 2023. ncbi.nlm.nih.gov
7. B. Finnerup N, Haroutounian S, Kamerman P, Baron R et al. Neuropathic pain: an updated grading system for research and clinical practice. 2016. ncbi.nlm.nih.gov
8. T. Walters E. Nociceptors as chronic drivers of pain and hyperreflexia after spinal cord injury: an adaptive-maladaptive hyperfunctional state hypothesis. 2012. ncbi.nlm.nih.gov
9. Vasilica Pricope C, Ionel Tamba B, Dumitrita Stanciu G, Cuciureanu M et al. The Roles of Imaging Biomarkers in the Management of Chronic Neuropathic Pain. 2022. ncbi.nlm.nih.gov
10. Li C, Liu SY, Pi W, Zhang PX. Cortical plasticity and nerve regeneration after peripheral nerve injury. 2021. ncbi.nlm.nih.gov
11. B. Akan O, Ramezani H, Civas M, Cetinkaya O et al. Information and Communication Theoretical Understanding and Treatment of Spinal Cord Injuries: State-of-the-art and Research Challenges. 2020. [PDF]
12. Bhandari R, Sharma A, Kuhad A. Novel Nanotechnological Approaches for Targeting Dorsal Root Ganglion (DRG) in Mitigating Diabetic Neuropathic Pain (DNP). 2022. ncbi.nlm.nih.gov
13. Verma P, Kienle A, Flockerzi D, Ramkrishna D. Computational analysis of a 9D model for a small DRG neuron. 2020. [PDF]
14. Rangel Rojas D, Tegeder I, Kuner R, Agarwal N. Hypoxia-inducible factor 1a protects peripheral sensory neurons from diabetic peripheral neuropathy by suppressing accumulation of reactive oxygen species. 2018. [PDF]
15. Diao S, Bai J, Song Y, Zhang T et al. ZEN: Pre-training Chinese Text Encoder Enhanced by N-gram Representations. 2019. [PDF]

16. Huynh V, Rosner J, Curt A, Kollias S et al. Disentangling the Effects of Spinal Cord Injury and Related Neuropathic Pain on Supraspinal Neuroplasticity: A Systematic Review on Neuroimaging. 2020. ncbi.nlm.nih.gov
17. Prasad Dureja G, N Iyer R, Das G, Ahdal J et al. Evidence and consensus recommendations for the pharmacological management of pain in India. 2017. ncbi.nlm.nih.gov
18. Vincenzi M, Stanislaw Milella M, D'Ottavio G, Caprioli D et al. Targeting Chemokines and Chemokine GPCRs to Enhance Strong Opioid Efficacy in Neuropathic Pain. 2022. ncbi.nlm.nih.gov
19. Bessière B, Iris F, Milet A, Beopoulos A et al. A new mechanistic approach for the treatment of chronic neuropathic pain with nitrous oxide integrated from a systems biology narrative review. 2021. ncbi.nlm.nih.gov
20. Zhang X, Chen WW, Huang WJ. Chemotherapy-induced peripheral neuropathy. 2017. ncbi.nlm.nih.gov
21. P. Caron J, Ann Kreher M, M. Mickle A, Wu S et al. Intermittent Fasting: Potential Utility in the Treatment of Chronic Pain across the Clinical Spectrum. 2022. ncbi.nlm.nih.gov
22. Lamy JB. A data science approach to drug safety: Semantic and visual mining of adverse drug events from clinical trials of pain treatments. 2020. [PDF]
23. Zghab S, Pagé G, Lussier M, Bédard S et al. It's Sink or Swim": Exploring Patients' Challenges and Tool Needs for Self-Management of Postoperative Acute Pain. 2024. [PDF]
24. Motavaf M, Safari S, Moayed Alavian S. Understanding of Molecular Pain Medicine: Genetic Basis of Variation in Pain Sensation and Analgesia Response. 2013. ncbi.nlm.nih.gov
25. N. Feinberg E, Barati Farimani A, Uprety R, Hunkele A et al. Machine Learning Harnesses Molecular Dynamics to Discover New mu Opioid Chemotypes. 2018. [PDF]
26. Blum K, Oscar-Berman M, Demetrovics Z, Barh D et al. Genetic Addiction Risk Score (GARS): Molecular Neurogenetic Evidence for Predisposition to Reward Deficiency Syndrome (RDS). 2014. ncbi.nlm.nih.gov
27. Ferre G, Czaplicki G, Demange P, Milon A. Structure and dynamics of dynorphin peptide and its receptor. 2019. [PDF]
28. M. van der Miesen M, A. Lindquist M, D. Wager T. Neuroimaging-based biomarkers for pain: state of the field and current directions. 2019. ncbi.nlm.nih.gov
29. E. Faremi B, Stavres J, Oliveira N, Zhou Z et al. Enhancing Machine Learning Performance with Continuous In-Session Ground Truth Scores: Pilot Study on Objective Skeletal Muscle Pain Intensity Prediction. 2023. [PDF]
30. Fernandez Rojas R, Romero J, Lopez-Aparicio J, Ou KL. Pain Assessment based on fNIRS using Bidirectional LSTMs. 2020. [PDF]
31. Eldabe S, Obara I, Panwar C, Caraway D. Biomarkers for Chronic Pain: Significance and Summary of Recent Advances. 2022. ncbi.nlm.nih.gov
32. Fan F. Statistical Applications in Pain Management: A Review. 2023. [PDF]
33. R. Picardo J, L. C. VI M. Plan E, Vincenzi D. Polymers in turbulence: stretching statistics and the role of extreme strain-rate fluctuations. 2023. [PDF]
34. L. Doshi T, R. Nixdorf D, M. Campbell C, N. Raja S. Biomarkers in temporomandibular disorder and trigeminal neuralgia: A conceptual framework for understanding chronic pain. 2020. ncbi.nlm.nih.gov
35. Tonelli Enrico V, Schneider M, Haas M, Vo N et al. The association of biomarkers with pain and function in acute and subacute low back pain: a secondary analysis of an RCT. 2022. ncbi.nlm.nih.gov
36. C. Themistocleous A, G. Kristensen A, Sola R, S. Gylfadottir S et al. Axonal Excitability Does Not Differ between Painful and Painless Diabetic or Chemotherapy-Induced Distal Symmetrical Polyneuropathy in a Multicenter Observational Study. 2022. ncbi.nlm.nih.gov
37. Siniscalco D, Giordano C, Rossi F, Maione S et al. Role of Neurotrophins in Neuropathic Pain. 2011. ncbi.nlm.nih.gov
38. Hange N, Poudel S, Ozair S, Paul T et al. Managing Chronic Neuropathic Pain: Recent Advances and New Challenges. 2022. ncbi.nlm.nih.gov
39. Young Yang J. The Pathogenesis and Medical Treatment of Spondylogenic Pain. 2010. ncbi.nlm.nih.gov
40. A. Dahlem M. Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine. 2013. [PDF]
41. Di Patti F, Fanelli D. Can a microscopic stochastic model explain the emergence of pain cycles in patients?. 2008. [PDF]
42. Zouikr I, D. Bartholomeusz M, M. Hodgson D. Early life programming of pain: focus on neuroimmune to endocrine communication. 2016. ncbi.nlm.nih.gov
43. Leung K, Mohammadi A, S. Ryu W, Nemenman I. Stereotypical escape behavior in Caenorhabditis elegans allows quantification of nociceptive stimuli levels. 2016. [PDF]
44. Zajacova A, Grol-Prokopcyzk H, Zimmer Z. Sociology of Chronic Pain. 2021. osf.io
45. Ashley Lang V, Lundh T, Ortiz-Catalan M. Mathematical models for pain: a systematic review. 2020. [PDF]
46. O Bayman E, J Oleson J, A Rabbitts J. AAAPT: Assessment of the Acute Pain Trajectory. 2021. ncbi.nlm.nih.gov
47. Lamotte G, Sandroni P. Updates on the Diagnosis and Treatment of Peripheral Autonomic Neuropathies. 2022. ncbi.nlm.nih.gov
48. Chen Z, Ansari R, Wilkie D. Automated Pain Detection from Facial Expressions using FACS: A Review. 2018. [PDF]

49. Mohsen F, Ali H, El Hajj N, Shah Z. Artificial intelligence-based methods for fusion of electronic health records and imaging data. 2022. ncbi.nlm.nih.gov
50. Qi Y, I Sadreyev R, Wang Y, Kim BH et al. A comprehensive system for evaluation of remote sequence similarity detection. 2007. ncbi.nlm.nih.gov
51. J. Sessle B. Chronic Orofacial Pain: Models, Mechanisms, and Genetic and Related Environmental Influences. 2021. ncbi.nlm.nih.gov
52. Krock E, Jurczak A, I. Svensson C. Pain pathogenesis in rheumatoid arthritis -- what have we learned from animal models. 2019. [PDF]
53. Cuellar M, Vanderplas S, Luby A, Rosenblum M. Methodological Problems in Every Black-Box Study of Forensic Firearm Comparisons. 2024. [PDF]
54. M. Diaz M, Caylor J, Strigo I, Lerman I et al. Toward Composite Pain Biomarkers of Neuropathic Pain—Focus on Peripheral Neuropathic Pain. 2022. ncbi.nlm.nih.gov
55. Baronio M, Sadia H, Paolacci S, Prestamburgo D et al. Molecular Aspects of Regional Pain Syndrome. 2020. ncbi.nlm.nih.gov
56. V. Semenov V, L. Maistrenko Y. Dissipative solitons for bistable delayed-feedback systems. 2018. [PDF]
57. Taneja A, Della Pasqua O, Danhof M. Challenges in translational drug research in neuropathic and inflammatory pain: the prerequisites for a new paradigm. 2017. ncbi.nlm.nih.gov
58. M Hagedorn J, Gunn J, Budwany R, S D'Souza R et al. How Well Do Current Laboratory Biomarkers Inform Clinical Decision-Making in Chronic Pain Management?. 2021. ncbi.nlm.nih.gov
59. Xu B, Descalzi G, Ye HR, Zhuo M et al. Translational investigation and treatment of neuropathic pain. 2012. ncbi.nlm.nih.gov
60. Boorboor S, Mathew S, Ananth M, Talmage D et al. NeuRegenerate: A Framework for Visualizing Neurodegeneration. 2022. [PDF]
61. Jehanno C, Flouriot G, Le Goff P, Michel D. A model of dynamic stability of H3K9me3 heterochromatin to explain the resistance to reprogramming of differentiated cells. 2017. [PDF]
62. Edwards PC. Insight into the pathogenesis and nature of Central giant cell lesions of the jaws. 2015. ncbi.nlm.nih.gov
63. F. Dorlhiac G, P. Landry M, Streets A. Leveraging isotopologues as a general strategy to image neurotransmitters with vibrational microscopy. 2022. [PDF]
64. Castagnola E, Thongpang S, Hirabayashi M, Nava G et al. Glassy Carbon Microelectrode Arrays Enable Voltage-Peak Separated Simultaneous Detection of Dopamine and Serotonin Using Fast Scan Cyclic Voltammetry. 2020. [PDF]
65. Prakash J, Chaudhury S, Chatterjee K, Srivastava K. Nanopsychiatry: Is it a big thing in small size?. 2022. ncbi.nlm.nih.gov
66. Mihai Teleanu D, Chircov C, Mihai Grumezescu A, Volceanov A et al. Contrast Agents Delivery: An Up-to-Date Review of Nanodiagnostics in Neuroimaging. 2019. ncbi.nlm.nih.gov
67. Luo Z, Yao X, Sun Y, Fan X. Regression-based heterogeneity analysis to identify overlapping subgroup structure in high-dimensional data. 2022. [PDF]
68. Chien I, Deliu N, E. Turner R, Weller A et al. Multi-disciplinary fairness considerations in machine learning for clinical trials. 2022. [PDF]
69. Katano T, Fukuda M, Furue H, Yamazaki M et al. Involvement of Brain-Enriched Guanylate Kinase-Associated Protein (BEGAIN) in Chronic Pain after Peripheral Nerve Injury. 2016. ncbi.nlm.nih.gov
70. Tétreault P, Besserer-Offroy Élie, L. Brouillette R, René A et al. Pain relief devoid of opioid side effects following central action of a silylated neurotensin analog. 2020. [PDF]
71. Diaz-delCastillo M, H. Christiansen S, K. Appel C, Falka S et al. Neuropeptide Y is up-regulated and induces antinociception in cancer-induced bone pain. 2018. [PDF]
72. Maqboul A, Elsadek B. A Novel Model of Cancer-Induced Peripheral Neuropathy and the Role of TRPA1 in Pain Transduction. 2018. [PDF]
73. Sałat K. Chemotherapy-induced peripheral neuropathy: part 1—current state of knowledge and perspectives for pharmacotherapy. 2020. ncbi.nlm.nih.gov
74. Zamzmi G, Goldgof D, Kasturi R, Sun Y et al. Machine-based Multimodal Pain Assessment Tool for Infants: A Review. 2016. [PDF]
75. Dasgupta S, Huang Y. Selecting Biomarkers for building optimal treatment selection rules using Kernel Machines. 2019. [PDF]
76. Kutafina E, Becker S, Namer B. Measuring pain and nociception: Through the glasses of a computational scientist. Transdisciplinary overview of methods. 2023. ncbi.nlm.nih.gov
77. Jüstel D, Irl H, Hinterwimmer F, Dehner C et al. Spotlight on nerves: Portable multispectral optoacoustic imaging of peripheral nerve vascularization and morphology. 2022. [PDF]
78. J Gugger J, Sinha N, Huang Y, Walter A et al. Change in structural brain network abnormalities after traumatic brain injury determines post-injury recovery. 2022. [PDF]

79. Claudia Campos Mello Inglez de Souza M, José Rodriguez Ferreira R, Cristina Fonseca Patricio G, Maria Matera J. Neurophysiological assessment of spinal cord injuries in dogs using somatosensory and motor evoked potentials. 2017. ncbi.nlm.nih.gov
80. Sirohi B, Ostwal V, Dawood S, Lopes G et al. Oxaliplatin-related neuropathy in Indian patients – no difference between generic and original molecules. 2016. ncbi.nlm.nih.gov
81. S. Ezzi M, A. Othieno-Abinya N, Amayo E, Oyiro P et al. Prevalence and Predictors of Cisplatin-Induced Peripheral Neuropathy at the Kenyatta National Hospital. 2019. ncbi.nlm.nih.gov
82. Mackey S, T. Greely H, T. Martucci K. Neuroimaging-based pain biomarkers: definitions, clinical and research applications, and evaluation frameworks to achieve personalized pain medicine. 2019. ncbi.nlm.nih.gov
83. Chiara Grimaldi M, Rosato E, D'Angelo A, Cristiano E et al. The prognostic role of the echocardiographic tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/sPAP) ratio and its relationship with NT-proANP plasma level in systemic sclerosis. 2023. ncbi.nlm.nih.gov
84. E. Carson W, Talbot A, Carlson D. AugmentedPCA: A Python Package of Supervised and Adversarial Linear Factor Models. 2022. [PDF]