

Decoding Chronic Orofacial Pain: Neuroimmune Crosstalk, Digital Phenotyping, and Artificial Intelligence for Precision Pain Medicine

Maria Perez Gonzalez^{1*}, Yennifer Rondon Lozada², Yndira Parchman³, Katiuska Taveras⁴, Joanith Medina Barreto⁵, Claudia Arias Molina⁶

¹Universidad de Ciencias Medicas de Matanzas, Cuba. ORCID: 0009-0008-7937-3884.

²Universidad Nacional Experimental de los Llanos Centrales Romulo Gallegos, Venezuela. ORCID: 0009-0007-3783-8367.

³Universidad Nororiental Privada Gran Mariscal de Ayacucho, Venezuela. ORCID: 0009-0004-1036-8893.

⁴Universidad Catolica del Cibao, Republica Dominicana. ORCID: 0009-0002-5344-7124.

⁵Universidad de Carabobo, Venezuela. ORCID: 0009-0004-0414-4156.

⁶Fundacion Universitaria Vision de las Americas, Colombia. ORCID: 0009-0000-7865-3798.

Abstract

Chronic orofacial pain is difficult to classify because similar symptoms may arise from different biological mechanisms, and symptom-based diagnoses often fail to explain why pain persists or to predict treatment response. This narrative review examines whether chronic orofacial pain can be reclassified according to biological mechanism rather than clinical symptom, and how emerging technologies might support that shift. It describes the mechanism-based framework of nociceptive, neuropathic, and nociplastic pain, together with the neuroimmune interactions, including microglial activation, peripheral neuroinflammation, cytokine signaling, and central sensitization, that sustain pain. It then considers digital phenotyping through wearable sensors, smartphone data, sleep tracking, jaw-movement analysis, and facial behavior, and the role of machine learning, radiomics, and multimodal artificial intelligence in multidimensional diagnosis. Finally, it outlines precision therapeutics through patient stratification, biomarkers, neuromodulation, and individualized pharmacological and behavioral care. Evidence supports a mechanism-informed direction, although prospective validation and standardization are still necessary before routine use.

Keywords: Orofacial pain; nociplastic; central sensitization; neuroimmune interactions; digital phenotyping; artificial intelligence.

INTRODUCTION

Chronic orofacial pain encompasses a wide range of conditions that affect the face, mouth, and jaw for longer than three months. Its consequences extend beyond pain itself, interfering with eating, speaking, sleeping, working, and emotional well-being, and reducing overall quality of life [1-2]. Diagnosis is difficult because similar or non-specific symptoms may appear in conditions with different causes, and as a result some patients move repeatedly between dental and medical clinicians or receive treatment aimed mainly at symptom control without a clear understanding of what keeps the pain active [3]. This challenge has driven growing interest in moving from classification based mainly on symptoms toward an approach that also considers the underlying mechanisms.

Current classification systems provide useful names and diagnostic criteria based on features such as pain location, duration, clinical presentation, and probable cause. These categories nevertheless do not always explain the biological process responsible for pain persistence [3-4]. The same symptom may be produced by different mechanisms, while a single diagnosis may encompass several mechanisms simultaneously [1].

Corresponding Author: Maria Perez Gonzalez, Universidad de Ciencias Medicas de Matanzas, Cuba. ORCID: 0009-0008-7937-3884.

Evidence is also difficult to apply because studies use different diagnostic groups, treatments, follow-up periods, and outcome measures [5], and experimental models often reproduce only selected features, such as inflammation, nerve injury, or sensitivity to stimulation, rather than the complete clinical experience [6]. These gaps limit the ability to identify the main pain driver, estimate prognosis, and select treatment for an individual patient.

Chronic pain is also highly heterogeneous, meaning that it can look and behave very differently from one person to another. Patients with the same diagnosis may report different levels of pain, disability, sleep disturbance, psychological distress, sensory change, and treatment response [7], while patients with different diagnostic labels may share biological, psychological, or social factors that shape their pain [8]. This variation may reflect differences in inflammation, nervous-system sensitivity, comorbidity, stress, coping, and previous pain experience, and treatment response may itself depend partly on how

an intervention is delivered, including clinician training and therapeutic quality [6]. A diagnostic label alone may therefore fail to describe the patient fully or to predict which treatment will help [9].

A mechanism-based framework instead organizes pain into nociceptive, neuropathic, and nociplastic processes. Nociceptive pain arises when tissue injury or inflammation continues to activate nociceptors through an intact somatosensory system [10]. Neuropathic pain is associated with a lesion or disease of the somatosensory pathways. Nociplastic pain involves altered nociceptive processing when the available evidence of tissue damage or nerve injury is insufficient to explain the pain experience [2-3,7]. These processes are compared in Figure 1. In chronic orofacial pain they should not be treated as entirely separate categories, because persistent peripheral input may coexist with nerve-related change and altered central processing, and their relative contribution may differ across patients or shift over time [7].

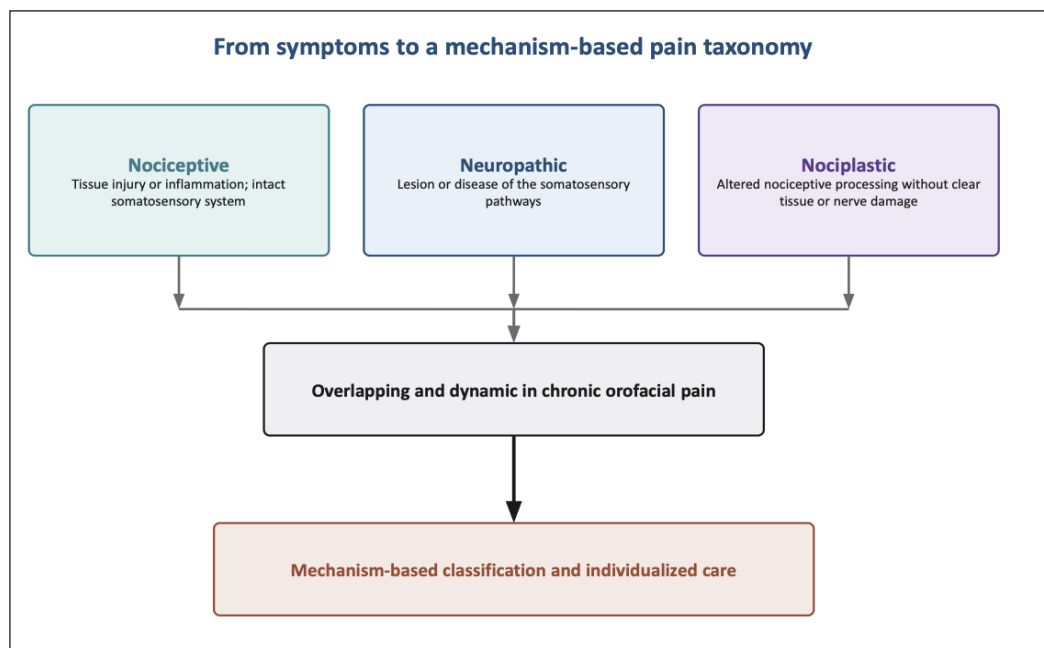


Figure 1. The mechanism-based framework of chronic orofacial pain. Nociceptive, neuropathic, and nociplastic processes overlap and shift over time within an individual, providing the basis for mechanism-based classification rather than symptom-based labels [2-3,7].

Clinical interpretation is further complicated because many signs and symptoms overlap, and no single examination or test can reliably confirm the dominant mechanism [11]. Considering a combination of clinical features is therefore more useful than relying on any one symptom or diagnostic label. Recognizing the principal mechanism could support more accurate patient classification and more individualized clinical decisions [12], and it provides the conceptual basis for connecting chronic orofacial

pain to neuroimmune mechanisms, digital phenotyping, artificial intelligence, and precision treatment [13].

Accordingly, this review addresses a single central question: can chronic orofacial pain be reclassified according to biological mechanisms rather than clinical symptoms? Setting aside acute and odontogenic pain and conventional temporomandibular disorder overviews, it focuses on chronic pain mechanisms and the transition

toward mechanism-based diagnosis and personalized treatment, examining in turn the neuroimmune basis of pain persistence, digital phenotyping, artificial intelligence for multidimensional diagnosis, and precision therapeutics.

METHODS

A structured narrative synthesis was conducted using PubMed and related biomedical databases to identify literature on the mechanisms and mechanism-based classification of chronic orofacial pain. Systematic reviews, observational studies, randomized clinical trials, and mechanistic investigations published principally within the last five years were prioritized, supplemented by foundational earlier work where relevant. Sources were selected for their relevance to neuroimmune signaling, digital phenotyping, artificial intelligence, and precision therapeutics in chronic orofacial pain, with acute, odontogenic, and purely descriptive temporomandibular disorder reviews excluded. Given the narrative design, no formal quality-scoring protocol or quantitative pooling was applied.

NEUROIMMUNE INTERACTIONS IN CHRONIC PAIN

Current evidence recognizes chronic pain as a persistent sensory and emotional experience involving continuous communication between the nervous and immune systems [12]. These neuroimmune interactions occur at both peripheral and central levels, where immune and neural cells communicate through multiple signaling pathways, and this bidirectional communication contributes to the initiation, maintenance, and persistence of chronic pain [14]. When such interactions become dysregulated, systemic immune disturbance and prolonged stress responses can further accelerate these cascades, creating a self-perpetuating loop [10].

Microglia are the resident immune cells of the central nervous system and normally remain in a surveillance state that maintains homeostasis. In response to injury, inflammation, or damage-associated signals they become activated and release inflammatory mediators that contribute to neuroinflammation and influence pain processing [15]. Peripheral neuroinflammation, by contrast, follows tissue injury: the inflammatory response releases mediators that modify the function and expression of ion channels on nociceptors, making them more sensitive to stimulation, so that peripheral sensitization increases and favors the transition from acute to chronic pain [12]. As local damage persists, recruited leukocytes sustain a localized inflammatory environment that lowers the activation threshold of primary afferent fibers and supports hyperalgesia [13,16].

Cytokines are central to this signaling. They coordinate inflammatory responses in both physiological and pathological states, and during chronic pain they promote and maintain neuroinflammation by mediating communication between immune and neural cells [14]. Persistent inflammation also disturbs neurotransmitter signaling: alterations in dopamine, serotonin, glutamate, and substance P contribute to abnormal neuronal communication and heightened pain sensitivity, enhancing excitability and supporting chronification [15]. Microglia, astrocytes, and satellite glial cells produce pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6, which increase neuronal excitability and promote both peripheral and central sensitization [16,17]. The principal mediators and mechanisms are summarized in Table 1.

The transition to chronic pain reflects the interaction between peripheral and central sensitization rather than either in isolation. After tissue injury or inflammation, N-methyl-D-aspartate receptors become more active

Table 1. Principal neuroimmune mediators and mechanisms implicated in the persistence of chronic pain [9,11-12,16].

Mediator or mechanism	Principal source	Contribution to chronic pain
Microglial activation	Resident CNS immune cells	Neuroinflammation and altered central pain processing
Peripheral neuroinflammation	Injured tissue and recruited leukocytes	Ion-channel sensitization; lowered nociceptor threshold
Pro-inflammatory cytokines	Microglia, astrocytes, satellite glial cells	TNF-alpha, IL-1 beta, IL-6 increase neuronal excitability
Neurotransmitter change	Persistent inflammation	Altered dopamine, serotonin, glutamate, substance P
Peripheral sensitization	Primary afferent fibers	Normally harmless stimuli become painful
Central sensitization	Spinal cord, brainstem, higher regions	Synaptic plasticity maintains and amplifies pain

in peripheral fibers, lowering the activation threshold so that normally harmless stimuli become painful [18]. As peripheral input continues, persistent nociceptive signaling reaches the central nervous system and induces long-lasting change in pain pathways [19]. Within the central nervous system, sustained receptor activation promotes synaptic plasticity in the spinal cord, brainstem, and higher regions, strengthening pain transmission so that pain may persist after the original injury has healed; peripheral sensitization thus initiates the process while central sensitization maintains and amplifies it [7,20].

DIGITAL PHENOTYPING OF PAIN

Digital phenotyping refers to the moment-to-moment quantification of individual behavior and physiological state using data collected from personal digital devices such as smartphones, wearables, and sensors [17,21]. In the context of pain it aims to move beyond traditional self-report, which is subjective, retrospective, and limited by memory bias, by capturing continuous real-world data that reveal patterns of pain intensity, flares, functional limitation, and associated behavior [18]. The core

objective is a more objective and dynamic phenotype of a person's pain experience, drawing together physiological signals such as heart rate variability, muscle activity, and movement; behavioral data such as activity, sleep, and device use; and communicative cues such as changes in speech or facial expression [22].

In chronic orofacial pain and temporomandibular disorders, this approach permits monitoring outside the clinic, reduces reliance on infrequent visits, and may identify early symptom worsening while linking specific digital markers to outcomes [23]. Important challenges nevertheless remain, including data privacy, the accuracy and reliability of consumer devices, patient adherence, and the need for clinical validation; digital signals must also be interpreted cautiously, since they do not measure pain directly but rather its physiological and behavioral correlates [21,24]. Applied to orofacial pain, digital phenotyping provides a framework for integrating wearable sensors, smartphone data, sleep tracking, jaw-movement analysis, and facial or speech features into a more comprehensive assessment, as summarized in Table 2.

Table 2. *Digital phenotyping modalities in chronic orofacial pain, with representative findings and current limitations [17,19-20,22-23].*

Modality	Representative finding	Principal limitation
Wearable sensors	Hydrogel sensor: 90% detection of disc displacement; ML accuracy 84.4%	Accuracy falls with movement or moisture; charging burden
Smartphone data	Real-time bruxism reporting rated positively by most users	Device variability; short response windows; privacy
Sleep tracking	Sleep time and wake after onset predict next-day pain	Less precise for detailed sleep-stage classification
Jaw-movement analysis	Kinematics plus EMG improve dysfunction classification	Needs larger validation and standardized protocols
Speech and facial behavior	Facial-recognition pain detection 70 to over 90% accuracy	Limited sensitivity to orofacial pain relief; privacy

Wearable devices are becoming useful tools for assessing chronic orofacial pain, particularly temporomandibular disorders, because they collect continuous data on muscle activity, jaw movement, and grinding during everyday life rather than relying on recall and brief examination [20]. A biocompatible hydrogel sensor developed for temporomandibular disorder diagnosis detects very small skin deformations near the joint; in testing with 120 participants it identified disc displacement with reduction in 90% of cases and detected joint clicking with sensitivity close to 100% against the Diagnostic Criteria for Temporomandibular Disorders, while a machine-learning model trained on its waveform features reached 84.4% accuracy [25]. Commercial smart earphones containing inertial sensors have similarly distinguished people with

and without temporomandibular disorder symptoms from jaw motion during mouth opening, achieving an area under the curve of 0.70 in a non-invasive, low-cost form suitable for daily screening [26]. Reviews of wearable oral-health technologies confirm a shift from bulky prototypes to compact wireless systems, while noting that accuracy can fall with head movement or moisture and that continuous data transmission raises privacy concerns [27].

Smartphones provide an accessible platform for behavioral data, recording screen time, app use, typing, and movement without constant active input [28]. Ecological momentary assessment is especially relevant: in a study of 32 patients with temporomandibular-disorder pain who reported awake bruxism in real time for one week, most rated the experience positively and valued the insight into their own

habits, with the main complaint being the short response window [29]. Intensive smartphone use has separately been linked with higher stress, increased bruxism, and greater likelihood of temporomandibular symptoms, and real-time reporting appears more accurate than single questionnaires for fluctuating behaviors, although device variability and privacy remain concerns [30].

Sleep and chronic orofacial pain influence each other bidirectionally: poor sleep intensifies next-day pain, while pain disrupts sleep continuity [31]. In 140 women with temporomandibular disorders and insomnia symptoms studied with wrist actigraphy and daily diaries, both total sleep time and time awake after sleep onset predicted next-day pain severity, and the impact of poor sleep was stronger on days when the rest-activity rhythm was more fragmented [32]. High levels of jaw overuse behavior are further associated with greater daytime sleepiness and jaw functional limitation, and sleeping in positions that load the jaws is reported by most patients across subtypes [33]. Consumer wearables estimate total sleep time and efficiency reasonably well, though they remain less precise for sleep staging [17].

Objective jaw-movement analysis is central to decoding chronic orofacial pain, quantifying opening range, speed, deviation, and joint sounds that are difficult to capture by observation alone [34]. The hydrogel sensor indicated the precise timing of joint clicking, and hearables with inertial units have recorded jaw motion during natural activity to support non-invasive screening [35]. Combining kinematic data with masseter electromyography improves diagnostic performance, and machine-learning models trained on these multimodal signals classify patterns of jaw dysfunction with increasing accuracy, although larger validation studies and standardized recording protocols are still needed [22,36].

Digital analysis of speech and facial expression is an emerging, non-invasive approach [19]. Systematic reviews of work from 2015 to 2025 report that facial-expression-

recognition models detect pain with accuracy from roughly 70% to over 90%, with deep-learning methods and multimodal systems outperforming simpler single-modality approaches [37]. Evidence specific to orofacial pain is limited: a 2025 study of automated face-coding software in 57 patients with dental pain found that although pain scores fell markedly after treatment, the software detected no significant change in facial expression, indicating limited current sensitivity to pain relief [38]. Performance is also affected by lighting, noise, head movement, and cultural differences in pain expression, and continuous facial and voice recording raises significant privacy concerns; speech and facial analysis is therefore best regarded at present as a complementary dimension rather than a primary diagnostic method [39].

ARTIFICIAL INTELLIGENCE FOR MULTIDIMENSIONAL PAIN DIAGNOSIS

Artificial intelligence has emerged as a valuable tool for diagnosis, clinical decision-making, and outcome prediction in chronic orofacial pain [40]. Machine learning is the most widely used approach, enabling algorithms to identify complex patterns in large datasets and to generate predictive models for classification, risk estimation, and outcome support through supervised, unsupervised, or semi-supervised methods [41]. In dentistry and orofacial healthcare, machine learning has shown promising diagnostic performance and the potential to function as an effective clinical decision-support tool [27]. The principal applications are summarized in Table 3.

One of the most developed imaging applications is radiomics, which extracts quantitative imaging biomarkers from conventional images beyond what visual assessment can appreciate [42]. With the widespread use of computed tomography and cone-beam computed tomography in oral and maxillofacial imaging, radiomic and deep-learning models can automatically detect, segment, and classify a broad range of conditions, including cysts, tumors, cervical lymph nodes, temporomandibular joint disorders,

Table 3. Artificial intelligence approaches applied to the multidimensional diagnosis of chronic orofacial pain [27-30].

AI approach	Application in orofacial pain	Current status
Machine learning	Classification, risk estimation, decision support	Promising performance; needs external validation
Radiomics	Quantitative imaging biomarkers from CT and CBCT	Detection, segmentation, and classification of lesions
Multimodal prediction	Integration of imaging, clinical, biological, psychosocial data	Higher accuracy than imaging alone
Clinical decision support	Diagnosis and outcome prediction alongside the clinician	Interpretability and integration still required

mandibular fractures, and maxillary sinus pathology, and have shown value in identifying occult nodal metastasis and joint osteoarthritis [28,43].

Because chronic pain is multifactorial, it cannot be characterized by imaging alone. Models that integrate imaging biomarkers with clinical, biological, genetic, and psychosocial data achieve greater diagnostic and prognostic accuracy: a UK Biobank analysis of more than 523,000 participants found that combining biological markers with psychosocial factors improved prediction of chronic-pain conditions, underlining the value of multimodal frameworks for capturing the mechanisms underlying chronic orofacial pain [29,30].

Several obstacles nevertheless remain before routine clinical use. Most models require external validation across diverse populations and standardized diagnostic protocols to ensure reproducibility, limitations driven largely by data heterogeneity and insufficient validation [44]. Ethical implementation, model interpretability, and integration with established frameworks such as the Diagnostic Criteria for Temporomandibular Disorders will be essential for clinician acceptance, and continued interdisciplinary collaboration and prospective multicenter studies are expected to support reliable, explainable, and personalized tools [30].

PRECISION THERAPEUTICS

Precision therapeutics represents the clinical translation of mechanism-based classification. Its objective is not merely to assign patients to categories but to determine which biological, sensory, psychological, and behavioral processes sustain pain in each individual, since patients with the same diagnosis may differ substantially in central sensitization, inflammatory activity, somatosensory dysfunction, emotional distress, functional limitation, and treatment responsiveness [45]. Precision care therefore requires an integrated pathway in which stratification informs biomarker interpretation, therapeutic selection, and continuous reassessment [46].

Patient stratification is the foundation of this model. Conventional labels often group biologically heterogeneous patients together, limiting prediction of prognosis or response. A more informative approach combines pain characteristics, quantitative sensory findings, psychosocial assessment, functional status, prior treatment response, and, where available, genetic or molecular information. Research on resistant myofascial temporomandibular disorder pain has shown that non-response may be associated with distinct somatosensory, psychosocial, and genetic profiles [33,46], and externally validated

models suggest that pain on mandibular movement, pain distribution, treatment expectation, and central sensitization may identify patients more likely to benefit from manual and rehabilitative therapy [47].

Once meaningful subgroups are identified, biomarkers may refine treatment selection and monitoring. Inflammatory cytokines, neuropeptides, oxidative-stress mediators, salivary proteins, and endocrine and circulating molecular signals have been investigated as indicators of pain mechanism and disease activity [35-36]. Saliva is particularly attractive because it can be collected non-invasively and repeatedly, allowing longitudinal assessment. Biomarker-guided treatment nonetheless remains emerging rather than established: differences in sampling, analysis, diagnostic criteria, and populations limit reproducibility, so biomarkers should complement rather than replace clinical and psychosocial assessment, with their most immediate value in identifying mechanistic subgroups and monitoring biological response [47,48].

Neuromodulation offers a direct example of mechanism-targeted therapy. Repetitive transcranial magnetic stimulation and related non-invasive techniques aim to modify dysfunctional cortical and subcortical pain-processing networks rather than simply suppress peripheral symptoms. Selected patients with chronic facial pain may experience meaningful analgesia after motor-cortex stimulation, while others respond poorly, and baseline disability, anxiety, pain duration, sensory abnormality, and pain intensity may influence outcome [37,49]. Neuromodulation should therefore be reserved for carefully characterized patients with persistent or refractory pain, with standardized outcome monitoring and reassessment of responder status.

Personalized treatment also requires matching pharmacological and behavioral interventions to the dominant mechanism. Neuropathic features may justify centrally acting medication, whereas nociplastic presentations may respond better to multimodal strategies addressing central sensitization, maladaptive beliefs, sleep disruption, stress, and functional avoidance. Comparative evidence and clinical guidelines support cognitive behavioral therapy, supervised exercise, manual therapy, education, relaxation, and biofeedback as components of chronic temporomandibular-disorder pain management [38-40]. These should not be delivered as uniform packages; intensity and combination should reflect psychosocial risk, functional impairment, preference, comorbidity, and prior experience. Taken together, precision therapeutics forms a coherent pathway from mechanism identification to individualized intervention that digital phenotyping and artificial intelligence may increasingly support [7,49].

CONCLUSION

Chronic orofacial pain can no longer be understood through symptom-based labels alone, and the evidence reviewed supports reframing it around the biological mechanisms that drive it, integrating neuroimmune dysregulation,

the nociceptive, neuropathic, and nociplastic framework, digital phenotyping, and artificial intelligence into a single precision-pain model whose elements and relationships are shown in Figure 2.

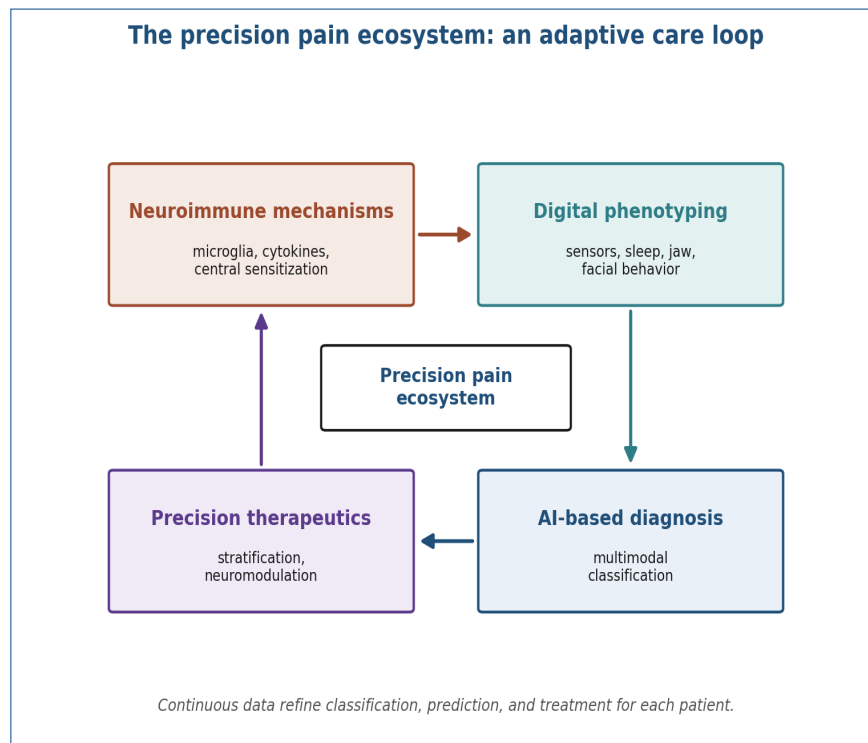


Figure 2. The precision pain ecosystem. Neuroimmune mechanisms, digital phenotyping, artificial intelligence, and precision therapeutics form an adaptive loop in which continuous data refine classification, prediction, and treatment for each patient [41-43].

Digital biomarkers derived from wearables, smartphones, and sensors are emerging as a bridge between mechanistic classification and clinical practice, capable of signaling the transition from health toward disease before symptoms become disabling, with body-movement and voice-based markers as early examples; no single biomarker is likely to capture the full complexity of pain, so a composite, multimodal signature integrating imaging, molecular, and behavioral data is more likely to succeed clinically. Continuous, AI-enabled remote monitoring shifts assessment from episodic snapshots to longitudinal observation, detecting early physiological change before it becomes clinically apparent and allowing treatment to be adjusted between visits. Predictive relapse modeling is a plausible further step, since machine-learning models already anticipate flares in other chronic inflammatory diseases such as rheumatoid arthritis, although comparable tools for myofascial and temporomandibular pain are not yet clinically available and require external validation, pointing ultimately toward digital-twin learning health systems. The overall answer is therefore a qualified one:

chronic orofacial pain can in principle be reclassified by mechanism rather than symptom, but this has not yet been shown to improve outcomes in routine practice, since prospective validation, standardized data protocols, and interdisciplinary integration remain largely absent. The direction is nonetheless clear, as management moves from static, symptom-based diagnosis toward a continuously adaptive, mechanism-informed, and personalized model of care.

REFERENCES

1. Priyank H, Shankar Prasad R, Shivakumar S, Sayed Abdul N, Pathak A, Cervino G, et al. Management protocols of chronic orofacial pain: a systematic review. *Saudi Dent J.* 2023;35(5):395-402. doi:10.1016/j.sdentj.2023.04.003.
2. Karamat A, Smith JG, Melek LNF, Renton T. Psychologic impact of chronic orofacial pain: a critical review. *J Oral Facial Pain Headache.* 2022;36(2):103-140. doi:10.11607/ofph.3010.

3. Canfora F, Ottaviani G, Calabria E, Pecoraro G, Leuci S, Coppola N, et al. Advancements in understanding and classifying chronic orofacial pain: key insights from biopsychosocial models and international classifications (ICHD-3, ICD-11, ICOP). *Biomedicines*. 2023;11(12):3266. doi:10.3390/biomedicines11123266.
4. Sadighparvar S, Al-Hamed FS, Sharif-Naeini R, Meloto CB. Preclinical orofacial pain assays and measures and chronic primary orofacial pain research: where we are and where we need to go. *Front Pain Res (Lausanne)*. 2023;4:1150749. doi:10.3389/fpain.2023.1150749.
5. Calabro RS, Calderone A, Bonanno L, Militi D, Militi A. Advanced, pharmacological and complementary interventions for chronic or recurrent orofacial pain conditions: a systematic evidence map with selective meta-analyses. *J Headache Pain*. 2026;27(1):95. doi:10.1186/s10194-026-02300-7.
6. Day MA, Ehde DM, Bindicsova I, Jensen MP. Understanding the role of therapist quality in accounting for heterogeneity of patient outcomes in psychosocial chronic pain treatments. *J Pain*. 2024;25(4):843-856. doi:10.1016/j.jpain.2023.10.007.
7. Kang Y, Fu Y, Jian K, Liu J, Shao L. Decoding orofacial pain: a translational review of mechanisms and novel therapies. *J Headache Pain*. 2025;26(1):252. doi:10.1186/s10194-025-02173-2.
8. Shraim MA, Sluka KA, Sterling M, Arendt-Nielsen L, Argoff C, Bagraith KS, et al. Features and methods to discriminate between mechanism-based categories of pain experienced in the musculoskeletal system: a Delphi expert consensus study. *Pain*. 2022;163(9):1812-1828. doi:10.1097/j.pain.0000000000002577.
9. Yang JX, Wang HF, Chen JZ, Li HY, Hu JC, Yu AA, et al. Potential neuroimmune interaction in chronic pain: a review on immune cells in peripheral and central sensitization. *Front Pain Res (Lausanne)*. 2022;3:946846. doi:10.3389/fpain.2022.946846.
10. Inslicht SS, Niles AN, Metzler TJ, Lipshitz SL, Otte C, Milad MR, et al. Neuroimmune mechanisms in chronic pain and trauma. *Front Integr Neurosci*. 2022;16:842751. doi:10.3389/fnint.2022.842751.
11. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Target Ther*. 2023;8(1):359. doi:10.1038/s41392-023-01588-0.
12. Schumacher MA. Peripheral neuroinflammation and pain: how acute pain becomes chronic. *Curr Neuropharmacol*. 2024;22(1):6-14. doi:10.2174/1570159X21666230808111908.
13. Hore Z, Denk F. Neuroimmune interactions in chronic pain: an interdisciplinary perspective. *Pain*. 2023. doi:10.1097/j.pain.0000000000002890.
14. Bhattacharya A, Drevets WC. Neuroimmune interactions in pain: mechanisms and therapeutic opportunities. *Nat Rev Drug Discov*. 2022. doi:10.1038/s41573-022-00557-6.
15. Yang S, Chang MC. Neuromodulatory signaling in chronic pain patients: a narrative review. *Cells*. 2025. PMID:40940732.
16. Su PP, Zhang L, He L, Zhao N, Guan Z. The role of neuro-immune interactions in chronic pain: implications for clinical practice. *J Pain Res*. 2022;15:2223-2248. doi:10.2147/JPR.S367437.
17. Mun CJ, Tsang S, Reid MJ, Tennen H, Haythornthwaite JA, Finan PH, et al. Effects of sleep and circadian rest-activity rhythms on daily pain severity in women with temporomandibular disorders. *Pain*. 2025;166(7):1487-1496. doi:10.1097/j.pain.0000000000003578.
18. Li Y, Wang M, Qiu S, Chen J, Wang F. Current status and future perspectives of wearable technologies for oral health in clinical applications. *Diagnostics (Basel)*. 2026;16(7):1015. doi:10.3390/diagnostics16071015.
19. Artificial intelligence for pain assessment via facial expression recognition (2015-2025): a systematic review. *Explor Med*. 2025. doi:10.37349/emed.2025.1001370.
20. Yan Y, Yu L, Zhang X, Han Q, Yang Z, Lu X, et al. Instantaneous self-recovery and ultra-low detection limit hydrogel electronic sensor for temporomandibular disorders intelligent diagnosis. *Nat Commun*. 2025;16(1):839. doi:10.1038/s41467-025-55996-7.
21. Stillhart A, Hafliger R, Takeshita L, Stadlinger B, Leles CR, Srinivasan M. Screening for dental pain using an automated face coding (AFC) software. *J Dent*. 2025;155:105647. doi:10.1016/j.jdent.2025.105647.
22. Tsuji H, Amesaka T, Usuda S, Muraoka W, Nakagawa T, Sugiura Y. HearTMD: detection of temporomandibular disorder using hearables. In: *Adjunct Proceedings of the 38th Annual ACM Symposium on User Interface Software and Technology (UIST Adjunct 25)*. 2025. doi:10.1145/3746058.3758416.

23. Colonna A, Bracci A, Ahlberg J, Segu M, Lombardo L, Manfredini D. The determination of patient-based experiences with smartphone-based report of awake bruxism using a diary. *Clin Oral Investig*. 2025;29(1):40. doi:10.1007/s00784-024-06114-2.
24. Yap AU, Lee DZR, Cao Y, Zhang MJ. Insights into oral behaviours among temporomandibular disorder patients: associations with psychological distress, sleep propensity and jaw function. *J Oral Rehabil*. 2025. doi:10.1111/joor.14028.
25. Kamath P, Kamath P, Saldanha SJR, Shetty TB, Rodrigues SJ, Mahato M, et al. A brief exploration of artificial intelligence in dental healthcare: a narrative review. *F1000Res*. 2024;13:37. doi:10.12688/f1000research.140481.2.
26. Feher B, Tussie C, Giannobile WV. Applied artificial intelligence in dentistry: emerging data modalities and modeling approaches. *Front Artif Intell*. 2024;7:1427517. doi:10.3389/frai.2024.1427517.
27. Farook TH, Jamayet NB, Abdullah JY, Alam MK. Machine learning and intelligent diagnostics in dental and orofacial pain management: a systematic review. *Pain Res Manag*. 2021;2021:6659133. doi:10.1155/2021/6659133.
28. Hung KF, Ai QYH, Wong LM, Yeung AWK, Li DTS, Leung YY. Current applications of deep learning and radiomics on CT and CBCT for maxillofacial diseases. *Diagnostics (Basel)*. 2022;13(1):110. doi:10.3390/diagnostics13010110.
29. Fillingim M, Tanguay-Sabourin C, Parisien M, Zare A, Guglietti GV, Norman J, et al. Biological markers and psychosocial factors predict chronic pain conditions. *Nat Hum Behav*. 2025;9(8):1710-1725. doi:10.1038/s41562-025-02156-y.
30. Iosif L, Imre M, Wagner AG, Tancu AMC, Didilescu AC, Brand HS, et al. Artificial intelligence in orofacial pain: diagnostic and predictive performance across machine learning and deep learning models. *Diagnostics (Basel)*. 2026;16(12):1801. doi:10.3390/diagnostics16121801.
31. Dhopte A, Singh V, Priya JSJ, Bhatt S, Ingale PC, Bagde H. Radiomics and machine learning in early detection of oral potentially malignant disorders. *J Pharm Bioallied Sci*. 2025;17(Suppl 4):S2852-S2854. doi:10.4103/jpbs.jpbs_1442_25.
32. Binaljadm TM, Al-Gabri RS, Saker S, AboAlrejal HO, Saeed MH, Alqutaibi AY. Temporomandibular disorders diagnosis: current challenges and the promising role of artificial intelligence. *Eur J Dent*. 2026. doi:10.1055/s-0046-1816081.
33. De la Torre Canales G, Christidis N, Grigoriadis A, Strandberg T, Montan V, Ernberg M, et al. Who is the patient with resistant myofascial temporomandibular disorder pain? Somatosensory, psychosocial, and genetic characterization. *J Headache Pain*. 2025;26. PMID:40329183.
34. Asquini G, Devecchi V, Borromeo G, Tessera P, Russillo A, Michelotti A, et al. External validation of a clinical prediction tool for the use of manual therapy in patients with temporomandibular disorders. *J Oral Rehabil*. 2026;53(2):515-528. doi:10.1111/joor.70092.
35. Soares JM, Carneiro BD, Pozza DH. The role of biomarkers in temporomandibular disorders: a systematic review. *Int J Mol Sci*. 2025;26(13):5971. doi:10.3390/ijms26135971.
36. Alam MK, Zaman MU, Alqhtani NR, et al. Salivary biomarkers and temporomandibular disorders: a systematic review conducted according to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. *J Oral Rehabil*. 2024;51:416-426. PMID:37731276.
37. Saisanen L, Huttunen J, Hypponen J, Nissen M, Kurki M, Julkunen P, et al. Efficacy and tolerability in patients with chronic facial pain of two consecutive treatment periods of repetitive transcranial magnetic stimulation applied over the facial motor cortex. *Neurophysiol Clin*. 2022;52(2):95-108. doi:10.1016/j.neucli.2022.03.001.
38. Yao L, Sadeghirad B, Li M, Li J, Wang Q, Crandon HN, et al. Management of chronic pain secondary to temporomandibular disorders: a systematic review and network meta-analysis of randomised trials. *BMJ*. 2023;383:e076226. doi:10.1136/bmj-2023-076226.
39. Busse JW, Casassus R, Carrasco-Labra A, Durham J, Mock D, Zakrzewska JM, et al. Management of chronic pain associated with temporomandibular disorders: a clinical practice guideline. *BMJ*. 2023;383:e076227. doi:10.1136/bmj-2023-076227.
40. Christidis N, Al-Moraissi EA, Al-Ak'hali MS, Minarji N, Zerfu B, Grigoriadis A, et al. Psychological treatments for temporomandibular disorder pain: a systematic review. *J Oral Rehabil*. 2024;51(7):1320-1336. doi:10.1111/joor.13693.
41. Smokovski I, Steinle N, Behnke A, Bhaskar SMM, Grech G, Richter K, et al. Digital biomarkers: 3PM approach revolutionizing chronic disease management. *EPMA*

- J. 2024;15(2):149-162. doi:10.1007/s13167-024-00364-6.
42. Patel PM, Green M, Tram J, Wang E, Murphy MZ, Abd-Elseyed A, et al. Beyond the pain management clinic: the role of AI-integrated remote patient monitoring in chronic disease management: a narrative review. *J Pain Res.* 2024;17:4223-4237. doi:10.2147/JPR.S494238.
 43. Mackey S, Darnall BD, Kao MC. Digital twin learning health systems and multimodal biomarkers transform pain care. *Pain.* 2025. doi:10.1097/j.pain.0000000000003567.
 44. Liikkanen S, Jalkanen T, Makinen M, Huttunen T, Kilpelainen R, Reijula J, et al. Body movement as a digital biomarker in chronic pain rehabilitation: a real-world pilot study using virtual reality. *Front Virtual Real.* 2025;6:1601823. doi:10.3389/frvir.2025.1601823.
 45. Tobey-Moore L, Iyer A, Wilkerson C, Annichiarico C. Leveraging voice biomarkers to quantify chronic pain: a rapid review. *Front Pain Res (Lausanne).* 2026;6:1678160. doi:10.3389/fpain.2025.1678160.
 46. Mackey S, Aghaeepour N, Gaudilliere B, Kao MC, Kaptan M, Lannon E, et al. Innovations in acute and chronic pain biomarkers: enhancing diagnosis and personalized therapy. *Reg Anesth Pain Med.* 2025;50:110-120. doi:10.1136/rapm-2024-105934.
 47. Zhong T, William HM, Jin MY, Abd-Elseyed A. A review of remote monitoring in neuromodulation for chronic pain management. *Curr Pain Headache Rep.* 2024. doi:10.1007/s11916-024-01327-2.
 48. Vodencarevic A, Tascilar K, Hartmann F, Reiser M, Hueber AJ, Haschka J, et al. Advanced machine learning for predicting individual risk of flares in rheumatoid arthritis patients tapering biologic drugs. *Arthritis Res Ther.* 2021;23:67. doi:10.1186/s13075-021-02439-5.

Cite this article: Maria Perez Gonzalez, Yennifer Rondon Lozada, Yndira Parchman, *et al.* *Decoding Chronic Orofacial Pain: Neuroimmune Crosstalk, Digital Phenotyping, and Artificial Intelligence for Precision Pain Medicine. International Journal of Research in Medical and Clinical Science (IJRMCS).* 2026; 4(2): 95-104.

Copyright: © 2026. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.