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# Review

# Using artificial intelligence to improve pain assessment and pain management: a scoping review

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#### **ABSTRACT**

**Context**: Over 20% of US adults report they experience pain on most days or every day. Uncontrolled pain has led to increased healthcare utilization, hospitalization, emergency visits, and financial burden. Recognizing, assessing, understanding, and treating pain using artificial intelligence (AI) approaches may improve patient outcomes and healthcare resource utilization. A comprehensive synthesis of the current use and outcomes of AI-based interventions focused on pain assessment and management will guide the development of future research.

**Objectives:** This review aims to investigate the state of the research on Al-based interventions designed to improve pain assessment and management for adult patients. We also ascertain the actual outcomes of Al-based interventions for adult patients.

**Methods:** The electronic databases searched include Web of Science, CINAHL, PsycINFO, Cochrane CENTRAL, Scopus, IEEE Xplore, and ACM Digital Library. The search initially identified 6946 studies. After screening, 30 studies met the inclusion criteria. The Critical Appraisals Skills Programme was used to assess study quality.

**Results:** This review provides evidence that machine learning, data mining, and natural language processing were used to improve efficient pain recognition and pain assessment, analyze self-reported pain data, predict pain, and help clinicians and patients to manage chronic pain more effectively.

**Conclusions:** Findings from this review suggest that using Al-based interventions has a positive effect on pain recognition, pain prediction, and pain self-management; however, most reports are only pilot studies. More pilot studies with physiological pain measures are required before these approaches are ready for large clinical trial.

Key words: artificial intelligence, pain assessment, pain management, pain, pain control

#### INTRODUCTION

More than 50 million American adults (20.5%) report pain on most or every day.<sup>29</sup> Pain has been linked to sleep disturbance, restrictions in physical activities, limitations in daily functioning (eg, social activities and activities of daily living), common mental problems,

and reduced quality of life.<sup>6,14,28,29,31</sup> Uncontrolled pain has also been found to increase healthcare utilization, hospitalization, emergency department visits, and financial burden.<sup>4,5,8</sup> According to the results of the Medical Expenditure Panel Survey, financial costs of managing pain had been up to \$635 billion in the United States.<sup>39</sup>

Recognizing, assessing, understanding, and treating pain can improve outcomes of patients and healthcare use. 4,5,8 A considerable amount of literature has been published on pain assessment and pain management, mainly focusing on finding comprehensive pain assessment and optimal multidisciplinary management approaches. 12,26 One review by Helfand and Freeman 12 synthesized pain assessment and pain management in adult medical inpatients. They proposed that more research is needed to provide timely care and effective pain management in clinical settings. 12 They further pointed out that little is known about automatic pain intensity screening. 12 Similarly, Nuseir et al<sup>26</sup> stated that pain management is multifactorial and complex, so it requires efforts from professionals from multiple disciplines. Together these papers indicate that automation-oriented approaches with multidisciplinary input could improve the quality of pain care. One such automation approach is artificial intelligence (AI).

In recent years, there has been an increasing interest in the implementation of AI in medicine. 10 The term AI has come to be used to refer to a branch of engineering that implements novel concepts and novel solutions to resolve complex challenges. 10 The spectrum of AI includes, but is not limited to, machine learning (ML), deep learning, data mining, and natural language processing. 10 ML is defined as the discovery and testing of algorithms that assist pattern recognition, classification, and prediction, based on models built from existing data.<sup>36</sup> ML does not use explicit programming but requires features defined by humans. 42 Deep learning is a subset of ML based on artificial neural networks (ANNs) that does not require any feature definition from humans.<sup>36</sup> Data mining refers to the process of uncovering patterns and transforming them into insight from large data sets.<sup>37</sup> In contrast to data mining, which solely seeks out patterns that already exist in the data, ML goes beyond the past to predict future outcomes based on the existing data. 42 Natural language processing is the computerized approach to understand, interpret, and manipulate spoken words and text.<sup>38</sup>

Literature reviews have recognized the critical role AI has in clinical settings. Triantafyllidis and Tsanas<sup>34</sup> conducted a review to appraise the literature on ML application in real-life digital health-care services. They found that digital health approaches integrating ML models into real-life research could be useful and efficient.<sup>34</sup> AI could be used to diagnose diseases, select treatments, monitor patients, and many others.<sup>24,25</sup> Specifically, AI have contributed to high-performance data-driven medicine, to refine care pathways, to recommend optimal medications for patients, and to enhance clinical assertions.<sup>11,33</sup> Although these articles outlined significant findings for AI use in medicine, they mainly focused on general health care in clinical settings. To date, little attention has been paid to AI in pain search specifically. It is hoped that this review will contribute to a deeper understanding of the use of AI in pain research to improve clinical practice.

Collectively, studies mentioned above have demonstrated that AI has advanced understanding in multiple areas of clinical care, but none has fully discussed the application of AI to enhance pain assessment and management. In the last 5 years, a growing number of studies have emerged that use AI-based interventions to improve pain recognition, prediction, and self-management. A comprehensive synthesis of the current use of AI-based interventions in pain assessment and management and their outcomes will help to guide the development of future research and inform best practices. Thus, two primary aims of this review are: (1) to investigate the state of the research of AI-based interventions designed to improve pain assessment and management for adult patients in clinical settings

and (2) to ascertain the outcomes of AI-based interventions in this population.

Since our goal is to synthesize findings that may help understand and evaluate potential clinical use, we exclude the studies that do not test an AI-based intervention. We exclude studies focused on the pediatric population because pediatric pain has different features, along with their physiology, assessment, management based on patient's age, developmental stage, communication skills, and their medical condition. We also exclude studies that used AI on physiological signals. Although such studies can illuminate the potential mechanisms of the pain experience, the AI plays a limited role in the clinician's or patient's decision-making process. A recently published systematic review provides a comprehensive summary of the current knowledge regarding the association between physiological signals and pain. <sup>56</sup>

#### **METHODS**

The process consists of five stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) summarizing and reporting the results.<sup>41</sup>

#### Information sources and search strategy

Sensitive search strategies comprised of both index and keyword terms were developed with the assistance of a health sciences librarian with expertise in conducting literature searches for systematic reviews for the following databases: Web of Science, PubMed, CINAHL (Cumulative Index for Nursing Allied Health Literature, EBSCO platform), PsycINFO (APA platform), Cochrane CENTRAL (Wiley platform), Scopus (Elsevier platform), IEEE Xplore (Institute of Electrical and Electronics Engineers), and ACM Digital Library (Association for Computing Machinery). A search was performed encompassing all articles on October 4, 2022. To enhance the comprehensiveness of our search strategies, we reviewed the references of relevant literature reviews and their search strategies, as well as consulted experts in pain management and AI. The full PubMed search strategy, as detailed in Supplementary Appendix S1, was adapted for use with the other electronic databases. Complete search strategies are available upon request.

# Inclusion and exclusion criteria

The inclusion criteria were: (1) study design: feasibility studies, pilot studies, evaluation studies, experimental studies, and quasi-experimental studies and (2) study focus: a study testing an AI including ML, data mining, and natural language processing to improve pain assessment and management for adult patients (older than 18 years old). The exclusion criteria were: (1) language: articles not written in English, (2) study design: studies that do not test an AI-based intervention or focus on physiological signals of pain, (3) article type: nonpeer-reviewed studies, case study, conference abstracts, editorials, and reviews, and (4) population: pediatric population.

#### Study selection process

The study selection process is summarized in Figure 1. The original search identified 6946 unique articles. After duplicates were deleted, a total of 3545 papers were imported into Rayyan, a web-based systematic review program, and two reviewers screened the titles and abstracts of the entire set independently by applying the inclusion and exclusion criteria (MZ and LZ). The percentage agreement of the initial title/abstract review between the two reviewers was 96%, and the discrepancies were resolved through discussion among the

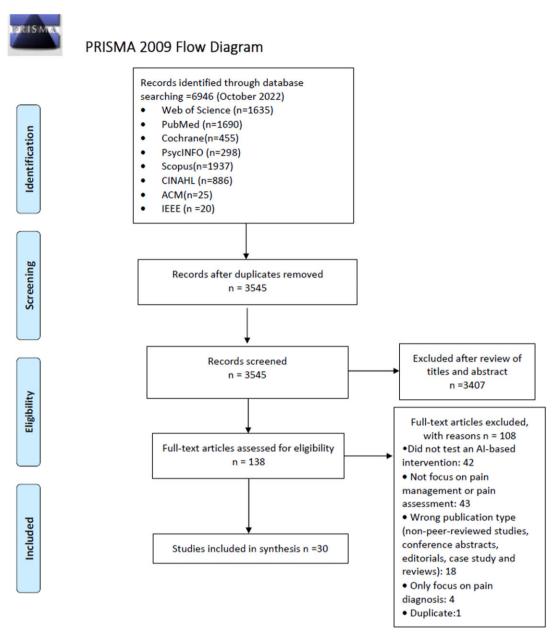


Figure 1. PRISMA flow diagram.

authors. After screening the titles and the abstracts, an additional 3407 articles were removed, and 138 full-text articles were reviewed in depth by the same two reviewers. The percentage agreement of the full-text review was 91.8%. Discrepancies were resolved through consensus discussions. We compared the included studies in our review with other reviews in the literature to ensure all important studies on this topic were included. Finally, 30 articles were included in this scoping review.

# Quality assessment

The quality of each included study was assessed using the Critical Appraisals Skills Programme (CASP).<sup>35</sup> The CASP classifies studies into eight broad categories: qualitative research; randomized controlled trials (RCTs); systematic reviews; cohort studies; case control

studies; economic evaluations; diagnostic studies; and clinical prediction rule. The CASP consists of different screening questions based on the study categories. A score in percentage was assigned to each study based on the number of criteria met.

### Data extraction

For each included study, information on study design, settings, diagnosis, sample, sample size, methods, and major outcomes is extracted.

## **RESULTS**

Thirty papers fulfilled the criteria for inclusion. Tables 1 and 2 list a summary of key characteristics of included studies.

**Table 1.** A summary of key characteristics of included studies (N-30)

= 30)	Number of studies (%)
	Number of studies (%)
blication year	
• Before 2010	4 (13%)
• 2010–2014	1 (3%)
• 2015–2020	14 (47%)
• 2021–2022	11 (37%)
ountry	
<ul> <li>United States</li> </ul>	13 (43.3%)
• China	3 (10%)
• Denmark	2 (7%)
• India	2 (7%)
Australia	1 (3%)
• Germany	1 (3%)
<ul> <li>Finland</li> </ul>	1 (3%)
Czech Republic	1 (3%)
• India	1 (3%)
<ul> <li>Kingdom of Saudi Arabia</li> </ul>	1 (3%)
• Iran	1 (3%)
• Korea	1 (3%)
• Japan	1 (3%)
<ul> <li>United Kingdom</li> </ul>	1 (3%)
• Taiwan	1 (3%)
pes of AI approaches	
Pain management	10 (33%)
Pain assessment	8 (27%)
• Others	12 (40%)
pes of pain	
Back pain	7 (23%)
Shoulder pain	5 (17%)
<ul> <li>General chronic pain</li> </ul>	5 (17%)
General pain	7 (23%)
<ul> <li>Not specify</li> </ul>	6 (20%)
mple size (# of participants)	
• >500	8 (27%)
• 100–499	10 (33%)
• 50–99	7 (27%)
• 11–49	4 (13%)
• ≤10	1 (3%)
udy design	
<ul> <li>Diagnostic study</li> </ul>	11 (37%)
Pilot study	3 (10%)
Cohort study	5 (17%)
Retrospective study	4 (13%)
<ul> <li>Longitudinal study</li> </ul>	4 (13%)
<ul> <li>Observational Study</li> </ul>	3 (10%)
ttings	
<ul> <li>Community</li> </ul>	18 (60%)
<ul> <li>Pain or primary care clinic</li> </ul>	5 (17%)
<ul> <li>Hospital</li> </ul>	7 (27%)

# Characteristics of included studies

Most included studies were published in the last 10 years (n = 24, 80%). About half of the studies were conducted in the United States (n = 13, 43%). The sample size ranged from 10 to 26 090, varying by the characteristics of the participants and the research aim. Nearly half of the studies (n = 12, 40%) had a sample size of less than 100. If the study was a secondary analysis, it tended to have a larger sample size. Most participants in the studies had experienced pain before the study, including low back pain (n = 7, 23%), shoulder pain (n = 5, 17%), general chronic pain (n = 5, 17%), or surgical pain (n = 2, 7%). Only 15 studies (50%) provided

patients' age information; the mean age ranged from 46.4 to 68 across studies.

### Types and definitions of interventions

We categorized the interventions into the following three main types: (1) AI-based approaches related to pain assessment, which is used here to refer to using AI to assist clinical judgment of pain based on the significance and context of the individual's pain experience, (2) AI-based approaches related to pain prediction and clinical decision support, and (3) AI-based approaches related to pain self-management, which is defined as the process of providing self-care to alleviate or reduce pain with AI-based approaches.

# Type 1: Al-based approaches related to the pain assessment (n = 12, 40%)

Seven studies developed novel models for pain recognition with ML (n=8, 23.3%).  $^{7,17,23,47,49-51}$  In 2011, Lucey et al<sup>23</sup> described an active appearance model-based computer vision system which can detect pain automatically through facial action units. Five years later, Kharghanian and coworkers reported a non-Action Unitsbased model, which entirely used unsupervised learning of facial expressions. 17 In 2018, Dutta and M7 proposed a hybrid model, which consisted of a combination of the Constrained Local Model, active appearance model, and Patch-Based Model. Finally, in 2022, Hosseini et al<sup>49</sup> achieved a promising increase in terms of estimation precision and performance. All of them used the UNBC-MacMaster Shoulder Pain Expression Archive dataset to test their model. 7,17,23,49 A total of 48 398 photographs are included in the database, which features 200 sequences across 25 subjects.<sup>7,17,23,49</sup> They all were able to detect pain successfully with relatively high accuracy. 7,17,23,49 Of note, the last two approaches contributed to automatic pain detection from a live stream even in low-light conditions and with a low-resolution recording device.<sup>7,49</sup> Similarly, Hossain et al found that cloud-assisted pain recognition servers could achieve more than 95% accuracy and generate the response within three seconds. 15 Besides, Wu et al 50 reported that advanced deep learning model could be used for automated pain assessment based on facial expressions in critically ill patients.

Both Fodeh et al<sup>9</sup> and Suominen et al<sup>32</sup> evaluated the AI-based approach to analyze clinical notes to identify components related to pain assessment (n = 2, 12%). To be more specific, Fodeh et al<sup>9</sup> successfully developed a random forest classifier to identify clinical notes with pain assessment information by employing ML algorithms. In the same vein, Suominen et al<sup>32</sup> suggested that pain-related notes encouraged the creation of new pain assessment instruments with human language technology.

Behrman et al evaluated whether ANNs could improve current pain scoring systems.<sup>3</sup> ANNs are computer-based techniques that have been frequently applied for classifying clinical data and patients.<sup>3</sup> They concluded that the accuracy obtained by ANN analysis was only slightly higher than traditional approaches.<sup>3</sup> Furthermore, Atee et al<sup>2</sup> proposed a novel system of pain assessment using a combination of technologies: automated facial recognition and analysis, smart computing, affective computing, and cloud computing for people with advanced dementia. After conducting two prospective observational studies with moderate to severe dementia patients, the author stated that this novel system might contribute to pain assessment for people who cannot verbalize.<sup>2</sup> Taken together, these studies support the notion that AI-based interventions potentially improve pain assessment.<sup>2,3</sup>

Table 2. Data extraction of included studies

Author/year/	Purpose	Study design		Sample			Methods	Major results		
country			Setting	Diagnosis	N	Age (years)				
Гуре 1: AI-based	approach related to the pain asse	ssment								
Lucey/2011/ USA	To describe an active appear- ance model (AAM)-based system that can automati- cally detect the frames in video in which a patient is in pain.	Diagnostic study	Community	Shoulder pain	25	NA	Automatically detecting pain in video through facial action units	<ul> <li>AAM can be used to analyze facial movement in videos compared to the current-state-of-the-art approaches which utilize similarity-normalized appearance features only</li> </ul>		
Kharghanian/ 2016/Iran	To propose a new method for continuous pain detection	Diagnostic study	Community	Shoulder pain	25	NA	A hierarchical unsupervised feature learning approach	<ul> <li>The proposed model was tested, and they achieved near 95% for the area under receiver operating characteristic curve metric that is prominent with respect to the other reported results</li> </ul>		
Dutta/2018/ India	To propose a hybrid model that allowed for efficient pain recognition	Diagnostic study	Community	Shoulder pain	22	NA	Combination of—Constrained Local Model (CLM), Active Appearance Model (AAM), Patch-Based Model, image alge- bra	• This model contributed to a system that enabled the successful detection of pain from a live stream, even with poor lighting and a low-resolution recording device. The final process and output allowed for memory for storage that was reduced up to 40%–55% and an improved processing time of 20%–25%		
Hosseini/ 2022/UK	To develop a highly accurate pain intensity estimation system	Diagnostic study	Community	Shoulder pain	25	NA	Deep Convolutional Neural Net- works model using the transfer learning technique, were a pre- trained Deep Convolutional Neu- ral Networks model is adopted by replacing its dense upper layers, and the model is tuned using painful facial	<ul> <li>The experiments show our method achieves a promising improvement in terms of accuracy and performance to estimate pain intensity and outper- form the-state-of-the-arts models</li> </ul>		
Behrman/ 2006/USA	To evaluate if artificial neural networks (ANNs) can improve upon current pain scoring systems	Diagnostic study	Pain clinic	Chronic pain of 6 months or longer	155	46.4 (21–79)	Classification of patients with pain based on neuropathic pain symp- toms: Comparison of an artificial neural network against an estab- lished scoring system	<ul> <li>The results confirm the clinical experience that groups of pain descriptors rather than single items differentiate between patients with neuropathic and nonneuropathic pain</li> <li>The accuracy obtained by ANN analysis was only slightly higher than that of the traditional approaches, indicating the absence of nonlinear relationships in this dataset</li> <li>Data analysis with ANNs provides a framework that extends what current approaches offer, especially for dynamic data, such as the rating of pain descriptors over time</li> </ul>		

Table 2. continued

Author/year/	Purpose	Study design		Sample			Methods	Major results
ountry			Setting	Diagnosis	N	Age (years)		
Atee/2018/ Australia	To describe a novel method and system of pain assessment using a combination of technologies: automated facial recognition and analysis (AFRA), smart computing, affective computing, and cloud computing (Internet of Things) for people with advanced dementia	and system of pain assess- ment using a combination of technologies: automated facial recognition and anal- ysis (AFRA), smart com- puting, affective computing, and cloud computing (Internet of Things) for people with advanced dementia		Residential Geriatric resi- 74 69 aged care dent facilities		69–98	In blind comparisons with the Abbey Pain Scale, PainChek has been clinically evaluated in aged care residents with moderate to severe dementia in two prospective observational studies. They also provided a comprehensive clinimetric analysis on the performance of the app	PainChek is a comprehensive and evidence-based pain management syster. This novel approach has the potentia to transform pain assessment in peop who are unable to verbalize because can be used by clinicians and carers is everyday clinical practice.
Fodeh/2017/ USA	To analyze unstructured nar- rative text data in the EHR to develop a reliable classi- fier that detects pain assess- ment in clinical notes	Diagnostic study	Department of Veterans Affairs	Patients with musculos- keletal diagnoses	92	Male mean: 68 Female mean: 58	Classifying clinical notes with pain assessment	Developed a Random forest classifier to identify clinical notes with pain asses ment information
Suominen/ 2009/Finland	To test the hypothesize that pain assessment can be supported through human language technology	Diagnostic study	Adult long- term inten- sive care unit	Long-term intensive care patients	516	NA	<ul> <li>Statistically comparing annotations of ten nursing professionals on a set of 1548 documents</li> <li>The aspects considered include the amount and writing style of pain-related notes, pain intensity, and given pain care</li> </ul>	<ul> <li>More than half of the documents cotained information relevant for patients' pain status but it was expressed usually indirectly</li> <li>Also, pain medication was commen as free text</li> <li>Although annotators' pain intensity evaluations diverged, the substantia amount of pain-related notes encou ages developing computational tool for pain assessment</li> </ul>
Hossain/2015/ Kingdom of Saudi Arabia	To better understand cloud- assisted elderly patient care	Diagnostic study	Community	NA	105	Elderly patient	The device captures participants' speech as well as their face image, and sends to the server located in the cloud. In the server, two modalities (speech and face) are processed separately in "voice detection" and "face recognition." Scores from these two components are fused to deliver the final decision of the person's state  Based on the decision, emergency services, regular doctors, or caregivers can be contacted	The proposed recognition system ca achieve more than 95 % accuracy using five instances of cloud server, and the server can generate the response within three seconds

Table 2. continued

Author/year/	Purpose	Study design		Sample			Methods	Major results
country			Setting	Diagnosis	N	Age (years)		
Umapathy/ 2021/India	To perform automated segmentation of facial regions from thermograms using k-means clustering algorithm and to classify the data into normal and orofacial pain categories using various machine learning classifiers     To implement the convolutional neural network for classification of normal and OFP subjects which involves automated feature extraction and feature selection process	Diagnostic study	Hospital patients with orofa- cial pain	Patients with orofacial pain	100	NA	Facial thermograms were segmented using k-means algorithm, then statistical features were extracted and classified into normal and orofacial pain using various machine learning classifier. Further, the deep learning networks such as VGG-16 and DenseNet-121 were used for automated feature extraction and classification of facial thermograms	Computer aided diagnosis of facial thermography could be used as a viable screening device for a reliable identification of tooth pathology before the occurrence of structural changes and complications
Wu/2022/ Taiwan	• to establish the deep learning-based pain classi- fier based on facial expressions	Diagnostic study	Hospital	Critically ill patients	63	NA	Established both image- and video- based pain classifiers through using convolutional neural net- work models, such as Resnet34, VGG16, and InceptionV1 and bidirectional long short-term memory networks	The practical application of deep learning-based automated pain assessment in critically ill patients, and more studies are warranted to validate our findings
Mallol- Ragolta/2020/ Germany	to develop new digital tools that can automatically and objectively assess pain intensity in individuals	Diagnostic study	Community	Chronic Lower Back Pain	36	NA	Curriculum learning approaches to predict the pain intensity level of individuals reported in an 11-point scale from facial expressions	The results obtained using the test partition support the use of Curriculum Learning -based approaches in the automatic prediction of pain from facial features
• •	approaches to pain prediction ar		* *	D	26000	3.7.4		<b>M</b> 1: 1
Nickerson/ 2016/USA	To compare the performance of conventional vs state-of- the-art machine learning techniques in predicting pain response	Cohort study	Shands Medi- cal Center	Patients who underwent nonambu- latory or nonobste- tric surgery	26090	INA	Constructed a neural network based on the long short-term memory architecture and trained it on pain score patterns	Machine learning techniques may offer much benefit for developing smarter postoperative pain management strategies
Lötsch/2018/ Germany	To create a simple question- naire with good predictive power for persisting pain after surgery	Cohort study	Hospital	Women who had unilat- eral non- metasta- sized breast cancer	1000	NA	Machine-learned predictors were first trained with the full-item set of Beck's Depression Inventory (BDI), Spielberger's State Trait Anxiety Inventory (STAI), and the State Trait Anger Expression Inventory (STAXI-2). Subsequently, features were selected from the questionnaires to create predictors having a reduced set of items	A combined seven-item set of 10% of the original psychological questions from STAI and BDI, provided the same predictive performance parameters as the full questionnaires for the development of persistent postsurgical pain

Table 2. continued

Author/year/	Purpose	Study design		Sample			Methods	Major results	
country			Setting	Diagnosis	N	Age (years)			
Honcu/2020/ Czech Repub- lic	To demonstrate the effective- ness of the diagnostic and therapeutic medical infor- mation system Computer Kinesiology in physiother- apy in patients with low back pain who were not responding to conventional therapy	Pilot study	Community	Acute and chronic back pain; healthy vol- unteers	173	<43.7 years: 48.8 (37.9– 59.9) ≥43.7 years: 62.1 (51.0– 72.3)	All subjects were examined three times by the diagnostic part of the Computer Kinesiology method	The author demonstrated a high therapeu tic efficacy of the Computer Kinesiology system in patients with back pain and in persons without back pain who used the Computer Kinesiology system for primary and secondary prevention of back pain	
Knab/2001/ USA	To test the hypothesis that computer-based decision support (CBDS) could allow primary care physicians (PCPs) to more effectively manage patients with chronic pain	Longitudinal study	Pain Clinic	Chronic pain	50	NA	<ul> <li>A pain specialist used a decision support system to determine appropriate pain therapy and sent letters to the referring physicians outlining these recommendations</li> <li>Separately, five board-certified PCPs used a CBDS system to "treat" the 50 cases</li> <li>Two pain specialists reviewed the PCPs' outcomes and assigned medical appropriateness</li> <li>One year later, the hospital database provided information on how the actual patients' pain was managed and the number of patients re-referred by their PCP to the pain clinic</li> </ul>	<ul> <li>On the basis of CBDS recommendations, the PCP subjects "prescribed" additional pain therapy in 213 of 250 evaluations (85%), with a medical appropriateness score of 5.5 ± 0.1</li> <li>Only 25% of these chronic pain patients were subsequently re-referred to the pain clinic within 1 year</li> <li>The use of a CBDS system may improve the ability of PCPs to manage chronic pain and may also facilitate screening of consults to optimize specialist utilization</li> </ul>	
Lopez-Marti- nez/2019/USA	To apply reinforcement learning for the recommen- dation of pain manage- ment regimes and the automatic dosing of anal- gesics	Retrospective study	Intensive care unit	Patient with pain	6843	NA	A sequential decision-making framework for opioid dosing based on deep reinforcement learning was presented. It provides real-time clinically interpretable dosing recommendations, personalized according to each patient's evolving pain and physiological condition. Morphine was the focus on morphine, one of the most prescribed opioids     To train and evaluate the model, Retrospective data was used from the publicly available MIMIC-3 database	Reinforcement learning may be used to aid decision-making in the intensive care setting by providing personalized pain management interventions	

Table 2. continued

Author/year/	Purpose	Study design		Sample			Methods	Major results	
country			Setting	Diagnosis	N	Age (years)			
Shim/2021/ Korea	To develop machine learning models that can accurately predict the risk of chronic lower back pain	Retrospective study	Community	Respondents who par- ticipated in the Korea National Health and Nutrition Examina- tion Sur- veys	6119	64 (56–72)	Classification models with machine learning algorithms were devel- oped and validated to predict chronic lower back pain	Machine learning could be effectively applied in the identification of populations at high risk of chronic lower back pain	
Hao/2022/ China	To investigate use of multi- data analysis based on an artificial neural network (ANN) to predict long- term pain outcomes after microvascular decompres- sion in patients with trige- minal neuralgia and to explore key predictors	Retrospective study	Hospital	Patients with trigeminal neuralgia	1041	53.6 ± 10.2	Multidata analysis based on an ANN to predict long-term pain outcomes	The ANN model, constructed using multi- ple data, predicted long-term pain prognosis after microvascular decom- pression in patients with trigeminal neuralgia objectively and accurately. The model was able to assess the importance of each factor in the predic- tion of pain outcome	
Guan/2021/ USA	To develop and evaluate deep learning (DL) risk assessment models for predicting pain progression in subjects with or at risk of knee osteoarthritis	Longitudinal study	Community	Subjects with or at risk of knee OA	4674	61 ± 9.2	A DL model was developed to predict pain progression using baseline knee radiographs. An artificial neural network was used to develop a traditional risk assessment model to predict pain progression using demographic, clinical, and radiographic risk factors	DL models using baseline knee radio- graphs had higher diagnostic perform- ance for predicting pain progression than traditional models using demo- graphic, clinical, and radiographic risk factors	
Gao/2021/ China	To evaluate the accuracy of back propagation artificial neural network model for predicting postoperative pain following root canal treatment	Cohort study	Hospital	Patients who received root canal treatment	300	≤20: 0; 20– 30: 0.25; 30–40: 0.5; 40–60: 0.75; ≥60:	Neural network model was trained and tested	Back propagation network model could be used to predict postoperative pain following root canal treatment and showed clinical feasibility and applica- tion value	
Goldstein/ 2020/USA	To develop a mobile platform for tracking pain patients' emotions, cliexa-EASE, which allows patients to self-report BSMs of emotional states, pain, stress and fatigue in a user-friendly and engaging way	Cohort study	Community	Chronic pain	84	43.23 ± 15.68	Developed a mobile platform for measuring pain, emotions, and associated bodily feelings in chronic pain patients in their daily life conditions	The best predictors of future pain were interactive effects of body maps of fatigue with negative affect and positive affect with past pain	

Table 2. continued

Author/year/	Purpose	Study design	Sample				Methods	Major results		
country			Setting	Diagnosis	N	Age (years)	-			
Type 3: AI-based Sandal/2020/ Denmark	To investigate the basis for recruitment and screening procedures for the subsequent randomized controlled trial     To test the inclusion process in relation to question-	management Pilot study	Primary care clinic	Low back pain within the past 8 weeks	51	45.5 ± 15	Use the selfBACK app for 6 weeks The app provided weekly tailored self-management plans targeting physical activity, strength and flexibility exercises, and education	<ul> <li>The primary outcome Roland-Morris Disability Questionnaire improved from 8.6 at baseline to 5.9 at 6-week follow-up</li> <li>Participants spent on average 134 min (range 0–889 min) using the app dur- ing the 6-week period</li> </ul>		
Sandal/2021/ Denmark	naires and app installation  To investigate the effectiveness of selfBACK app, an evidence-based, individually tailored self-management support system delivered via an app as an adjunct to usual care for adults	Randomized clinical trial	Primary care clinic	Low back pain within the past 8 weeks	461	47.5 ± 14.7	<ul> <li>Use the selfBACK app for 6 weeks</li> <li>The app provided weekly tailored self-management plans targeting physical activity, strength and flexibility exercises, and education</li> </ul>	<ul> <li>The percentage of participants who reported a score improvement of at least 4 points on the Roland-Morris Disability Questionnaire was 52% in the intervention group vs 39% in the control group</li> <li>The improvement in pain-related disability was small and of uncertain clirical significance</li> </ul>		
Rabbi/2018/ USA	<ul> <li>To determine whether the MyBehaviorCBP recommendations were perceived as easy and actionable compared to randomly generated recommendations</li> <li>To examine preliminary evidence to see whether the intentions led to an actual increase in physical activity behavior</li> <li>To Solicit participant feedback on using the app to fine-tune future versions of the app</li> </ul>	Pilot study	Wellness Center and retiree	Chronic back pain (≥6 months in duration)	10	31–60	A week long baseline period with no recommendations, participants received generic recommendations from an expert for 2 weeks, which served as the control condition     In the next 2 weeks, MyBehaviorCBP recommendations were issued     An exit survey was conducted to compare acceptance toward the different forms of recommendations and map out future improvement opportunities	<ul> <li>MyBehaviorCBP's automated approach was found to have positive effects. Specifically, the recommendations were actualized more, and perceived to be easier to follow</li> <li>MyBehaviorCBP recommendations were actualized more with an increase in approximately 5 min of further walking per day compared to the control</li> </ul>		

(continued)

Table 2. continued

Author/year/	Purpose	Study design	Sample					Methods	Major results		
country			Setting	Diagnosis	N	Age (years)					
Lo/2018/ China	To investigate the self-per- ceived benefits of an AI- embedded mobile app to self-manage chronic neck and back pain	Observational study	Active users of the spe- cific AI- embedded mobile app	Neck and low back pain within the past 3 months	161	18-25: n = 30 $26-30: n = 31$ $31-40: n = 56$ $41-50: n = 19$ $51-60: n = 21$		Active users of the specific AI- embedded mobile app user was invited to participant the study The evaluation questionnaire included 14 questions that were intended to explore if using the AI rehabilitation system may (1) increase time spent on therapeu- tic exercise, (2) affect pain level (assessed by the 0–10 Numerical Pain Rating Scale), and (3) reduce the need for other inter- ventions	• The Scauss 3 pa em mo	n increase in time spent on therapeu- exercise per day was observed he median Numerical Pain Rating ale scores were 6 before and 4 after ing the AI-embedded mobile app. A point reduction was reported by the rticipants who used the AI- abedded mobile app for more than 6 bonths reduction in the usage of other inter- ntions while using the AI-embedded obbile app was also reported	
Huang/2011/ USA	To present a machine learning approach to analyze self-reporting data collected from the integrated biopsychosocial treatment	Observational study	Centre for Pain Services	Chronic pain	187	NA	•	Four different feature selection methods were applied to rank the questions Four supervised learning classifiers were used to investigate the relationships between the numbers of questions and classification performance	be for tice received (A car for The har on who over the control of	there were no significant differences tween the feature ranking methods or each classifier in overall classification accuracy or area under the teiver operating characteristic curve UC); however, there were signifient differences between the classifiers or each ranking method the multilayer perceptron classifier definitely the best classification performance an optimized subset of questions, nich consisted of ten questions. Its erall classification accuracy and UC were 100% and 1, respectively	
Meheli/2022/ USA	<ul> <li>To evaluate the perceived needs of users with chronic pain conditions</li> <li>To evaluate the app engagement and disengagement patterns of users with chronic pain</li> </ul>	Observational study	Community	Chronic pain	2194	NA		he users voluntarily downloaded the Cognitive Behavioral Ther- apy-Based Artificial Intelligence Mental Health App and com- pleted the questionnaires	<ul> <li>The foot the he iss</li> <li>The broch str</li> </ul>	the findings indicate that users look in tools that can help them address the concerns related to mental alth, pain management, and sleep uses the study findings also indicate the eadth of the needs of users with ronic pain and the lack of support ructures, and suggest that Wysa can ovide effective support to bridge the	

(continued)

Table 2. continued

Author/year/	Purpose	Study design		Sample			Methods	Major results
country			Setting	Diagnosis	N	Age (years)	•	
Piette/2022/ USA	To determine if a CBT-CP program that personalizes patient treatment using reinforcement learning and interactive voice response (IVR) calls is noninferior to standard telephone CBT-CP and saves therapist time	the that personalizes clinical treatment using trial trial trial trive voice response calls is noninferior adard telephone		Patients with chronic back pain	chronic back pain		All patients received 10 weeks of CBT-CP. For the AI-CBT-CP group, patient feedback via daily IVR calls was used by the AI engine to make weekly recommendations for either a 45- or 15-min therapist-delivered telephone session or an individualized IVR-delivered therapist message. Patients in the comparison group were offered 10 therapist-delivered telephone CBT-CP sessions (45 min/session)	The findings of this randomized comparative effectiveness trial indicated that AI-CBT-CP was noninferior to therapist-delivered telephone CBT-CP and required substantially less therapist time
Anan/2021/ Japan	To evaluate the improvements in musculoskeletal symptoms in workers with neck/shoulder stiffness/pain and low back pain after the use of an exercise-based AI -assisted interactive health promotion system that operates through a mobile messaging app (the AI-assisted health program)	Two-armed, random- ized, con- trolled, and unblinded trial	Community	Workers with neck/ shoulder pain/stiff- ness	94	$41.8 \pm 8.7$	Intervention group received the AI-assisted health program, in which the chatbot sent messages to users with the exercise instructions at a fixed time every day through the smartphone's chatting app (LINE) for 12 weeks	This study shows that the short exercises provided by the AI-assisted health program improved both neck/shoulder pain/stiffness and low back pain in 12 weeks

Abbreviations: CBT-CP: cognitive behavioral therapy for chronic pain; AI: artificial intelligence; NA: not applicable.

# Type 2: Al-based approaches related to pain prediction and clinical decision support (n = 10, 33%)

There are several published studies on AI-based approaches for improved pain prediction. 13,21,27,48,52-55 Lötsch et al 21 used supervised ML to generate a short type of questionnaire that performed as effectively as the complete questionnaire in predicting persistent postsurgical pain. Likewise, Nickerson et al<sup>27</sup> used Neural Network Architectures for predicting pain response. They proposed that this new approach offered superior results to conventional approaches.<sup>27</sup> AI-based techniques may also have positive effects on pain treatment, such as assisting pain physiotherapy and facilitating screening of consults to optimize specialist utilization. A pilot study by Honcu et al<sup>13</sup> pointed out that a computer kinesiology system could aid physiotherapy in patients with low back pain. Interestingly, Guan et al developed a deep learning model for predicting pain progression using demographic, clinical, and radiographic risk factors.<sup>54</sup> In view of all that has been mentioned so far, AI-based interventions could potentially improve pain prediction and pain treatment. 13,21,27

Two studies developed AI-based approaches to support physicians  $(n=2,\ 12\%).^{18,20}$  One study established a computer-based decision support system to help pain specialists choose proper pain treatment. As a result, this system increased the physician's ability to manage chronic pain and further positively affected the optimization of specialist utilization in hospital settings. Another study has shown that reinforcement learning could help pain specialists make better decisions about patient's opioid dosing. Thus far, the studies present evidence that an AI-based approach could help both patients and physicians to improve patient's pain management.  $^{18,20}$ 

# Type 3: Al-based approaches related to pain self-management (n = 8, 27%)

Five studies developed an app to facilitate patients' pain management with an ML algorithm. 1,19,30,43,44 One study aimed to optimize pain questionnaires using support vector ML with recursive feature elimination. 16 The length of intervention ranges from 5 weeks to 6 months. 1,19,30 Sandal et al developed and tested the effectiveness of the selfBACK app to provide weekly tailored selfmanagement plans targeting physical activity, strength and flexibility exercises, and education for patients with low back pain. 1,43 Similarly, Lo et al<sup>19</sup> evaluated a mobile APP that is designed to increase adherence to therapeutic exercises, affect pain levels, and reduce the need for other interventions for patients with chronic neck and back pain. Rabbi et al, 30 in contrast, constructed a new mobile app to address psychological barriers of chronic pain with auto-personalized physical activity recommendations. Reinforcement learning was used to make their recommendations continually adaptive. 30 Meheli et al 44 found that Cognitive Behavioral Therapy-Based Artificial Intelligence Mental Health App could help to address users' concerns related to mental health, pain management, and sleep issues for patients with chronic pain. In addition, Huang et al<sup>16</sup> pointed out that feature selection and classification models also play an essential role in optimizing subset questions of a pain questionnaire to assist self-management for patients with chronic

Outcomes of all above studies were measured at baseline and postintervention. <sup>1,19,30,43–46</sup> Most of the studies used a questionnaire or interview to evaluate if the intervention is effective before and after the intervention, and all of the mobile apps have some positive effects on patient's health outcomes. <sup>1,19,30,43,44</sup> To explain it further, the automated approach has achieved preliminary success

to decrease patient's pain levels (n=5, 17%),  $^{1,30,43,44,46}$  promote physical activity in a chronic pain context (n=2, 7%),  $^{16,30}$  assist with adherence of physician's recommendations (n=1, 3%),  $^{19}$  improve primary health outcomes (n=1, 3%),  $^{30}$  and reduce the usage of other interventions (n=1, 3%).

## Study quality assessment

The study quality was assessed using the CASP. A score in percentage was assigned to each study based on its study design and the corresponding criteria (please see detailed evaluation in Table 3). Six studies (20%) with a qualitative design scored 70% or 80% on CASP, indicating relatively high levels of study quality. Some studies did not meet all the criteria because they did not consider ethical issues, or the relationship between researcher and participants was not addressed adequately. Ten studies (33%) with a diagnostic test study design scored 44% on CASP, indicating relatively low levels of study quality. The primary reason of the low quality is that they did not provide a comparison with an appropriate reference standard result. Two RCTs (7%) scored 91% on CASP. They meet most of the criteria except that they did not fully explain if the experimental intervention provided greater value to the patient's care than any existing interventions. Two studies (7%) with a cohort study design scored 100% on CASP, indicating high levels of study quality. The other two studies (7%) with a cohort study design scored 80%. They did not meet all the criteria because the exposure was not accurately measured to minimize bias. Also, one study lost follow-up with some participants due to surgery, and another study did not explain whether the results of their study fit with other available evidence. To sum up, the quality of included studies is closely related to their study design. Diagnostic research tends to have relatively low quality, and other studies have moderate to high quality.

#### DISCUSSION

This review synthesized existing research evidence on AI-based interventions designed to enhance pain assessment and management for adult patients and identified three major types of interventions: AI-based approaches to pain assessment, AI-based approaches to pain prediction and clinical decision support, and AI-based approaches to pain self-management. Compared to prior systematic reviews which focused on ML in pain research only or low back pain only, this paper extended these previous results, included all main AI technologies (ML, data mining, and natural language processing) and different types of pain, canvased the state of the science of AI-based pain interventions for adult patients, and ascertained patient outcomes of such interventions.<sup>22</sup> We also provide some suggestions for clinical practice and future research.

#### Type 1: Al-based approach related to pain assessment

Several lines of evidence suggested that technology could improve pain recognition, pain scoring and facilitate the use of clinical notes with pain assessment information to identify pain automatically. 7,17,23,47,49–51 One source of weakness in the pain recognition studies which may affect the generalizability of the results is that most of them use the same database to test the model. A natural progression of this type of work is to analyze their models in other databases and compare different strategies in real-life clinical use. Further research could also be conducted to develop an updated model to improve the accuracy of pain recognition and allow it to work in a more complex environment. Computational tools may

Table 3. quality assessment of each included study

Study					Assessme	ent items					Percentage items meeti the criteri	ing
					Qualitative	design						-
	Clear aim	Methodolog appropriate		Recruitment strategy appropriate	Data appropriate	Consider relationship	Consider ed ethical issues	Rigorous data analy- sis	clear state- ment of findings	Research valuable		
Rabbi et al <sup>30</sup>	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	70	
Lo et al <sup>19</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	80	
Huang et al <sup>16</sup>	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	70	
Knab et al <sup>18</sup>	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	70	
Lopez-Martinez	et al <sup>20</sup> Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	70	
Honcu et al <sup>13</sup>	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	70	
					Randomized con	trolled trials						
	Clearly focused research question	Randomizeo	All participants in conclusion	Blind intervention	Study groups similar	Treated equally	Reported comprehensively	Precision of the estimate	Benefits outwe harms	igh Applied to your loca populatio	l value	
Sandal et al <sup>1</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	91
Sandal et al <sup>43</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	91
Piette et al <sup>45</sup>	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NA	82
Anan et al <sup>46</sup>	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NA	82
					Diagnostic to	est study						
		Clear question	Compare with appropriate standard	Get diagnostic test and standard test	Standard tes influence	st Patier diseas		described detail	Results be applied		Outcomes mportant	
Lucey et al <sup>23</sup>		Y	N	N	NA	Y		Y	N	N	Y	44
Kharghanian et	al <sup>17</sup>	Y	N	N	NA	Y		Y	N	N	Y	44
Dutta and M <sup>7</sup>		Y	N	N	NA	Y		Y	N	N	Y	44
Atee et al <sup>2</sup>		Y	N	N	NA	Y		Y	N	N	Y	44
Fodeh et al <sup>9</sup>		Y	N	N	NA	Y		Y	N	N	Y	44
Suominen et al <sup>3</sup>	2	Y	N	N	NA	Y		Y	N	N	Y	44
Hossain and Mu	uhammad <sup>15</sup>	Y	N	N	NA	Y		Y	N	N	Y	44

(continued)

Table 3. continued

Diagnostic test study												
	Clear question	Compare with appropriate standard	Get diagnostic test and standard test	Standard test influence	Patient disease	Methods described in detail	Results be applied	Test be applied	Outcomes important			
Behrman et al <sup>3</sup>	Y	N	N	NA	Y	Y	N	N	Y	44		
Hosseini et al <sup>49</sup>	Y	N	N	NA	Y	Y	N	N	Y	44		
Wu et al <sup>50</sup>	Y	N	Y	NA	Y	Y	N	N	Y	55		
Shim et al <sup>52</sup>	Y	N	Y	NA	Y	Y	N	N	Y	55		
Hao et al <sup>53</sup>	Y	Y	Y	NA	Y	Y	N	N	Y	67		
Mallol-Ragolta et al <sup>51</sup>	Y	N	N	NA	Y	Y	N	N	Y	44		
Umapathy and Krishnan <sup>57</sup>	Y	Y	Y	NA	Y	Y	N	N	Y	67		

					•						
	Clearly focused issue	Recruited in an acceptable way	Exposure accurately measured	Confounding factors	Taken account of confounding factors	Follow-up of subjects	Believe the results	Be applied to the local population	Fit with other available evidence	Implications for practice	
Nickerson et al <sup>27</sup>	Y	Y	NA	N	Y	Y	Y	Y	NA	Y	70
Lötsch et al <sup>21</sup>	Y	Y	NA	N	Y	N	Y	Y	Y	Y	70
Lötsch and Ultsch <sup>22</sup>	Y	Y	NA	N	N	N	Y	Y	Y	Y	60
Goldstein et al <sup>48</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Guan et al <sup>54</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Gao et al <sup>55</sup>	Y	Y	NA	Y	Y	N	Y	Y	Y	Y	80
Meheli et al <sup>44</sup>	Y	Y	NA	N	Y	N	Y	Y	Y	Y	80

Abbreviations: N: no; NA: not applicable; NI: no information; Y: yes.

detect patient's pain status from clinical notes automatically, although this reflects provider documentation and not real-time assessment of patient expressions of pain The most important limitation of these studies lies in the fact that the tools could only determine the presence or absence of a pain note; they did not have the capability to detect the specific quality and quantity of pain, highlighting an area in need of further exploration. A combination of technologies could also help conduct pain assessment for patients who are nonverbal or have limited language skills, such as those with severe dementia. Further work is required to establish the viability of these novel systems and test different combinations of technologies. Also, comparison with an appropriate reference standard should be considered in future research.

# Type 2: Al-based approaches related to pain prediction and clinical decision support

AI-based approaches can facilitate postoperative pain prediction. 13,21,27,48,52-55 It has been shown that the ML approach can be used to select key questions in a pain questionnaire to predict pain persistence with relatively high accuracy. This is an important issue for future research since this approach could decrease patient's burden (eg, less time to fill out the questionnaire) significantly. In future investigations, it is essential to test this approach in other cohorts of patients. In another promising study, Nickerson et al<sup>27</sup> proposed that modern neural network architectures could be used to predict pain response for patients with analgesic administration. However, the data were limited to postoperative subjects. Further research should be undertaken to investigate the best model and test it with more patients or more types of pain. One pilot study found that a computer diagnostic and therapeutic medical information system could improve low back pain treatment. 13 The result is promising, but it should be interpreted with caution. Some potential bias includes different duration of pain treatment and the different pain assessment tools. 13 Thus, research using controlled trials is needed to assess the effectiveness of these novel systems to improve pain therapy.

Computational support systems for physicians were promising. These systems could facilitate optimizing physician utilization, recommending doses of medication, and aid decision-making. <sup>18,20</sup> However, these systems still faced some impediments. First, the content in a rule-based expert system was static, and it was difficult to update the system to align with the current pain practice guideline timely and continuously. <sup>18,20</sup> An additional barrier was the reluctance of many specialists to use the system during actual patient care if they were the experts in this field. <sup>18,20</sup> Moreover, these studies were limited to a single center. <sup>18,20</sup>

# Type 3: Al-based approach related to pain self-management

AI-embedded apps were found to have positive effects on pain management, including reducing pain level, reducing the usage of other interventions, and assisting therapeutic exercise. <sup>1,19,30,43–46</sup> However, the generalizability of these results is subject to certain limitations. For instance, some studies only assessed the general pain level instead of the pain on each specific site. In addition, since the studies were limited to the immediate post intervention effects (eg, decrease patient's pain levels, promote patient's physical activity, and assist with adherence of physician's recommendations) of AI-embedded mobile app, it was impossible to know the sustained effects of those interventions. <sup>1,19,30,44–46</sup> Therefore, research is needed to determine

if the improvement of pain level could lead to changes in other functions or other long-term physiological changes. These studies did not evaluate adherence to use of these AI-based apps. In addition, further research should compare these interventions with routine clinical pain care to establish benefit in adopting an innovative methodology to optimize pain assessment and management. Finally, these studies were limited by small sample size and self-reported subjective data. More pilot studies with physiological pain measures are required before these approaches are ready for large clinical trial.

#### **Implications**

This combination of findings provides some evidence that AI could facilitate pain assessment and self-management, primarily through ML. However, there is abundant room for further progress in pain prediction or developing clinical support systems for pain treatment with AI approaches. It is somewhat surprising that only one study was noted using electronic health record (EHR) data. Thus, further research should be undertaken to explore how to use EHR data with AI-based approaches to improve pain care. Most of these approaches only apply ML and extension to study of data mining or natural language processing techniques is therefore suggested. It is also essential that future research involving these interventions include more diverse populations and settings.

#### LIMITATIONS

This review was limited to studies published in English and excluded editorials, dissertations, conference abstracts, and reviews. This review is also limited to nonpediatric populations and excluded the physiological signals studies.

#### CONCLUSION

Findings from this review suggest that using AI-based interventions to improve pain recognition, prediction, and self-management is effective; however, most studies are pilot studies. Future research should focus on examining AI-based approaches in larger cohorts and over a longer period to evaluate sustained effects.

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# **AUTHOR CONTRIBUTIONS**

MZ and LZ screened the title and abstract of the searched articles and extracted data from full-text articles with guidance from CC. All authors drafted the manuscript. All authors reviewed, revised, and approved the final draft for publication.

# **SUPPLEMENTARY MATERIAL**

Supplementary material is available at Journal of the American Medical Informatics Association online.

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#### **CONFLICT OF INTEREST STATEMENT**

None declared.

### **DATA AVAILABILITY**

No new data were generated or analyzed in support of this research.

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