Advanced Intelligent Discovery

WILEY VCH

ADVANCED INTELLIGENT DISCOVERY Open Access

REVIEW OPEN ACCESS

Artificial Intelligence for Bone: Theory, Methods, and Applications

Dongfeng Yuan[1,2,3] | Haicang Zhang[4] | Liping Tong[1] | Di Chen[1,2]

[1]Center for AI-Driven Medical Research, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China | [2]Department of Pharmacology, Faculty of Pharmaceutical Sciences, Shenzhen University of Advanced Technology, Shenzhen, China | [3]University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing, China | [4]Medicinal Bioinformatics Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence: Liping Tong (lp.tong@siat.ac.cn) | Di Chen (di.chen@siat.ac.cn)

Received: 10 April 2025 | **Revised:** 4 June 2025 | **Accepted:** 9 June 2025

Funding: National Key Research and Development Program of China, Grant/Award Number: 2023YFC2415800; National Natural Science Foundation of China (NSFC), Grant/Award Number: 82394445, 82172397, 82030067, 82161160342; Shenzhen Science and Technology Research Funding, Grant/Award Number: JCYJ20220818101414032

Keywords: artificial intelligence | bone research | clinical orthopedics | deep learning | precision medicine

ABSTRACT

Artificial intelligence (AI), a transformative technology rooted in decades of computational evolution, from early symbolic reasoning to modern deep learning breakthroughs, is bringing great impact and opportunities to scientific research. Synchronously, AI is rapidly transforming traditional approaches in bone research. The surge in orthopedic big data, advancements in high-performance computing, as well as innovative AI algorithms, has led to an explosive growth in applications across bone fundamental research and orthopedic clinical practice. These applications span pathological investigation, biomarker discovery, screening of critical intervention targets, drug discovery, disease diagnosis, treatment assistance, postoperative rehabilitation, and prediction of disease recurrence, highlighting vast potential of AI to facilitate bone research. However, challenges persist regarding data quality, data sharing, interpretability, and ethical considerations. In the future, advances in AI are expected to drive significant progress in drug target identification and new drug discovery, moving orthopedic clinical practice from symptom management toward precision medicine. Additionally, the integration of large language models and parallel intelligence in orthopedics could bring revolutionary changes. We hope this review can provide basis for AI applications in biological research and clinical translation, advancing intelligent and personalized management of musculoskeletal system diseases.

1 | Introduction

Bones, central organs in the human body, play a vital role in supporting various physiological functions, including hematopoiesis, immune regulation, endocrine activities, and calcium–phosphate storage [1, 2]. Diseases arising from bone dysfunction, such as osteoporosis, fractures, osteoarthritis (OA), spine degeneration, and bone tumors, not only pose significant health risks to individuals but also impose substantial economic burdens on society. Globally, OA affects over 528 million adults, while the prevalence of osteoporosis is as high as 19.7% [3, 4]. These challenges are further exacerbated by the accelerating trend of global population aging, intensifying the need for innovative solutions.

In recent decades, rapid developments in radiomics and multiomics techniques and combined with the emergent AI technologies, including advancements in machine learning (ML), deep learning (DL), and natural language processing (NLP), make it possible to efficiently analyze and interpret vast amounts of intricate medical data. By uncovering subtle patterns and constructing predictive

models, AI enhances diagnostic precision and supports clinical decision-making and personalized interventions in orthopedics [5–7]. Moreover, the integration of AI with multiomics provides valuable insights into the pathogenesis of bone disorders, facilitates the identification of key genetic targets and signaling pathways, and paves the way for the development of novel targeted therapies [8].

In this review, we have systematically and comprehensively reviewed publications on AI applications in bone research, and summarized the current progress in this rapidly evolving field. We discussed challenges related to clinical practice, pathological evaluation, and mechanism studies, as well as ethical considerations. Particularly, we explored the integration of AI with orthopedic big data, emphasizing its potential to elucidate critical disease mechanisms, identify therapeutic targets, and accelerate drug discovery. Additionally, the incorporation of large language models and parallel intelligence technologies in clinical orthopedics promises to propel the field toward intelligent and precision medicine. This review aims to provide an up-to-date perspective for orthopedic clinicians and researchers, inspiring innovative approaches in AI-driven bone research and advancing the discipline toward a future of enhanced accuracy, efficiency, and intelligence.

2 | What is the Artificial Intelligence?

2.1 | The Brief History of AI

AI was originally defined as enabling computers and machines to simulate human cognitive processes and intelligent behaviors, such as learning, reasoning, planning, perception, and language understanding. Its core principle lies in enabling machines to learn from large datasets, recognize patterns and relationships within the data, and apply this knowledge to make informed decisions on new data [9]. Today, AI has evolved into a driving force behind the latest technological and industrial revolutions, achieving remarkable success across numerous disciplines. Figure 1a illustrates the historical milestones in the development of AI.

In 1950, the concept of AI was first proposed by Alan Turing, regarded as the "father of artificial intelligence," sparking widespread interest among scholars [10]. The term "Artificial Intelligence" was formally coined at the Dartmouth Summer Workshop in 1956, signifying the official launch of this emerging field. This period witnessed rapid progress in AI research, including the establishment of the International Joint Conference on Artificial Intelligence (IJCAI) in 1969, and the inaugural publication of the journal *Artificial Intelligence* in 1970, both of which significantly fostered further academic exchange and research in the field. In subsequent years, AI made significant strides in logic reasoning, problem-solving, and expert systems, breakthrough achievements like Logic Theorist [11], the Lisp programming language [12], General Problem Solver (GPS) [13], and pioneering expert systems like DENDRAL and MYCIN [14, 15]. However, limitations in reasoning methods, data acquisition, computational power, and hardware capability caused progress to stall.

Entering the 21th century, rapid advancements in computer hardware, algorithms, and the emergence of the internet and big data fueled new progress in AI. These breakthroughs triggered a new era of AI research. Landmark achievements included IBM's AI program—Watson, outperforming humans in a trivia competition in 2011 [16], and Google's AlphaGo defeating world champion Lee Sedol in Go through self-learning in 2016 [17]. In 2024, Google DeepMind's AlphaFold3 model revolutionized structural biology by accurately predicting nearly all biomacromolecular structures, including proteins, DNA, and RNA [18]. These milestones demonstrate that AI can now rival or even surpass human capabilities in specific domains. Today, the scope of AI has expanded to encompass a wide range of subfields, including ML, DL, and NLP, as shown in Figure 1b. These technologies have begun to integrate into areas such as bone research, fostering the growth of orthopedics-AI and ushering transformation from traditional orthopedic medicine.

2.2 | ML

ML, the backbone of AI, is designed to enable computers to learn and improve performance without explicit programming. The ML process typically involves three key stages: data preprocessing, model training, and evaluation [19]. Common ML algorithms, including Naive Bayes, logistic regression, support vector machines (SVM), decision trees, and artificial neural networks (ANN), derive decision rules from datasets with known features and labels to solve classification and regression tasks [20, 21]. In orthopedics, ML has demonstrated significant clinical value across various applications. Now ML is widely employed in image recognition, where algorithms assist in analyzing medical imaging like X-rays, CT scans, and magnetic resonance imaging (MRI), to identify fractures, tumors, and other abnormalities with remarkable accuracy [22]. ML also shows a strong ability in diagnostic assistance by integrating patients' data and imaging results to support clinicians in making accurate diagnoses [23]. Additionally, ML has been increasingly applied in prognosis prediction, enabling personalized treatment plans by predicting disease progression, surgical outcomes, and potential complications [24]. The data processing and learning workflow of the ML model is shown in Figure 1c.

2.3 | DL

DL, a specialized subset of ML, emerged from the development of deep neural networks (DNNs) algorithms introduced by Hinton [25]. Its defining feature lies in the construction of multilayered neural networks that mimic neuronal functions in the human brain, enabling the system to learn and process complex data patterns through hierarchical information processing. Unlike traditional ML, DL models perform end-to-end learning, autonomously extracting and refining features from raw data during training. This approach reduces the reliance on manual intervention and allows DL to excel in handling unstructured data, such as text, images, and audio [26]. Among various DL architectures, convolutional neural networks (CNNs) are particularly prominent, which use convolutional layers to extract localized features, pooling layers to reduce spatial dimensions and prevent overfitting, and fully connected layers to map inputs to outputs [27]. These capabilities make CNNs invaluable in orthopedic

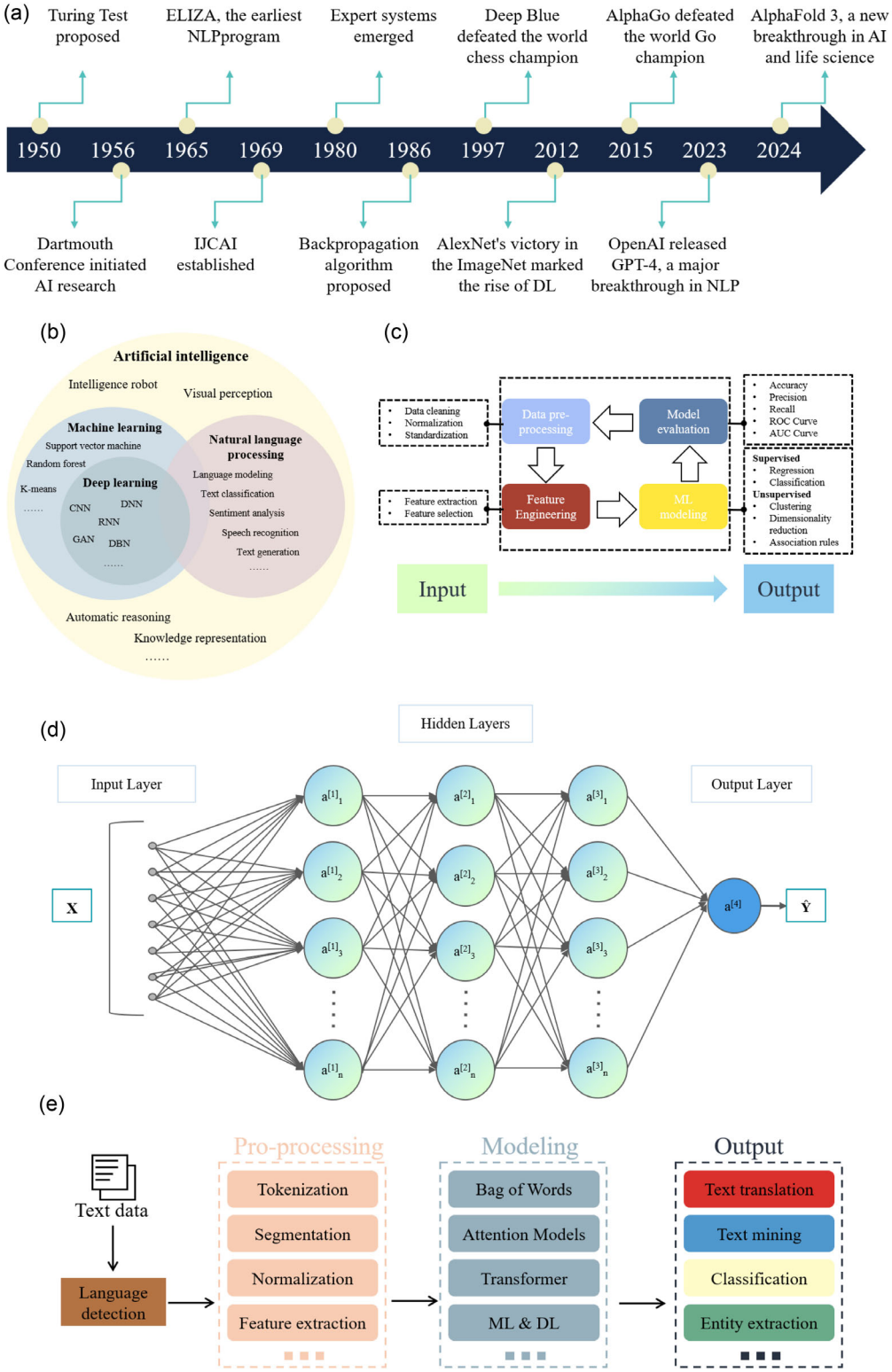

FIGURE 1 | Overview of AI. (a) The history of AI. (b) The relationship between AI, ML, DL, NLP, and various application scenarios. (c) The typical data process of ML. (d) The neural network framework of DL. (e) The process of NLP algorithm.

applications. They have been effectively applied in automatic detection of conditions like fractures, OA, and bone tumors using stained tissue sections or imaging data [28–30]. This automation not only improves accuracy but also provides clinical insights into the screening, diagnosis, and prognosis of skeletal diseases. The basic framework of the DL model is shown in Figure 1d.

2.4 | NLP

NLP sits at the intersection of computer science, AI, and linguistics, focusing on equipping computers with the ability to analyze unstructured text or spoken data and extract knowledge from complex multimodal sources [31]. Early NLP systems

predominantly relied on rule-based methods, such as keyword and pattern matching, which limited their flexibility and applicability [32]. Modern NLP frameworks are built upon advanced DL models like CNNs, recurrent neural networks (RNNs), and transformer models [33, 34], which enable models to learn universal language representations from large-scale, unannotated text datasets. This foundation has enabled NLP systems to expand beyond traditional text analysis, to incorporate applications in speech recognition and multimodal data understanding [35, 36]. Today, NLP has emerged as a powerful tool in orthopedics and bone biology research, surpassing traditional models in tasks like text mining, diagnostic reports analysis, and multimodal data integration. Its applications include standardized disease screening, automated report generation, and tailored health management recommendations, driving advancements in clinical decision-making and operational efficiency [37–39]. The training and analysis framework of the NLP model are shown in Figure 1e.

3 | The Application of AI in Bone Research

To provide a comprehensive overview of the applications of AI in bone research, we conducted a bibliometric analysis encompassing 2837 publications, with search and screening details provided in the Supporting Information. Our retrieval analysis revealed that majority of the existing studies focus on using AI to assist clinical applications, while relatively few of them explore AI application in fundamental biological research. These will be detailed in the following sections.

3.1 | AI Application in Fundamental Bone Biological Research

3.1.1 | Exploration of Pathological Mechanisms

The advent of orthopedic big data fueled by breakthroughs in sequencing technologies, genomic data and large-scale biological datasets, has positioned AI as a transformative tool to decode disease mechanisms. By bridging computational power with biological complexity, AI empowers researchers to uncover latent patterns and causal relationships in bone pathophysiology.

The convergence of AI and multiomics data has accelerated understanding of disease mechanisms and discovery of novel biomarkers. Recently, ML approaches have been used to identify novel diagnostic and prognostic markers across bone disorders from multiomics data, including *CDH2* and *PFKFB3* for OA diagnosis [40], *SQLE* for osteosarcoma prognosis [41], *CRTAC1* and *COL9A1* for OA risk stratification [42], and *SOST* and *ADIPOQ* for osteoporosis susceptibility [43]. Beyond static analyses, AI-driven dynamic modeling of single-cell RNA sequencing (scRNA-seq) data deepens our understanding of cellular heterogeneity and cellular interactions within the pathological microenvironment. For example, Zhou et al. combined t-SNE/UMAP clustering with the trajectory inference algorithms Monocle 2 and Slingshot to analyze scRNA-seq data from tumor samples of 11 osteosarcoma patients. Through comprehensive examination of the transcriptomic properties, regulators networks, and dynamics of malignant osteosarcoma cells, together with stromal and immune cells of the tumor microenvironment, they identified a transdifferentiation trajectory whereby malignant osteoblastic cells arise from malignant chondroblastic precursors. Moreover, they observed lower infiltration of osteoclasts in chondroblastic, recurrent, and lung metastatic osteosarcoma lesions compared to primary osteoblastic osteosarcoma lesions, suggesting distinct microenvironmental remodeling across osteosarcoma subtypes and progression stages [44]. Additionally, TIGON, a dynamic unbalanced optimal transport algorithm, further advanced this field by coupling Wasserstein–Fisher–Rao metrics with neural networks, which has successfully enhanced the robustness and accuracy in predicting cell state transition and cell population growth, while revealing dynamic transcriptional regulation by *SNAI1* during epithelial–mesenchymal transition and offering new perspectives on bone remodeling and pathologic cellular behavior [45]. Complementarily, Rauch et al. employed the newly developed ML tool, IMAGE, to map bidirectional regulatory networks of pro-osteogenic and antiadipogenic transcription factors in mesenchymal stem cells (MSCs), uncovering *RUNX2*/*SMAD3*-mediated osteogenesis–adipogenesis crosstalk, which informs therapeutic strategies for metabolic bone disorders [46].

In addition, AI facilitates systematic extraction of mechanistic insights from large-scale biomedical datasets. For example, Xu et al. developed an attention-based U-Net model using MRI data from approximately 47 000 UK Biobank participants. By integrating genome-wide association studies (GWAS) and transcriptome-wide association studies (TWAS), they identified numerous functional sex-specific genes, such as *TIMP4* and *PPARG*, which are involved in adipocyte differentiation and bone remodeling. These findings offer novel insights into the pathogenesis of osteoporosis [47]. Similarly, Kun et al. applied DL models to characterize individuals with skeletal diseases in total 31 221 individuals with X-ray analysis from the UK Biobank and they identified 145 genome-wide loci associated with skeletal diseases and OA-specific hip/knee morphological signatures [48]. Notably, Garg et al. further demonstrated the power of AI in multimodal data integration through their MILTON framework, which integrated diverse datasets from the UK Biobank, including longitudinal health records, whole-genome sequencing data from 484 230 individuals, and plasma proteomics profiles from 46 327 participants. In their efforts to predict the risk of multiple myeloma, investigators identified that TNF receptor superfamily proteins (e.g., TNFRSF13B/17) are key contributors, highlighting their potential as predictive biomarkers and therapeutic targets [49]. Collectively, these studies exemplify AI's capacity to transform multimodal data into mechanistic discoveries and therapeutic targets.

More importantly, emerging AI approaches are unraveling the neurobiological complexity of OA-related chronic pain. Cheng and his colleagues used a network-based multivariable ML approach to reveal that dynamic functional connectivity (dFC) across brain networks is closely associated with characteristics of chronic neuropathic pain [50]. Liu et al. constructed a phenotypic screening platform by integrating a high throughput all-optical electrophysiology and a computational framework to explore the chronic pain associated with OA and to screen the potential therapeutics. The optical electrophysiology system

captured membrane voltage dynamics in dorsal root ganglion (DRG) sensory neurons, which were sensitized by a defined mixture of disease-relevant inflammatory mediators (termed as SPARC). In parallel, the computational framework was developed to model a multiparametric OA-SPARC neuronal phenotype and to quantitatively assess the reversal of this phenotype in response to candidate pharmacology. This platform achieved a remarkable throughput of up to 500 000 neurons per day at single-cell and single-action potential resolution. Approximately 3000 approved drugs and compounds were screened for their efficacy in alleviating OA-associated pain. Notably, the study suggested the involvement of "Raf-MEK-ERK" signaling axis in mediating inflammatory pain in DRG neurons [51]. This work exemplifies the powerful processing capacities of AI-driven platform in the acquisition and analysis of high-dimensional data. Intriguingly, the brain age predicted difference (brain-PAD), defined as the predicted brain age minus chronological age, has been hypothesized to be associated with chronic pain. Recently, Valdes-Hernandez et al. employed DeepBrainNet, a novel convolutional neural network for predicting brain-PADs, to examine this relationship, and results revealed that individuals with OA pain exhibited a brain-PAD that was 3–4.7 years higher than those with chronic low back pain (CBP) and healthy controls [52].

Finally, cutting-edge AI methodologies hold untapped potential for structural prediction of bone-related disease targets. For example, intrinsically disordered proteins (IDPs), which lack stable tertiary structures, have long posed a formidable challenge for structural prediction due to their inherent heterogeneity and conformational dynamics. Addressing this issue, Brotzakis et al. recently introduced AlphaFold-Metainference, a hybrid approach that synergistically integrates the sequence-based predictive power of AlphaFold with the physics-based sampling of molecular dynamics simulation, enabling accurate prediction of the dynamic structures of IDPs [53]. This methodological breakthrough provides a valuable tool for elucidating the functional plasticity of bone-related IDPs, such as Noggin and Chordin (key regulators of BMP signaling pathway), RANKL (a crucial osteoclast differentiation factor), and c-Myc (overexpressed in osteosarcoma) [54–56]. Parallel to these advances, DL techniques have catalyzed breakthroughs in functional annotation of phosphorylation, which is of critical importance in regulating bone metabolism and bone homeostasis. Two pioneering methods—MMFuncPhos and EFuncType—now enable multimodal prediction of functional phosphorylation sites and precise determination of their regulatory effects (activation/inhibition) on enzymatic activity [57]. Given the centrality of phosphorylation in maintaining the delicate balance between bone formation and resorption, these tools are poised to accelerate the discovery of dysregulated phosphorylation sites in various bone diseases [58, 59]. Equally important is the PIONEER framework in protein–protein interaction (PPI) prediction, which leverages multimodal DL to achieve genome-scale mapping of protein-binding partner-specific interfaces with reliable precision [60]. Notably, the regulation of bone homeostasis is largely dependent on protein interactions. For example, missense mutation of the *LRP5* gene results in the mutation of translated protein (LRP5 p.A214V) which could not properly bind to its partner protein frizzled receptor, leading to the disruption of Wnt signaling and alteration of bone density. Similarly, the perturbations in the RANK–RANKL–OPG ternary complex will affect osteoclast formation and bone resorption and influence the development of osteoporosis [61, 62]. By enabling systematic construction of bone-specific PPI perturbation maps, PIONEER could bridge genotype–phenotype correlations with interface drug design, providing multiscale network insights into skeletal pathology and fostering the development of interface-targeted therapeutics.

3.1.2 | Development of Treatment Targets and Drug Design

The development of therapeutic strategies remains the frontier in fundamental bone biology research. While traditional experimental approaches are often labor-intensive and costly, AI is emerging as a transformative solution for deciphering drugtarget interactions, optimizing molecular design, and predicting toxicity profiles.

Recent innovations highlight AI's capacity to expedite therapeutic discovery. For example, Cathepsin K serves as an important therapeutic target for osteoporosis, Parwez et al. integrated ML, QSAR modeling, and molecular dynamics simulations to identify five novel Cathepsin K inhibitors with validated binding modes [63]. Similarly, Cai et al. developed an NLP-based unsupervised DL framework to discover the osteogenic pentapeptide AIB5P, which enhances bone regeneration *via* integrin α5/FAK signaling and outperforms parathyroid hormone (PTH) in animal models [64]. Beyond novel compound discovery, AI is also a powerful aid for drug repurposing. Wang et al. employed a DL-based efficacy prediction system (DLEPS) to screen antiosteoporosis drugs from TargetMol database, identifying dihydroartemisinin that modulates the GCN5-H3K9ac epigenetic axis to enhance osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) [65]. This is further exemplified by SHAFTS (a 3D molecular similarity algorithm), which uncovered the micromolar-level inhibition of tamsulosin on TMEM16A, a calcium-activated chloride channel pivotal in osteoporosis pathophysiology [66]. Notably, AI-driven combinatorial drug screening has also gained attraction. The BATCHIE model enables accurate prediction of unknown drug synergies, successfully identifying PARP and topoisomerase I inhibitor combinations with therapeutic potential for osteosarcoma [67, 68].

In addition to these advances, deep generative models are unlocking new paradigms for structure-based drug design. The GENTRL model, a de novo small-molecule design tool, has been successfully applied to generate small molecules with favorable pharmacokinetic properties and biological activity [69]. Similarly, DeepICL, a 3D molecular generation framework based on protein-ligand interactions, has been employed to design ligands that fit novel target binding pockets [70], while DeepBlock, a DL method targeting protein sequences, outperforms conventional methods in generating low-toxicity, high-affinity ligands with synthetic feasibility and drug-like properties [71]. Interestingly, a groundbreaking tool, VideoMol, introduces dynamic molecular representation by encoding 3D conformations into 60-frame videos, overcoming the limitations of traditional molecular descriptors (e.g., SMILES or graphs) and enabling superior performance in tasks such as predicting ligand-GPCR binding activity and identifying drug targets for common diseases [72]. Complementary tools like Cyto-Safe, an ML-based cytotoxicity screening platform, and KGE_NFM,

a knowledge graph-enhanced framework for prediction of drug-target interactions and understanding the relationships between drugs, targets, and diseases, further expand AI utility in early-stage drug discovery [73, 74]. Although these tools have not yet been widely applied in bone diseases, their potential to accelerate the development of therapeutic drugs is worthy of in-depth exploration by bone researchers.

In brief, despite remarkable progress, AI applications in bone biology remain nascent, with most studies relying on small-scale sequencing or public datasets. Future integration of large-scale genetic data, such as GWAS or TWAS, could unlock deeper insights into bone disease mechanisms and therapeutic targets. Additionally, the advent of AI virtual cell (AIVC), a multiscale and multimodal neural network model, can dynamically depict and simulate the behaviors of molecules, cells, and tissues under various states. It is expected to revolutionize the modeling of bone microenvironment, and enable high-fidelity simulations of osteoblasts, osteoclasts, and MSCs in the contexts of diseases [75]. Such advancements will propel a new era of precision medicine, bridging computational innovation with experimental validation for high-fidelity digital experimentation in skeletal research.

3.2 | AI Application in Orthopedics Clinical Practice

3.2.1 | Detection and Diagnosis

Compared to human experts, AI has exhibited better performance in various orthopedic clinical tasks, ranging from bone age assessment to bone density prediction, as well as disease diagnosis and classification. By utilizing DL and ML algorithms to analyze large medical image datasets, AI can identify patterns and features indicative of orthopedic diseases, significantly enhancing the efficiency and accuracy of orthopedic disease detection and diagnosis.

Bone age assessment is an important tool for evaluating children's growth and development, predicting adult height, and diagnosing skeletal dysplasia. The traditional Greulich and Pyle (GP) method has limited efficiency due to its reliance on standard reference charts [76]. However, with advancements in DL technologies, automated bone age assessment tools are simplifying the process and improving evaluation accuracy. For example, an improved GP method integrating DL algorithm has exhibited lower absolute error and higher accuracy in assessments [77]. Additionally, AI-driven tools such as Deeplasia, MABAL, RAGCN, and the Fully Automated Deep Learning System have further advanced the efficiency and standardization degree of bone age assessment [78–81].

One of the most promising applications of AI in orthopedic clinical diagnosis is the use of DL algorithms to analyze medical images like CT, MRI, and histological images. DL-based computer-aided diagnostic systems can automatically detect vertebral, rib, and pelvic fractures from X-ray or CT images [82–84]. Since a decrease in bone mineral density (BMD) is an early indicator of osteoporosis, early AI-assisted methods primarily relied on traditional ML models, such as SVM and ANNs, to screen for osteoporosis using survey and routine check-up data [85, 86]. Recently, DL technologies have enabled AI to more accurately predict bone density from imaging data. For example, the DeepDXA model successfully predicted BMD values of the femur with a correlation coefficient (R) of 0.85 and an accuracy of 0.88 in predicting osteoporosis from pelvic X-rays [87]. Yasaka et al. applied CNN to analyze CT images, revealing significant correlations with BMD values obtained from dual-energy X-ray absorptiometry (DXA). Using this tool, osteoporosis can be predicted with high accuracy [88]. Osteo-Net, a low-cost and high-precision AI tool based on X-Ray images, shows significant potential in regions with limited medical resources [89]. Beyond imaging, AI has also been used to predict BMD from genomic data. Wu et al. analyzed the genomic and phenotypic data of osteoporotic fractures in men study, and compared with the BMD prediction models established by random forest, gradient boosting, neural network, and linear regression. They found that the gradient boosting model performs the best [90]. More importantly, AI-assisted BMD assessment can help optimize treatment plans and improve patient outcomes [91].

OA diagnosis presents another clinical challenge. The Kellgren–Lawrence (KL) grading system, which is based on imaging remains the gold standard for evaluating the severity of knee OA. A meta-analysis showed that the DL-based multiclassification method for X-ray imaging achieves sensitivity greater than 80% for K-L0, K-L3, and K-L4 [92]. However, the application of DL in OA diagnosis has not been limited to image analysis [93, 94], but also has extended to signal data such as Raman spectroscopy and surface electromyography (sEMG), and satisfactory results have been achieved [95, 96]. Moreover, AI-assisted algorithms have been instrumental in the diagnosis of ankylosing spondylitis (AS). For instance, the LHR-Net algorithm proposed by Guo et al. achieved an accuracy of 81.58% in lesion segmentation and grading from MRI images, making it a promising model for automated AS diagnosis [97].

AI is also widely applied in the classification and grading of orthopedic diseases, which play a critical role in informing subsequent treatment decisions. Schilcher et al. developed a multimodal DL model that combines electronic health records (EHRs) and imaging data, accurately distinguishing atypical femoral fractures from normal femoral fractures [98]. Tibbo et al. employed NLP algorithms to extract key information from unstructured text in EHRs, accurately distinguishing periprosthetic femoral fractures (PFF) while providing the correct Vancouver classification [99]. In bone tumors classification, AI demonstrated performance comparable to that of experienced radiologists and improved the accuracy and confidence [100]. Specifically, in osteosarcoma detection, DL algorithms based on transfer learning have achieved diagnostic accuracy rates of up to 96% [101].

The application of AI in orthopedic clinical diagnosis continues to evolve, offering enhanced precision, efficiency, and accessibility. With ongoing advancements in DL and ML technologies, AI is poised to further revolutionize orthopedic diagnostics, improving patient outcomes and clinical decision-making.

3.2.2 | Treatment and Rehabilitation

Beyond disease prediction, clinical diagnosis, and classification, AI is advancing in treatment decision-making, intraoperative assistance, prognostic prediction, and rehabilitative care in

orthopedics. For example, scaphoid fracture detection remains challenging in radiological imaging. Su et al. developed a CNN model to automatically identify scaphoid fractures from X-ray images, assisting in decision-making regarding surgical or non-surgical treatment [102]. Spinal surgery is inherently complex due to the dense concentration of nerves and blood vessels near the spine. Advanced surgical robotic systems, such as Mazor X, Excelsius GPS, and TiRobot, have become invaluable tools for orthopedic surgeons in performing these procedures. Mazor X, an intelligent navigation robot for spine surgery, assists in significantly reducing intraoperative blood loss, shortening hospital stays, and lowering dependence on surgical tools [103, 104]. Surgeries guided by Excelsius GPS enable accurate pedicle screw placement without complications [105]. The TiRobot, developed by Beijing Jishuitan Hospital in collaboration with multiple institutions, represents the third generation of orthopedic surgical robotics and achieves an impressive 98.9% accuracy in pedicle screw insertion. It surpasses traditional fluoroscopic techniques in precision, reduces blood loss, shortens postsurgery hospital stays [106–108]. Enabled by 5G technology, TiRobot has facilitated remote control of orthopedic surgeries across multiple locations with positive clinical outcomes [109]. Although orthopedic surgical robotics have achieved substantial progress, current systems primarily serve as precision-guided robotic arms rather than autonomous AI-driven systems. As AI technology continues to evolve, it is anticipated that future surgical robots will possess greater intelligence and robustness.

In orthopedic rehabilitation and postoperative care, AI-enabled wearable devices and sensors have improved patient outcomes by continuously monitoring movement patterns and rehabilitation progress. For instance, exercise therapy is widely recommended for OA treatment as it alleviates pain and enhances joint function. However, long-term adherence to rehabilitation regimens remains a challenge for patients, limiting therapeutic efficacy [110, 111]. The knee monitoring wearable developed by Papi et al. has gained high patient acceptance, serving not only as a tracker to encourage sustained exercise but also as a facilitator for informed interactions between patients and clinicians [112, 113]. Furthermore, hand function rehabilitation is a crucial aspect of orthopedic recovery. The HERO Grip Glove, a robotic orthotic hand-stretching device developed by Yurkewich et al., assists stroke patients with severe hand impairments in performing daily activities independently, significantly enhancing their quality of life [114].

3.2.3 | Recurrence and Prediction

Early prediction of disease recurrence is crucial for patient treatment and prognosis. AI aids in health management and monitoring for high-risk groups by analyzing imaging, behavioral patterns, and EHRs to identify potential health issues and prevent risk events. Osteosarcoma is the most common primary malignant bone tumor, accounting for over 44% of all cases, and is known for its high recurrence and metastasis rates [115]. Currently, researchers have developed several AI-aided methods for predicting recurrence in osteosarcoma patients. Chen et al. developed a radiomics nomogram combining a radiological feature using LASSO algorithm and MRI variables. This method demonstrated strong predictive ability for early recurrence for osteosarcoma, with a C-index of 0.907 (95% CI: 0.838–0.977) in the training cohort and 0.811 (95% CI: 0.653–0.970) in the external validation cohort [116]. Similarly, Liu et al. constructed a radiomics nomogram based on CT incorporating radiomic features and clinical risk factors, which also showed a good discriminatory for early recurrence in osteosarcoma patients both in training and validation cohorts (C-index of 0.779, C-index 0.710, respectively) [117]. The development of these tools could contribute to precision treatment of bone tumors.

AI has also advanced in the prediction of fracture risk and osteoporosis recurrence. Traditional tools like FRAX and QFracture, while widely used, are limited by their reliance on predefined risk factors and long-term prediction models [118, 119]. In contrast, DL-based models offer improved accuracy and broader applicability. For example, the CNN-based DeepSurv model enhances fracture risk prediction from spinal X-ray images [120], while the Crystal Bone model utilizes EHR data to predict fractures within 1–2 years [121], enabling early intervention. Additionally, AI exhibits great performance in predicting the risk of osteoporosis via identifying risk factors, such as gender, age, BMI, and smoking history, enhancing interpretability [122, 123]. AI also aids in predicting the risk of fracture recurrence. DL and ML models have been successfully used to predict the risk of recurrent fractures in elderly patients with hip fractures within 2–5 years [124, 125], guiding early interventions. Furthermore, DeepBackRib, a DL-based model, predicts readmission risk after rib fractures in nonelderly individuals with 91% recall. This model quantified key factors, such as chronic obstructive pulmonary disease and length of hospital stay, which were positively associated with 3-month readmissions [126]. This enhances interpretability and applicability across different populations.

Predicting progression of OA through radiographic methods remains a challenge, as evidenced by the limited performance of top models in the 2020 Knee Osteoarthritis Prediction Challenge [127]. However, recent AI advancements show promise. Kundu et al. developed a method that combined optimal mass transport theory with statistical pattern recognition to predict OA progressors. They tracked OA progression in subjects over a 3-year follow-up and trained a classifier to differentiate progressors from nonprogressors based on baseline cartilage texture maps, achieving a robust test accuracy of 78% in detecting future symptomatic OA progression 3 years prior to symptom onset [128]. Complementarily, Han et al. integrated regularized generative adversarial networks with a latent nearest neighbor algorithm to generate knee radiographs at future time points, achieving superior predictive performance and enhancing radiologists' diagnostic specificity and sensitivity compared to conventional approaches [129]. Furthermore, the AutoML framework, combining with clinical, biochemical, radiographic, and MRI data, can predict rapid knee OA progression within 2 years, while identifying key predictive variables, facilitating clinical translation beyond traditional "black-box" methods [130]. These innovations not only advance early OA detection but also offer insights for studying complex bone-related pathologies.

We provide a detailed summary of the application of AI in bone from fundamental bone research to orthopedic clinical applications, as shown in Figure 2. To sum up, AI has been increasingly applied across various fields of bone research, offering valuable

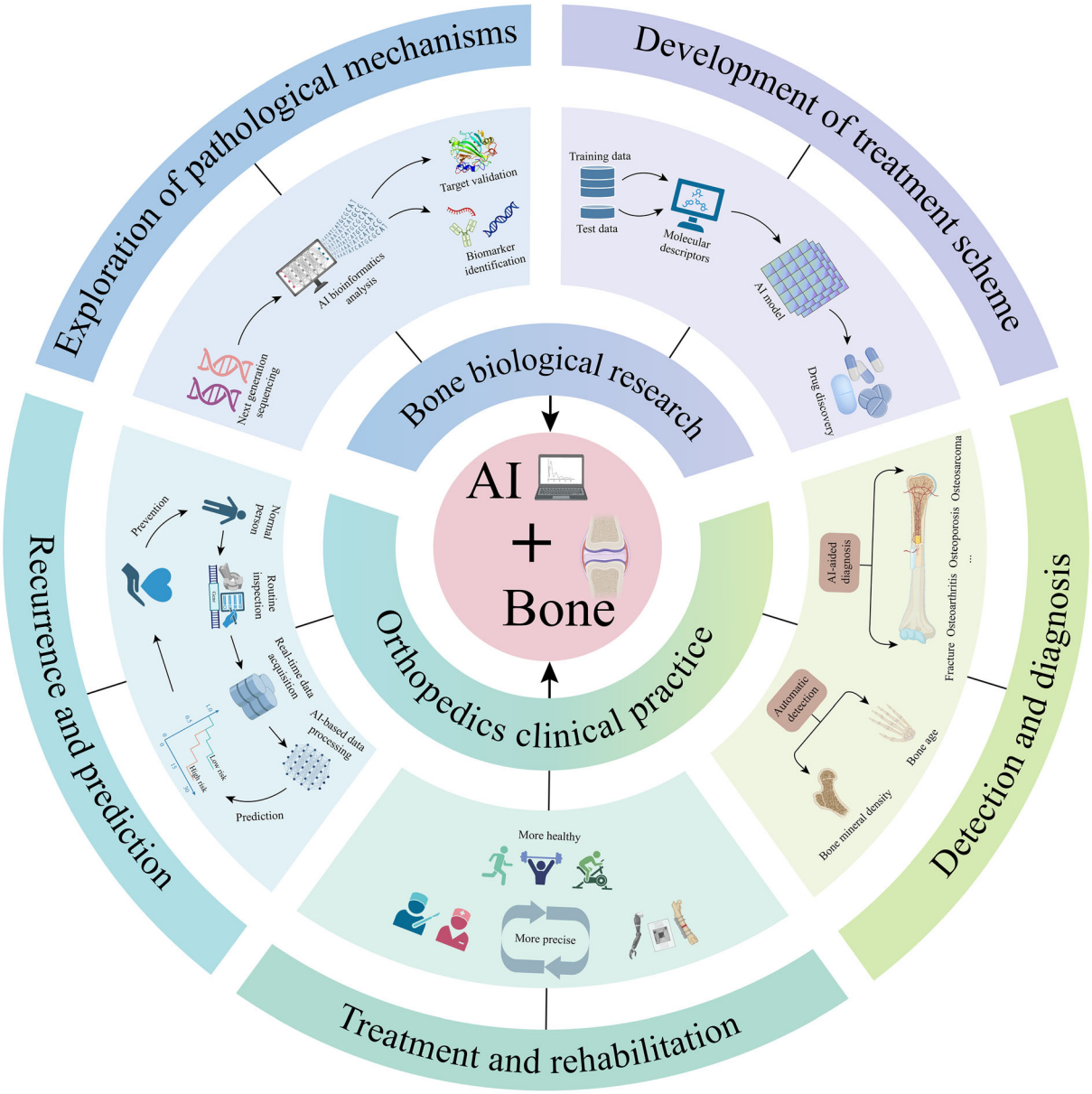

FIGURE 2 | The potential applications of AI in orthopedics, including fundamental biological research and clinical applications.

insights into bone health and disease progression. From fundamental bone research to orthopedic clinical applications, AI offers several advantages, including automated processing and interpretation of large, complex datasets, the development of accurate predictive models, and the identification of potential biomarkers. These contributions collectively enhance precision medicine. Table 1 lists the developed algorithms and tools currently applied in clinical practice.

4 | Challenges of AI in Bone Research and Clinical Applications

As discussed above, AI has had a profound impact on bone research, revolutionizing diagnostic and therapeutic strategies in orthopedics. However, these technological advancements also come with challenges and ethical considerations. Addressing these issues is indispensable to ensuring that AI-driven technologies are implemented effectively, equitably, and responsibly in clinical practice.

4.1 | In Clinical Applications

By leveraging big data, AI can offer insights beyond current capabilities and holds the potential to transform clinical orthopedics pattern. However, low data quality, inconsistent data formats, difficulty in data sharing, and limited model interpretability are significant challenges. Addressing these issues is essential for maximizing the benefits of AI for both clinicians and patients.

The performance of AI models is intrinsically linked to the quality of data on which they are trained. Thus, ensuring the accuracy, consistency, and integration of data from diverse sources is the primary challenge (Figure 3a). Orthopedic medical data, such as imaging, surgical records, EHRs, and genomic data,

TABLE 1 | AI methods and tools for orthopedic clinical applications.

Developer	Tools	Training data	Algorithm	Application
Rassmann et al. [78]	Deeplasia	X-ray image	CNN	Assessment of bone age and skeletal dysplasia
Mutasa et al. [79]	MABAL	Radiographs	CNN	Bone age assessment
Li et al [80]	RAGCN	X-ray image	CNN	Bone age assessment
Tomita et al. [82]	Vertebral fractures detection system	CT image	CNN	Automatic detection of vertebral fractures
Ho et al. [86]	DeepDXA	X-ray image	CNN	Bone mineral density assessment
Kumar [89]	Osteo-Net	X-ray image	DNN	Diagnosis of osteoporosis
Ibraheem [96]	PESDL	sEMG signal	RNN	Diagnosis of Patellofemoral OA
Guo et al. [97]	LHR-Net	MRI image	CNN	Grading of AS
Nguyen et al. [131]	Semixup	Radiographs	DL	Grading of Knee OA
Khan et al. [104]	Mazor X	/	/	Spinal surgery intelligent navigation robot
Kanaly et al. [105]	Excelsius GPS	/	/	Spinal surgery intelligent navigation robot
Tian et al. [106]	TiRobot	/	/	Spinal surgery intelligent navigation robot
Yurkewich et al. [114]	HERO	/	/	Hand function rehabilitation for stroke patients
Kong et al. [120]	DeepSurv	X-ray image	CNN	Predicting fracture risk
Almog et al. [121]	Crystal Bone	EHR	NLP, ML	Predicting fracture risk
Choi et al. [126]	DeepBackRib	EHR	DNN	Predicting fracture progression
Hu et al. [132]	DeepKOA	MRI image	CNN	Predicting Knee OA progression
Yin et al. [133]	BikNet	X-ray image	CNN	Predicting Knee OA progression

"/": The methods or techniques were not described in the literature.

are often unstructured and recorded in various formats. Imaging data, including X-rays, MRIs, and CT scans, are constrained by equipment resolution [134, 135], while EHRs data may contain noise, missing values, or inconsistencies in annotation criteria across clinicians [136]. These discrepancies complicate data integration and model training. To mitigate these issues, standardized data collection and processing protocols must be established [137]. For example, adopting international standards like Digital Imaging and Communications in Medicine (DICOM) and Health Level Seven (HL7) can harmonize data formats [138, 139]. Additionally, advanced data preprocessing and fusion algorithms can be developed to remove noise and redundant information, improving data quality [140]. Finally, establishing interinstitutional collaboration mechanisms and expert consensus will further enhance data consistency and accuracy in diagnostic annotation and clinical workflows.

Beyond data quality, data sharing poses another challenge (Figure 3b). Patient medical records often contain highly sensitive patient information, protected under strict privacy laws such as the EU's General Data Protection Regulation (GDPR) and the U.S. Health Insurance Portability and Accountability Act (HIPAA) [141, 142]. In addition, technical barriers arise from the use of disparate EHR systems across healthcare institutions, leading to issues with compatibility and interoperability. Institutional competition further exacerbates the problem by creating information silos that hinder data sharing [143]. To address these challenges, researchers are developing optimized data-sharing mechanisms. Federated learning, a privacy-preserving technique, allows decentralized data storage while enabling cross-institutional model training, which safeguards patient privacy and promotes collaborative AI development [144]. Additionally, interoperability standards like Fast Healthcare Interoperability Resources (FHIR) and openEHR protocols facilitate seamless data exchange across platforms, gradually dismantling information silos and fostering a more connected healthcare ecosystem [145, 146].

From a clinical perspective, model interpretability remains a key limitation to AI adoption. As algorithms become more complex, many models exhibit "black-box" characteristics, making their decision-making processes opaque and difficult to understand (Figure 3c). Insufficient interpretability may lead to reluctance among clinicians to trust AI-driven recommendations, and may also generate skepticism among patients regarding diagnostic or predictive outcomes, potentially undermining the clinician–patient relationship. Therefore, developing models that are both accurate and interpretable will enhance the applicability of AI in clinical settings. Techniques like SHapley Additive Explanations (SHAP) or Local Interpretable Model-Agnostic Explanations (LIME) can help elucidate critical variables and key features that drive AI predictions, thereby increasing transparency and credibility in clinical decision-making [147].

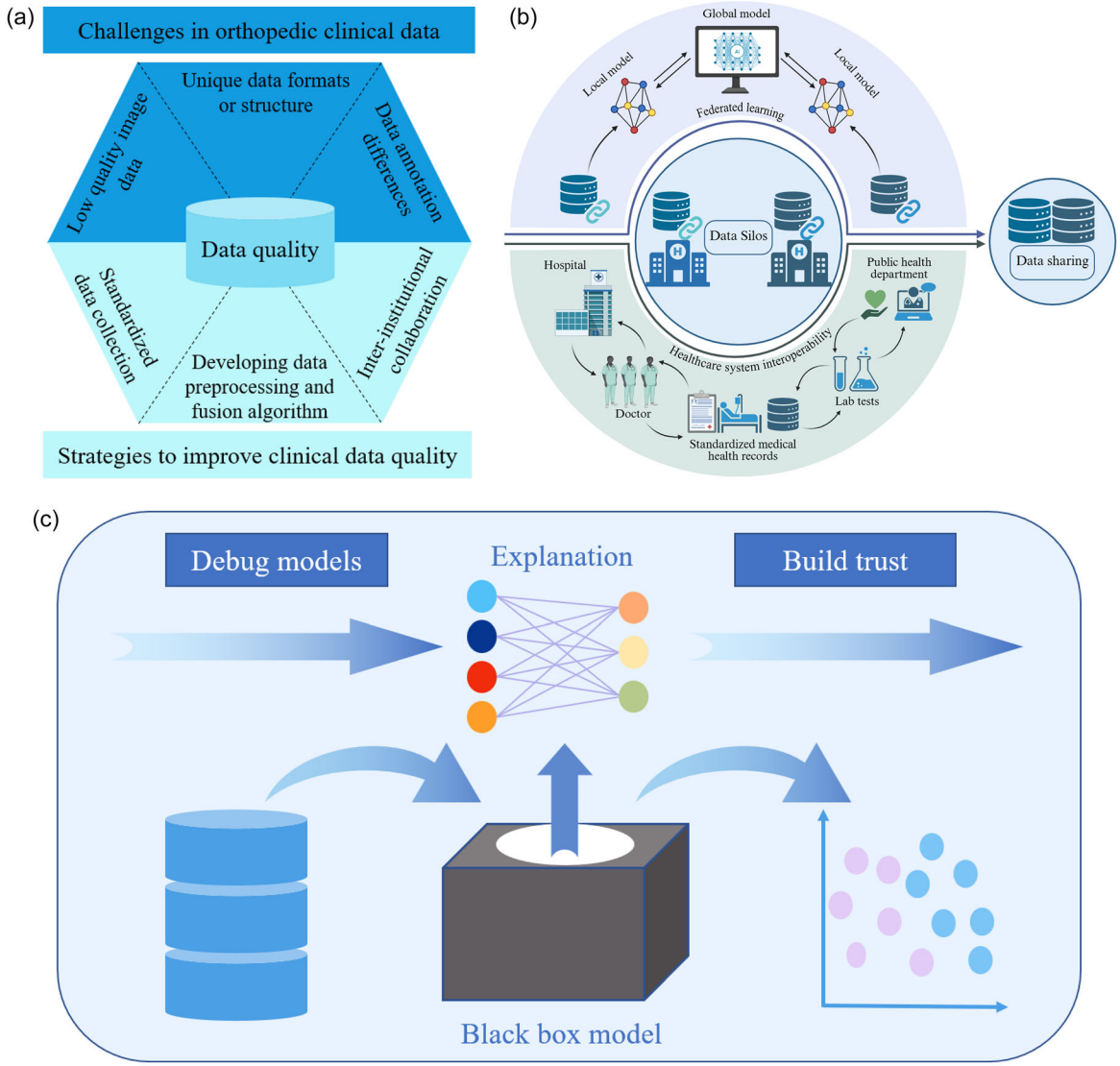

FIGURE 3 | Navigation of the current challenges and potential solutions faced by AI in orthopedic clinical practice. (a) Potential strategies for addressing data quality challenges. (b) Adopting federated learning and increased interoperability in healthcare systems to facilitate data sharing. (c) Opening the "black box" to enhance model interpretability, focusing on methods that balance model accuracy with lucid explanations.

4.2 | In Pathological and Mechanistic Studies

Traditionally, the study of mechanisms of orthopedic diseases has heavily relied on molecular biology techniques such as Western blotting, molecular labeling, and PCR. Although these methods allow for detailed analysis of the expression and function of specific molecules within cells or tissues, they are often costly, time-consuming, and inherently limited in uncovering the multifactorial and multilayered complexities of orthopedic diseases. Consequently, these traditional approaches focus on localized molecular features rather than providing a holistic understanding of disease mechanisms.

With rapid advancements in proteomics, scRNA-seq, and spatial transcriptomics, researchers have enabled to obtain vast amounts of high-dimensional data encompassing genetic, proteomic, and spatial information. These datasets span various cell types, molecular processes, and spatiotemporal dynamics, greatly expanding the horizons of orthopedic disease research. However, effectively leveraging AI to process and analyze these high-dimensional datasets and extract meaningful biological insights remains a primary challenge.

To meet this challenge, developing more efficient data preprocessing algorithms is essential for data cleaning, dimensionality reduction, denoising, and the standardization of biological data formats [148]. The correlated clustering and projection (CCP) algorithm is a prime example, which enables dimensionality reduction and feature extraction in scRNA-seq [149]. Similarly, the spatial transcriptomics graph neural network k-sums clustering (STGNNks) algorithm, which integrates graph neural networks, autoencoders, and k-sums clustering, improves spatial transcriptomics data analysis, facilitating more accurate cell type identification [150].

Beyond these algorithmic advancements, the integration of transcriptomic, proteomic, and imaging data is crucial for establishing a comprehensive multimodal data platform for orthopedic diseases research, as described in Figure 4. Existing large-scale

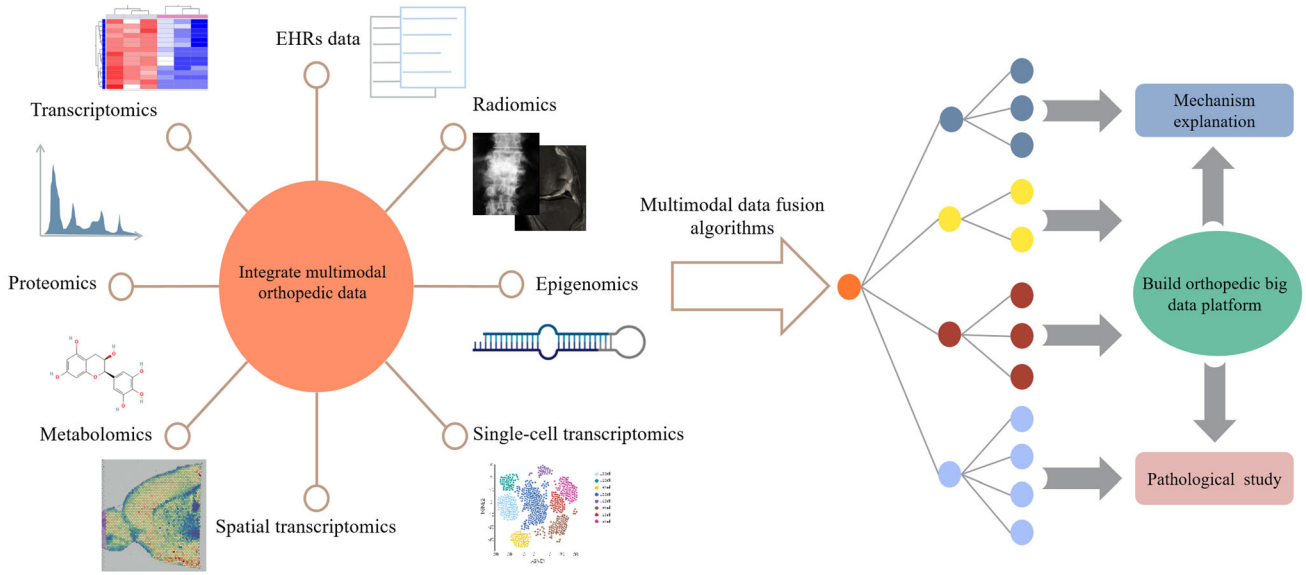

FIGURE 4 | Establishment of a comprehensive multimodal platform by integrating orthopedic clinical data, molecular biological information and self-evolving algorithms across multiple dimensions can significantly enhance the understanding of orthopedic disease mechanisms.

orthopedic datasets like FracAtlas and the osteoarthritis initiative (OAI) primarily focus on imaging data [151, 152]. In contrast, the field of oncology provides a valuable template for data integration and processing. Multimodal datasets, such as The Cancer Genome Atlas (TCGA), The Cancer Imaging Archive (TCIA), and the Genomic Data Commons (GDC), exemplify a more holistic approach by integrating genomics, clinical, pathological, and imaging data. This comprehensive framework has significantly advanced AI model training and the study of cancer molecular mechanisms, offering a blueprint for future orthopedic research [153–155]. Finally, establishing interdisciplinary collaboration mechanisms is essential for the effective integration of AI and bioinformatics in bone research. Research institutions, healthcare organizations, and data science experts should actively share data, participate in the construction of multimodal orthopedic datasets, and establish unified data standards. By promoting interdisciplinary collaboration, AI can be better to support the elucidation of orthopedic disease mechanisms, leading to intelligent solutions for disease diagnosis and treatment.

4.3 | Ethical and Regulatory Considerations

The application of AI in orthopedics introduces new ethical and regulatory challenges, particularly concerning patient privacy protection. The development and deployment of AI models rely on substantial patient data, necessitating stringent data regulations to ensure that data collection and usage adhere to ethical standards [156]. Additionally, to minimize the risks of unauthorized access and data breaches, the informed consent of the patients should be required before collecting and using private data [157]. Therefore, a unified data governance framework is essential to ensure data security and confidentiality during storage and transmission, with strict ethical guidelines to prevent misuse by data users. For example, the World Health Organization (WHO) outlines six considerations for AI in health regulation, including transparency, risk management, data usage, privacy protection, and promoting collaboration among patients, physicians, regulatory bodies, and government entities [158].

4.4 | Concern of Overreliance on AI

AI has shown amazing charm across various fields. However, admittedly, AI technology still has inherent limitations and potential risks, necessitating a balanced reliance on AI. Not all AI models outperform traditional methods, particularly when faced with insufficient or low-quality data. Ahmed and Imran found that while AI achieved a 99.13% accuracy rate in distinguishing between normal and severe Knee OA cases, its accuracy dropped to 67% for other classifications, indicating its limitations in nuanced clinical decision-making [159]. Additionally, despite the methodological advancements, its clinical effectiveness is not always guaranteed. A systematic review of 65 randomized controlled trials revealed that approximately 40% of AI-based interventions showed no statistically significant improvement over standard care [160]. Therefore, prior to integrating AI technologies into clinical practice, healthcare teams should critically evaluate their performance relative to traditional methods. This careful evaluation is essential to optimize computational resources allocation and ensuring meaningful improvements in patient outcomes.

5 | Future Perspective of AI in Bone Research

5.1 | Discovery of Drug Targets for Bone Disease Driven by AI

The integration of AI and big data in orthopedics is expected to yield significant breakthroughs in three key areas: target discovery, drug development, and data-driven precision treatment. These developments may shift orthopedic disease treatment from mere symptom relief to precise medicine.

5.1.1 | Accelerated Target Discovery: AI-Driven Molecular Network Analysis

Traditional target discovery relies on stepwise experimental screening and validation, which can be time-consuming and labor-intensive [161–164]. As the genomics and systems biology improves by leaps and bounds, it provides us a more comprehensive view to analyze complex gene-to-gene and protein-to-protein interaction networks. However, these networks remain intricate and challenging to decipher [165]. The advance of AI algorithms facilitates the processing and analysis of high-dimensional, multi-layered data, gradually unveiling the molecular regulatory networks behind complex diseases, such as Alzheimer's [166], cancer [167], and cardiovascular diseases [168]. Similarly, bone, as a central organ, exhibits a multifactorial and complex pathophysiological relationship. Recent studies demonstrate the potential of AI in identifying crucial targets for bone diseases that are challenging to detect through traditional experimental methods [169, 170]. With the accumulation of orthopedic big data, AI-driven molecular network analyses in bone diseases will increasingly enable systematic, intelligent target discovery. However, when applying AI to orthopedic data, it is crucial to prioritize model interpretability and reliability. Due to the "black box" nature of many AI algorithms, their real-world application may be limited, underscoring the need to combine AI models with experimental validation.

5.1.2 | Optimizing Drug Development: Paradigm Shift from Experiment-Driven to Data-Driven

Drug development is a costly and time-intensive process, with a success rate of less than 10% for drugs that reach phase I clinical trials [171]. This complex process involves three main stages: understanding disease mechanisms and identifying key targets, developing therapeutics for these targets, and validating drug efficacy and safety. Against this backdrop, AI-driven drug discovery has made notable strides, utilizing physics- or chemistry-based algorithms to enhance drug design efficiency, thus revolutionizing traditional drug development models.

AI applications in drug development encompass virtual screening, de novo molecular design, docking, and property prediction. Despite this broad scope, the success of AI in drug discovery has lagged behind other fields. Studies indicate that ML models often generalize poorly to data outside their training sets, reducing accuracy and practical utility [172]. This limitation may be partly due to algorithmic shortcomings, but primarily reflects limitations in training data. Currently, public datasets are limited to tens or hundreds of thousands of samples, which is far below the trillions of data points in imaging fields. Unfortunately, generating biological and chemical data is costly and challenging to automate, so a rapid increase in data volume is unlikely in the short term. Consequently, maximizing the utility of existing data is essential. Data augmentation techniques or federated learning approaches could improve data quality and quantity. Additionally, developing novel data sources is equally crucial. As data volumes increase, data-driven research in orthopedic drug development is likely to expand, potentially shifting the current experiment-driven paradigm.

5.1.3 | Moving toward Precision Therapy: Treatment Shifting from Symptom Relief to Precision Medicine

AI is progressively advancing orthopedic treatment from traditional symptom relief toward intelligent precision medicine. Through large-scale real-world data modeling, AI can leverage genetic, imaging, and clinical data from patients to create personalized treatment maps for orthopedic diseases. For example, in heterogeneous conditions like OA and osteoporosis, AI can classify patients based on unique genetic expression profiles and clinical features, identifying disease subtypes or stratifying risk [173, 174]. By integrating this in-depth analysis, AI can further optimize treatment protocols and improve patient outcomes [175]. Furthermore, fostering communication between AI algorithm developers and clinical orthopedic practitioners is crucial to realizing precision medicine in orthopedics. Algorithm researchers should prioritize developing tools that are user-friendly for doctors and patients, while clinicians should explore nontraditional challenges and provide new requirements to guide researchers in designing more precise and applicable AI models.

5.2 | Integrating Multiple Models for Orthopedic: Bone-GPT

In recent years, the emergency of large language models (LLMs) like ChatGPT-4, along with advancements in generative AI and inference models like openAI o1 and DeepSeek, has driven a paradigm shift in AI research from "small-scale workshops" to "large-scale factories" and ultimately to "intelligent manufacturing." The success of PathChat in pathology demonstrates the broad potential for LLMs in medical field [176]. Against this backdrop, we introduce the concept of Bone-GPT—a generative large language model for orthopedics, with versatile applications spanning clinical practice, community health, and medical training. Clinical applications include: (1) assisting in the analysis of medical imaging and pathology data to enhance diagnostic accuracy; (2) utilizing patient-specific data, like EHR records to offer tailored therapeutic strategies; (3) supporting orthopedic surgeons with preoperative guidance and virtual surgical simulations to improve success rates and safety; (4) monitoring patient recovery data to provide customized rehabilitation plans and early warnings for potential complications; and (5) offering emotional support to patients undergoing diagnosis and treatment to alleviate psychological stress. Bone-GPT can extend beyond clinical settings to serve the broader community by: (1) providing general orthopedic health consultations and bone health information for the public; (2) aiding preliminary diagnosis based on symptoms and offering guidance on whether medical attention is necessary; and (3) offering daily health management advice for patients with chronic conditions (e.g., osteoporosis, osteoarthritis). In addition, Bone - GPT can be utilized in orthopedic clinical training: enhancing clinial skills of medical students and orthopedic trainees through simulated clinical scenarios, interactive case studies and clinical decision-making exercise.

Realizing Bone-GPT is a comprehensive project that faces multiple challenges: (1) Data quality and availabilityorthopedic data collection and annotation are often complex and resource-intensive,

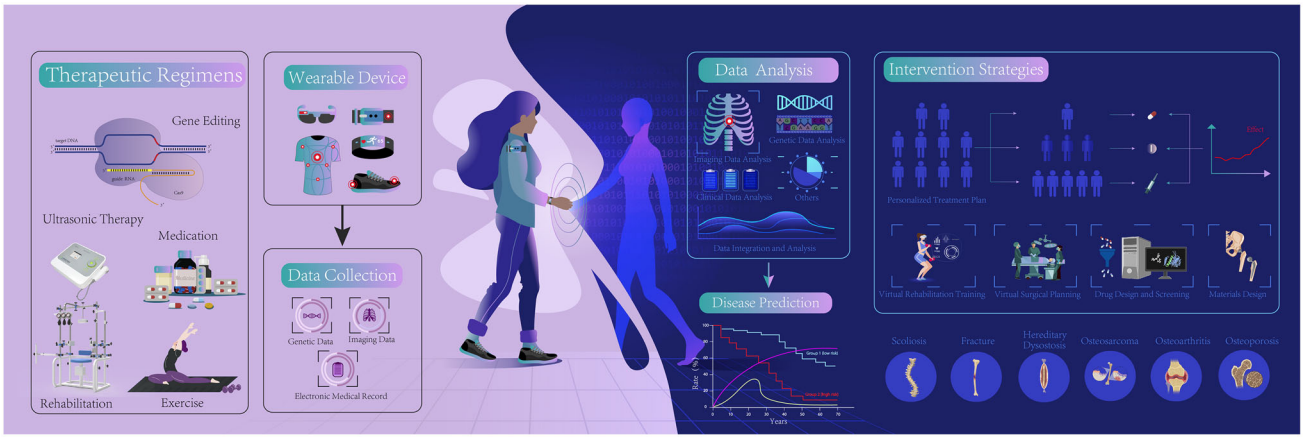

FIGURE 5 | Blueprint of parallel intelligence in orthopedics. The parallel intelligence system facilitates dynamic simulation of orthopedic disease evolution, providing actionable feedback that enhances the prevention and precision personalized interventions.

embarrassing traditional supervised learning methods. Therefore, advanced data analysis and annotation algorithms for limited data are required. (2) Ethical and bias considerations—ensuring fairness are free from potential biases related to race, gender, region, or other factors. (3) Interdisciplinary collaboration—successful application of close Bone-GPT required synergy among orthopedic specialists, data scientists, physicists, biomedical engineers, and ethicists to navigate the complexities of medical AI applications. (4) Causal inference and explainability—current AI models excel at generating highly accurate predictions but are limited in their understanding of causality. To improve medical decision-making, Bone-GPT should incorporate causal inference methods (e.g., structural causal models, SCMs) and reinforcement learning to establish cause-and-effect relationships within complex pathological networks.

5.3 | Parallel Virtual and Reality: Parallel Intelligence Advancing Orthopedic Medicine New Frontiers

The future of healthcare management envisions a comprehensive approach that spans the entire life course. It begins with dynamic monitoring of health to infer possible diseases and propose early interventions. Parallel intelligence presents a transformative opportunity to realize this vision. Parallel intelligence aims to enhance the understanding and control of complex processes by enabling parallel interactions between artificial systems and real-world systems. This framework, grounded in the ACP methodology (artificial systems, computational experiments, and parallel execution), establishes a continuous loop of data generation, knowledge extraction, and action implementation [177]. Such an iterative process ensures dynamic evolution and real-time adjustments, leading to more precise and efficient operation of complex healthcare systems. Here, we outline the blueprint of parallel intelligence in orthopedic care, as shown in Figure 5.

In modern medical research, AI has revolutionized our ability to predict biological processes. For example, the AlphaMissense model can predict the pathogenicity of missense mutations in proteins [178], the PrimateAI-3D model identifies individuals at high risk for disease based on rare genetic variants [179], and the LucaProt model has identified over 160 000 new RNA viruses, revealing viral evolutionary paths [180]. These breakthroughs showcase AI's potential in genetic analysis, early diagnosis, biological evolution, and precision medicine. Integrating these cutting-edge technologies within a parallel intelligence framework, the bidirectional interaction between the virtual and real-world systems can fundamentally reshape orthopedic healthcare models. Here, we propose four potential applications for parallel intelligence in orthopedic clinical practice: (1) Prediction of genetic pathogenicity: A parallel intelligence system combined with tools like AlphaMissense and PrimateAI-3D can analyze missense mutation data to predict disease risk, progression, and therapeutic response. This capability enables the development of targeted pharmacological or gene therapies. (2) Disease progression simulation: By utilizing real-world data, parallel intelligence systems can create virtual models to simulate the natural course of diseases, such as osteoarthritis and osteoporosis. This simulation facilitates the prediction of characteristic disease progression patterns, forming the foundation for personalized and proactive disease management strategies. (3) Treatment strategy validation: Virtual systems can simulate the efficacy and side effects of different treatment strategies (e.g., pharmacotherapy, physical therapy, and surgical interventions), facilitating pre-evaluation of their effectiveness and safety, and offering reliable scientific support for individualized treatment plans. (4) Dynamic disease management: Parallel intelligence systems enable real-time patient condition monitoring, with virtual simulations continuously updating based on incoming clinical data. This dynamic system predicts disease trends, adjusts therapeutic strategies accordingly, and fosters an iterative data-driven feedback cycle. Ultimately, orthopedic disease management becomes more precise, more adaptable, and capable of optimizing long-term patient prognosis and health outcomes.

6 | Conclusion

In conclusion, the integration of AI into bone research offers unprecedented opportunities for advancing precision medicine. However, challenges remain, including complex scenario with clinical applications, interpretation of pathological mechanisms, ethical considerations, and concerns about overreliance on AI.

Addressing these obstacles requires a multidisciplinary team comprising orthopedic specialists, molecular biologists, data scientists, bioinformaticans, policymakers, and regulatory agency personnel. Prospects for the future, the deep integration of AI with orthopedic big data holds promise for significant breakthroughs in targets discovery and drug development. Moreover, advancements in LLMs and parallel intelligence technologies could further propel orthopedic treatment from symptom relief toward health risk avoidance, offering intelligent solutions for early prevention, diagnosis, and personalized interventions. Albeit not perfect yet, as more researchers, clinicians, and patients incorporate AI into their routine research and practice, more data will be generated, which, in turn, will enhance AI performance and the quality of clinical applications.

Acknowledgments

This project was supported by the National Key Research and Development Program of China (2023YFC2415800) to L.T., National Natural Science Foundation of China (NSFC) grants (82394445, 82172397, 82030067, 82161160342) to D.C. and L.T., and Shenzhen Science and Technology Research Funding (JCYJ20220818101414032) to L.T.

Conflicts of Interest

The authors declares no conflicts of interest.

References

1. L. Tong, A. Wijnen, H. Wang, et al., "Advancing Bone Biology: The Mutual Promotion of Biology and Pioneering Technologies," *The Innovation Life* 2, no. 3 (2024): 100078.

2. Y. Wang, Z. Yuan, Y. Pang, et al., "Injectable, High Specific Surface Area Cryogel Microscaffolds Integrated with Osteoinductive Bioceramic Fibers for Enhanced Bone Regeneration," *ACS Applied Materials & Interfaces* 15, no. 17 (2023): 20661–20676.

3. H. Long, Q. Liu, H. Yin, et al., "Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019," *Arthritis & Rheumatology* 74, no. 7 (2022): 1172–1183.

4. P. L. Xiao, A. Y. Cui, C. J. Hsu, et al., "Global, Regional Prevalence, and Risk Factors of Osteoporosis According to the World Health Organization Diagnostic Criteria: A Systematic Review and Meta-Analysis," *Osteoporosis International* 33, no.10 (2022): 2137–2153.

5. X. Fan, A. R. Sun, R. S. E. Young, et al., "Spatial Analysis of the Osteoarthritis Microenvironment: Techniques, Insights, and Applications," *Bone Research* 12, no. 1 (2024): 7.

6. R. Y. L. Kuo, C. Harrison, T-A. Curran, et al., "Artificial Intelligence in Fracture Detection: A Systematic Review and Meta-Analysis," *Radiology* 304, no. 1 (2022): 50–62.

7. V. Karhade, M. E. R. Bongers, and O. Q. Groot, et al., "Natural Language Processing for Automated Detection of Incidental Durotomy," *The Spine Journal* 20, no. 5 (2020): 695–700.

8. A. M. R. Karim, T. Islam, M. Shajalal, et al., "Explainable AI for Bioinformatics: Methods, Tools and Applications," *Briefings in Bioinformatics* 24, no. 5 (2023): bbad236.

9. H. Wang, T. Fu, Y. Du, et al., "Scientific Discovery in the Age of Artificial Intelligence," *Nature* 620, no. 7972 (2023): 47–60.

10. A. M. Turing, "Computing Machinery and Intelligence," in Parsing the Turing Test, eds. R. Epstein, G. Roberts, and G. Beber (Springer, Dordrecht, 2009).

11. A. Newell and H. Simon, "The Logic Theory Machine—A Complex Information Processing System," *IRE Transactions on Information Theory* 2, no. 3 (1956): 61–79.

12. J. McCarthy, "History of LISP," *SIGP* 13, no. 8 (1978): 217–223.

13. G. W. Ernst, "GPS and Decision Making: An Overview," in Theoretical Approaches to Non-Numerical Problem Solving, Vol. 28, **Lecture Notes in Operations Research and Mathematical Systems**, eds. R. B. Banerji and M. D. Mesarovic (Springer, Berlin Heidelberg, 1970).

14. R. K. Lindsay, B. G. Buchanan, and E. A. Feigenbaum, et al., "DENDRAL: A Case Study of the First Expert System for Scientific Hypothesis Formation," *Artificial Intelligence* 61, no. 2 (1993): 209–261.

15. W. R. Swartout, "Rule-Based Expert Systems: The Mycin Experiments of the Stanford Heuristic Programming Project: B.G. Buchanan and E.H. Shortliffe, (Addison-Wesley, Reading, MA, 1984); 702 pages, $40.50," *Artificial Intelligence* 26, no. 3 (1985): 364–366.

16. Y. Chen, J. D. Elenee Argentinis, and G. Weber, "IBM Watson: How Cognitive Computing Can Be Applied to Big Data Challenges in Life Sciences Research," *Clinical Therapeutics* 38, no. 4 (2016): 688–701.

17. D. Silver, A. Huang, C. J. Maddison, et al., "Mastering the Game of Go with Deep Neural Networks and Tree Search," *Nature* 529, no. 7587 (2016): 484–489.

18. J. Abramson, J. Adler, J. Dunger, et al., "Accurate Structure Prediction of Biomolecular Interactions with AlphaFold 3," *Nature* 630, no. 8016 (2024): 493–500.

19. R. C. Deo, "Machine Learning in Medicine," *Circulation* 132, no. 20 (2015): 1920–1930.

20. M. P. Hosseini, A. Hosseini, K. Ahi, et al., "A Review on Machine Learning for EEG Signal Processing in Bioengineering," *IEEE Reviews in Biomedical Engineering* 14 (2021): 204–218.

21. S. Visweswaran, J. B. Colditz, P. O'Halloran, et al., "Machine Learning Classifiers for Twitter Surveillance of Vaping: Comparative Machine Learning Study," *Journal of Medical Internet Research* 22, no. 8 (2020): e17478.

22. P. Lakhani, A. B. Prater, R. K. Hutson, et al., "Machine Learning in Radiology: Applications Beyond Image Interpretation," *Journal of the American College of Radiology* 15, no. 2 (2018): 350–359.

23. B. Mehta, S. Goodman, E. DiCarlo, et al., "Machine Learning Identification of Thresholds to Discriminate Osteoarthritis and Rheumatoid Arthritis Synovial Inflammation," *Arthritis Research & Therapy* 25, no. 1 (2023): 31.

24. L. Arbeeva, M. C. Minnig, K. A. Yates, et al., "Machine Learning Approaches to the Prediction of Osteoarthritis Phenotypes and Outcomes," *Current Rheumatology Reports* 25, no. 11 (2023): 213–225.

25. G. E. Hinton, S. Osindero, and Y. W. Teh, "A Fast Learning Algorithm for Deep Belief Nets," *Neural Computation* 18, no. 7 (2006): 1527–1554.

26. R. Y. Choi, A. S. Coyner, J. Kalpathy-Cramer, M. F. Chiang, and J. P. Campbell, "Introduction to Machine Learning, Neural Networks, and Deep Learning," *Translational Vision Science & Technology* 9, no. 2 (2020): 14.

27. M. Sarıgül, B. M. Ozyildirim, M. Avci, et al., "Differential Convolutional Neural Network," *Neural Networks* 116 (2019): 279–287.

28. Y. D. Pranata, K. C. Wang, and J. C. Wang, et al., "Deep Learning and SURF for Automated Classification and Detection of Calcaneus Fractures in CT Images," *Computer Methods and Programs in Biomedicine* 171 (2019): 27–37.

29. V. Georgeanu, M. L. Mamuleanu, D. Selişteanu, et al., "*Convolutional Neural Networks for Automated Detection and Classification of Bone Tumors in Magnetic Resonance Imaging*," in 2021 IEEE International Conference on Artificial Intelligence, Robotics, and Communication (ICAIRC), (2021).

30. M. Janotheepan, S. D. H. S. Wickramarathna, S. Bavathaaranie, et al., "Detection and Classification of Knee Osteoarthritis Using Convolutional Neural Network," *paper presented at the 4th International Conference on Advanced Research in Computing (ICARC)*, 2024.

31. N. Sager, M. Lyman, C. Bucknall, N. Nhan, and L. J. Tick, "Natural Language Processing and the Representation of Clinical Data," *Journal of the American Medical Informatics Association* 1, no. 2 (1994): 142–160.

32. H. Wang, Y. Li, S. A. Khan, and Y. Luo, "Prediction of Breast Cancer Distant Recurrence Using Natural Language Processing and Knowledge-Guided Convolutional Neural Network," *Artificial Intelligence in Medicine* 110 (2020): 101977.

33. S. Wu, K. Roberts, S. Datta, et al., "Deep Learning in Clinical Natural Language Processing: A Methodical Review," *Journal of the American Medical Informatics Association* 27, no. 3 (2020): 457–470.

34. Z. Li, Z. Zhang, H. Zhao, et al., "Text Compression-Aided Transformer Encoding," *IEEE Transactions on Pattern Analysis and Machine Intelligence* 44, no. 7 (2022): 3840–3857.

35. W. Sun, Z. Qin, H. Deng, et al., "Vicinity Vision Transformer," *IEEE Transactions on Pattern Analysis and Machine Intelligence* 45, no. 10 (2023): 12635–12649.

36. A. Revuelta-Martínez, L. Rodríguez, I. García-Varea, et al., "Multimodal Interaction for Information Retrieval Using Natural Language," *Computer Standards & Interfaces* 35, no. 5 (2013): 428–441.

37. M. C. Chen, R. L. Ball, L. Yang, et al., "Deep Learning to Classify Radiology Free-Text Reports," *Radiology* 286, no. 3 (2018): 845–852.

38. A. W. Olthof, P. Shouche, E. M. Fennema, et al., "Machine Learning Based Natural Language Processing of Radiology Reports in Orthopaedic Trauma," *Computer Methods and Programs in Biomedicine* 208 (2021): 106304.

39. C. Friedman, L. Shagina, Y. Lussier, and G. Hripcsak, "Automated Encoding of Clinical Documents Based on Natural Language Processing," *Journal of the American Medical Informatics Association* 11, no. 5 (2004): 392–402.

40. J. S. Zhang, R. S. Pan, G. L. Li, et al., "Comprehensive Analysis of Anoikis-Related Genes in Diagnosis Osteoarthritis: Based on Machine Learning and Single-Cell RNA Sequencing Data," *Artificial Cells, Nanomedicine, and Biotechnology* 52, no. 1 (2024): 156–174.

41. Y. Wang, X. Ma, E. Xu, et al., "Identifying Squalene Epoxidase as a Metabolic Vulnerability in High-Risk Osteosarcoma Using an Artificial Intelligence-Derived Prognostic Index," *Clinical and Translational Medicine* 14, no. 2 (2024): e1586.

42. R. L. Nielsen, T. Monfeuga, R. R. Kitchen, et al., "Data-Driven Identification of Predictive Risk Biomarkers for Subgroups of Osteoarthritis Using Interpretable Machine Learning," *Nature Communications* 15, no. 1 (2024): 2817.

43. Y. Zheng, J. Li, Y. Li, et al., "Plasma Proteomic Profiles Reveal Proteins and Three Characteristic Patterns Associated with Osteoporosis: A Prospective Cohort Study," *Journal of Advanced Research* (2024), https://doi.org/10.1016/j.jare.2024.10.019.

44. Y. Zhou, D. Yang, Q. Yang, et al., "Single-Cell RNA Landscape of Intratumoral Heterogeneity and Immunosuppressive Microenvironment in Advanced Osteosarcoma," *Nature Communications* 11, no. 1 (2020): 6322.

45. Y. Sha, Y. Qiu, P. Zhou, and Q. Nie, "Reconstructing Growth and Dynamic Trajectories from Single-Cell Transcriptomics Data," *Nature Machine Intelligence* 6, no. 1 (2024): 25–39.

46. A. Rauch, A. K. Haakonsson, J. G. S. Madsen, et al., "Osteogenesis Depends on Commissioning of a Network of Stem Cell Transcription Factors That Act as Repressors of Adipogenesis," *Nature Genetics* 51, no. 4 (2019): 716–727.

47. W. Xu, I. Mesa-Eguiagaray, D. M. Morris, et al., "Deep Learning and Genome-Wide Association Meta-Analyses of Bone Marrow Adiposity in the UK Biobank," *Nature Communications* 16, no. 1 (2025): 99.

48. E. Kun, E. M. Javan, O. Smith, et al., "The Genetic Architecture and Evolution of the Human Skeletal Form," *Science* 381, no. 6655 (2023): eadf8009.

49. M. Garg, M. Karpinski, D. Matelska, et al., "Disease Prediction with Multi-Omics and Biomarkers Empowers Case-Control Genetic Discoveries in the UK Biobank," *Nature Genetics* 56, no. 9 (2024): 1821–1831.

50. J. C. Cheng, A. Rogachov, K. S. Hemington, et al., "Multivariate Machine Learning Distinguishes Cross-Network Dynamic Functional Connectivity Patterns in State and Trait Neuropathic Pain," *Pain* 159, no. 9 (2018): 1764–1776.

51. P. W. Liu, H. Zhang, C. A. Werley, et al., "A Phenotypic Screening Platform for Chronic Pain Therapeutics Using All-Optical Electrophysiology,"*Pain* 165, no. 4 (2024): 922–940.

52. P. A. Valdes-Hernandez, C. Laffitte Nodarse, A. J. Johnson, et al., "Brain-Predicted Age Difference Estimated Using DeepBrainNet Is Significantly Associated with Pain and Function—A Multi-Institutional and Multiscanner Study," *Pain* 164, no. 12 (2023): 2822–2838.

53. Z. F. Brotzakis, S. Zhang, M. H. Murtada, and M. Vendruscolo, "AlphaFold Prediction of Structural Ensembles of Disordered Proteins," *Nature Communications* 16, no. 1 (2025): 1632.

54. D. P. Brazil, R. H. Church, S. Surae, C. Godson, and F. Martin, "BMP Signalling: Agony and Antagony in the Family," *Trends in Cell Biology* 25, no. 5 (2015): 249–264.

55. E. M. Go, J. H. Oh, J. H. Park, et al., "Spi-C Positively Regulates RANKL-Mediated Osteoclast Differentiation and Function, "*Experimental & Molecular Medicine* 52, no. 4 (2020): 691–701.

56. R. Akkawi, O. Hidmi, A. Haj-Yahia, et al., "WWOX Promotes Osteosarcoma Development via Upregulation of Myc," *Cell Death & Disease* 15, no. 1 (2024): 13.

57. J. Xie, R. Dong, J. Zhu, et al., "MMFuncPhos: A Multi-Modal Learning Framework for Identifying Functional Phosphorylation Sites and Their Regulatory Types," *Advanced Science* 12 (2025): e2410981.

58. S. Bailey, G. E. Sroga, B. Hoac, et al., "The Role of Extracellular Matrix Phosphorylation on Energy Dissipation in Bone," *eLife* 9 (2020): e58184.

59. K. Kamei, Y. Yahara, J. D. Kim, et al., "Impact of the SIK3 Pathway Inhibition on Osteoclast Differentiation via Oxidative Phosphorylation," *Journal of Bone and Mineral Research* 39, no. 9 (2024): 1340–1355.

60. D. Xiong, Y. Qiu, J. Zhao, et al., "A Structurally Informed Human Protein-Protein Interactome Reveals Proteome-Wide Perturbations Caused by Disease Mutations," *Nature Biotechnology* (2024), https://doi.org/10.1038/s41587-024-02428-4.

61. Q. L. Liang, H. G. Xu, L. Yu, et al., "Binding-Induced Fibrillogenesis Peptide Inhibits RANKL-Mediated Osteoclast Activation against Osteoporosis," *Biomaterials* 302 (2023): 122331.

62. C. Y. Janda, L. T. Dang, C. You, et al., "Surrogate Wnt Agonists That Phenocopy Canonical Wnt and β-Catenin Signalling," *Nature* 545, no. 7653 (2017): 234–237.

63. S. Parwez, A. Chaurasia, P. P. Mahapatra, S. Ahmed, and M. I. Siddiqi, "Integrated Machine Learning-Based Virtual Screening and Biological Evaluation for Identification of Potential Inhibitors against Cathepsin K," *Molecular Diversity* (2024), https://doi.org/10.1007/s11030-024-10845-5.

64. M. Cai, B. Xiao, F. Jin, et al., "Generation of Functional Oligopeptides That Promote Osteogenesis Based on Unsupervised Deep Learning of Protein IDRs," *Bone Research* 10, no. 1 (2022): 23.

65. R. Wang, Y. Wang, Y. Niu, et al., "Deep Learning-Predicted Dihydroartemisinin Rescues Osteoporosis by Maintaining Mesenchymal Stem Cell Stemness through Activating Histone 3 Lys 9 Acetylation," *ACS Central Science* 9, no. 10 (2023): 1927–1943.

66. S. Li, W. Sun, S. Li, et al., "Tamsulosin Ameliorates Bone Loss by Inhibiting the Release of Cl– through Wedging into an Allosteric Site of TMEM16A," *Proceedings of the National Academy of Sciences of the United States of America* 122, no. 1 (2025): e2407493121.

67. C. Tosh, M. Tec, J. B. White, et al., "A Bayesian Active Learning Platform for Scalable Combination Drug Screens," *Nature Communications* 16, no. 1 (2025): 156.

68. H. J. Park, J. S. Bae, K. M. Kim, et al., "The PARP Inhibitor Olaparib Potentiates the Effect of the DNA Damaging Agent Doxorubicin in Osteosarcoma," *Journal of Experimental & Clinical Cancer Research* 37, no. 1 (2018): 107.

69. A. Zhavoronkov, Y. A. Ivanenkov, A. Aliper, et al., "Deep Learning Enables Rapid Identification of Potent DDR1 Kinase Inhibitors," *Nature Biotechnology* 37 (2019): 1038–1040.

70. W. Zhung, H. Kim, W. Y. Kim, et al., "3D Molecular Generative Framework for Interaction-Guided Drug Design," *Nature Communications* 15, no. 1 (2024): 2688.

71. P. Li, K. Zhang, T. Liu, et al., "A Deep Learning Approach for Rational Ligand Generation with Toxicity Control via Reactive Building Blocks," *Nature Computational Science* 4, no. 11 (2024): 851–864.

72. H. Xiang, L. Zeng, L. Hou, et al., "A Molecular Video-Derived Foundation Model for Scientific Drug Discovery," *Nature Communications* 15, no. 1 (2024): 9696.

73. F. L. Feitosa, V. F. Cabral, I. H. Sanches, et al., "Cyto-Safe: A Machine Learning Tool for Early Identification of Cytotoxic Compounds in Drug Discovery," *Journal of Chemical Information and Modeling* 64, no. 24 (2024): 9056–9062.

74. Q. Ye, C. Y. Hsieh, Z. Yang, et al., "A Unified Drug-Target Interaction Prediction Framework Based on Knowledge Graph and Recommendation System," *Nature Communications* 12, no. 1 (2021): 6775.

75. C. Bunne, Y. Roohani, Y. Rosen, et al., "How to Build the Virtual Cell with Artificial Intelligence: Priorities and Opportunities," *Cell* 187, no. 25 (2024): 7045–7063.

76. D. Alaimo, M. C. Terranova, E. Palizzolo, et al., "Performance of Two Different Artificial Intelligence (AI) Methods for Assessing Carpal Bone Age Compared to the Standard Greulich and Pyle Method," *Radiologia Medica* 129, no. 10 (2024): 1507–1512.

77. I. Pan, G. L. Baird, S. Mutasa, et al., "Rethinking Greulich and Pyle: A Deep Learning Approach to Pediatric Bone Age Assessment Using Pediatric Trauma Hand Radiographs," *Radiology: Artificial Intelligence* 2, no. 4 (2020): e190198.

78. S. Rassmann, A. Keller, K. Skaf, et al., "Deeplasia: Deep Learning for Bone Age Assessment Validated on Skeletal Dysplasias," *Pediatric Radiology* 54, no. 1 (2024): 82–95.

79. S. Mutasa, P. D. Chang, C. Ruzal-Shapiro, et al., "MABAL: A Novel Deep-Learning Architecture for Machine-Assisted Bone Age Labeling," *Journal of Digital Imaging* 31, no. 4 (2018): 513–519.

80. X. Li, Y. Jiang, Y. Liu, et al., "RAGCN: Region Aggregation Graph Convolutional Network for Bone Age Assessment From X-Ray Images," *IEEE Transactions on Instrumentation and Measurement* 71 (2022): 1–12.

81. H. Lee, S. Tajmir, J. Lee, et al., "Fully Automated Deep Learning System for Bone Age Assessment," *Journal of Digital Imaging* 30, no. 4 (2017): 427–441.

82. N. Tomita, Y. Y. Cheung, S. Hassanpour, et al., "Deep Neural Networks for Automatic Detection of Osteoporotic Vertebral Fractures on CT Scans," *Computers in Biology and Medicine* 98 (2018): 8–15.

83. M. A. Kassem, S. M. Naguib, H. M. Hamza, et al., "Explainable Transfer Learning-Based Deep Learning Model for Pelvis Fracture Detection," *International Journal of Intelligent Systems* 10 (2023): 3281998.

84. Q. Q. Zhou, J. Wang, W. Tang, et al., "Automatic Detection and Classification of Rib Fractures on Thoracic CT Using Convolutional Neural Network: Accuracy and Feasibility," *Korean Journal of Radiology* 21, no. 7 (2020): 869–879.

85. C. Ordóñez, J. M. Matías, J. F. de Cos Juez, et al., "Machine Learning Techniques Applied to the Determination of Osteoporosis Incidence in Post-Menopausal Women," *Mathematical and Computer Modelling* 50, no. 5–6 (2009): 673–679.

86. F. J. de Cos Juez, F. J. Suárez-Suárez, F. Sánchez Lasheras, et al., "Application of Neural Networks to the Study of the Influence of Diet and Lifestyle on the Value of Bone Mineral Density in Post-Menopausal Women," *Mathematical and Computer Modelling* 54, no. 7–8 (2011): 1665–1670.

87. C. S. Ho, Y. P. Chen, T. Y. Fan, et al., "Application of Deep Learning Neural Network in Predicting Bone Mineral Density from Plain X-Ray Radiography," *Archives of Osteoporosis* 16, no. 1 (2021): 153.

88. K. Yasaka, H. Akai, A. Kunimatsu, S. Kiryu, and O. Abe, "Prediction of Bone Mineral Density from Computed Tomography: Application of Deep Learning with a Convolutional Neural Network," *European Radiology* 30, no. 6 (2020): 3549–3557.

89. A. Kumar, R. C. Joshi, M. K. Dutta, et al., "*Osteo-Net: A Robust Deep Learning-Based Diagnosis of Osteoporosis Using X-Ray Images*," in Proceedings of the 2022 45th International Conference on Telecommunications and Signal Processing (TSP), (Prague, Czech Republic, 2022), 91–95.

90. Q. Wu, F. Nasoz, J. Jung, et al., "Machine Learning Approaches for the Prediction of Bone Mineral Density by Using Genomic and Phenotypic Data of 5130 Older Men," *Scientific Reports* 11, no. 1 (2021): 4482.

91. T. Tanphiriyakun, S. Rojanasthien, P. Khumrin, et al., "Bone Mineral Density Response Prediction Following Osteoporosis Treatment Using Machine Learning to Aid Personalized Therapy," *Scientific Reports* 11, no. 1 (2021): 13811.

92. H. Zhao, L. Ou, Z. Zhang, L. Zhang, K. Liu, and J. Kuang, "The Value of Deep Learning-Based X-Ray Techniques in Detecting and Classifying K-L Grades of Knee Osteoarthritis: A Systematic Review and Meta-Analysis," *European Radiology* 35, no. 1 (2024): 327–340.

93. A. Tiulpin, J. Thevenot, E. Rahtu, P. Lehenkari, and S. Saarakkala, "Automatic Knee Osteoarthritis Diagnosis from Plain Radiographs: A Deep Learning-Based Approach," *Scientific Reports* 8, no. 1 (2018): 1727.

94. R. Castro-Zunti, E. H. Park, Y. Choi, G. Y. Jin, and S-B. Ko, "Early Detection of Ankylosing Spondylitis Using Texture Features and Statistical Machine Learning, and Deep Learning, with Some Patient Age Analysis," *Computerized Medical Imaging and Graphics* 82 (2020): 101718.

95. Y. E. Kok, A. Crisford, A. Parkes, S. Venkateswaran, R. Oreffo, S. Mahajan, and M. Pound, "Classification of Osteoarthritic and Healthy Cartilage Using Deep Learning with Raman Spectra," *Scientific Reports* 14, no. 1 (2024): 15902.

96. M. R. Ibraheem, S. N. Almuayqil, A. A. Abd El-Aziz, et al., "Diagnosis of Patellofemoral Osteoarthritis Using Enhanced Sequential Deep Learning Techniques," *Egyptian Informatics Journal* 24, no. 3 (2023): 100391.

97. S. Gou, Y. Lu, N. Tong, L. Huang, N. Liu, and Q. Han, "Automatic Segmentation and Grading of Ankylosing Spondylitis on MR Images via Lightweight Hybrid Multi-Scale Convolutional Neural Network with Reinforcement Learning," *Physics in Medicine & Biology* 66, no. 20 (2021): 205002.

98. J. Schilcher, A. Nilsson, O. Andlid, and A. Eklund, "Fusion of Electronic Health Records and Radiographic Images for a Multimodal Deep Learning Prediction Model of Atypical Femur Fractures," *Computers in Biology and Medicine* 168 (2024): 107704.

99. M. E. Tibbo, C. C. Wyles, S. Fu, et al., "Use of Natural Language Processing Tools to Identify and Classify Periprosthetic Femur Fractures," *The Journal of Arthroplasty* 34, no. 10 (2019): 2216–2219.

100. R. Liu, D. Pan, Y. Xu, et al., "A Deep Learning-Machine Learning Fusion Approach for the Classification of Benign, Malignant, and Intermediate Bone Tumors," *European Radiology* 32, no. 2 (2022): 1371–1383.

101. D. M. Anisuzzaman, H. Barzekar, L. Tong, et al., "A Deep Learning Study on Osteosarcoma Detection from Histological Images," *Biomedical Signal Processing and Control* 69 (2021): 102931.

102. J-H. Su, Y-C. Tung, Y-W. Liao, et al., "Deep Learning-Based Surgical Treatment Recommendation and Nonsurgical Prognosis Status Classification for Scaphoid Fractures by Automated X-Ray Image Recognition," *Biomedicines* 12, no. 6 (2024): 1198.

103. W. Mualem, C. Onyedimma, A. K. Ghaith, et al., "R2 Advances in Robotic-Assisted Spine Surgery: Comparative Analysis of Options, Future Directions, and Bibliometric Analysis of the Literature," *Neurosurgical Review* 46, no. 1 (2022): 18.

104. A. Khan, J. E. Meyers, I. Siasios, et al., "Next-Generation Robotic Spine Surgery: First Report on Feasibility, Safety, and Learning Curve," *Operative Neurosurgery* 17, no. 1 (2019): 61–69.

105. C. W. Kanaly, D. M. Backes, N. Toossi, et al., "A Retrospective Analysis of Pedicle Screw Placement Accuracy Using the ExcelsiusGPS Robotic Guidance System: Case Series," *Operative Neurosurgery* 24, no. 3 (2023): 242–247.

106. W. Tian, H. Wang, Y.-J. Liu, et al., "Robot-Assisted Anterior Odontoid Screw Fixation: A Case Report," *Orthopaedic Surgery* 8 (2016): 400–404.

107. W. Tian, "Robot-Assisted Posterior C1-2 Transarticular Screw Fixation for Atlantoaxial Instability: A Case Report," *Spine* 41 (2016): B2–B5.

108. M. Fan, Y. Liu, D. He, et al., "Improved Accuracy of Cervical Spinal Surgery with Robot-Assisted Screw Insertion: A Prospective, Randomized, Controlled Study," *Spine* 45, no. 5 (2020): 285–291.

109. W. Tian, Q. Zhang, Z. Li, et al., "Clinical Application of One to Many 5G Remote Orthopedic Robot-Assisted Surgery," *Journal of Clinical Orthopaedics and Research* 4, no. 16 (2019): 349–354.

110. A. Boudenot, N. Presle, R. Uzbekov, et al., "Effect of Interval-Training Exercise on Subchondral Bone in a Chemically-Induced Osteoarthritis Model," *Osteoarthritis and Cartilage* 22, no. 8 (2014): 1176–1185.

111. C. H. van Gool, B. W. Penninx, G. I. Kempen, et al., "Effects of Exercise Adherence on Physical Function Among Overweight Older Adults With Knee Osteoarthritis," *Arthritis & Rheumatism* 53, no. 1 (2005): 24–32.

112. E. Papi, A. Belsi, and A. H. McGregor, "A Knee Monitoring Device and the Preferences of Patients Living With Osteoarthritis: A Qualitative Study," *BMJ Open* 5, no. 9 (2015): e007980.

113. A. Belsi, E. Papi, and A. H. McGregor, "Impact of Wearable Technology on Psychosocial Factors of Osteoarthritis Management: A Qualitative Study," *BMJ Open* 6, no. 2 (2016): e010064.

114. A. Yurkewich, I. J. Kozak, D. Hebert, R. H. Wang, and A. Mihailidis, "Hand Extension Robot Orthosis (HERO) Grip Glove: Enabling Independence Amongst Persons With Severe Hand Impairments After Stroke," *Journal of NeuroEngineering and Rehabilitation* 17, no. 1 (2020): 33.

115. J. Ritterand S. S. Bielack, "Osteosarcoma," *Annals of Oncology* 21 (2010): vii320–vii325.

116. H. Chen, J. Liu, Z. Cheng, et al., "Development and External Validation of an MRI-Based Radiomics Nomogram for Pretreatment Prediction for Early Relapse in Osteosarcoma: A Retrospective Multicenter Study," *European Journal of Radiology* 129 (2020): 109066

117. J. Liu, T. Lian, H. Chen, et al., "Pretreatment Prediction of Relapse Risk in Patients With Osteosarcoma Using Radiomics Nomogram Based on CT: A Retrospective Multicenter Study," *BioMed Research International* 2021 (2021): 6674471.

118. M. Schini, H. Johansson, N. C. Harvey, M. Lorentzon, J. A. Kanis, and E. V. McCloskey, "An Overview of the Use of the Fracture Risk Assessment Tool (FRAX) in Osteoporosis," *Journal of Endocrinological Investigation* 47, no. 3 (2024): 501–511.

119. J. A. Kanis, J. Compston, C. Cooper, et al., "SIGN Guidelines for Scotland: BMD Versus FRAX Versus QFracture," *Calcified Tissue International* 98, no. 5 (2016): 417–425.

120. S. H. Kong, J. W. Lee, B. U. Bae, et al., "Development of a Spine X-Ray-Based Fracture Prediction Model Using a Deep Learning Algorithm," *Endocrinology and Metabolism* 37, no. 4 (2022): 674–683.

121. Y. Almog, A. Rai, P. Zhang, et al., "Deep Learning With Electronic Health Records for Short-Term Fracture Risk Identification: Crystal Bone Algorithm Development and Validation," *Journal of Medical Internet Research* 22, no. 10 (2020): e22550.

122. C. Qiu, K. Su, Z. Luo, et al., "Developing and Comparing Deep Learning and Machine Learning Algorithms for Osteoporosis Risk Prediction," *Frontiers in Artificial Intelligence* 7 (2024): 1355287.

123. B. Suh, H. Yu, H. Kim, et al., "Interpretable Deep-Learning Approaches for Osteoporosis Risk Screening and Individualized Feature Analysis Using Large Population-Based Data: Model Development and Performance Evaluation," *Journal of Medical Internet Research* 25 (2023): e40179.

124. Y. Kim, Y. G. Kim, J. W. Park, et al., "A CT-Based Deep Learning Model for Predicting Subsequent Fracture Risk in Patients With Hip Fracture," *Radiology* 310, no. 1 (2024): e230614.

125. W. Huang, J. Wang, J. Xu, G. Guo, Z. Chen, and H. Xue, "Multivariable Machine Learning Models for Clinical Prediction of Subsequent Hip Fractures in Older People Using the Chinese Population Database," *Age and Ageing* 53, no. 3 (2024): afae045.

126. J. Choi, J. Alawa, L. Tennakoon, and J. D. Forrester, "DeepBackRib: Deep Learning to Understand Factors Associated With Readmissions After Rib Fractures," *Journal of Trauma and Acute Care Surgery* 93, no. 6 (2022): 757–761.

127. J. Hirvasniemi, J. Runhaar, R. A. van der Heijden, et al., "The KNee OsteoArthritis Prediction (KNOAP2020) Challenge: An Image Analysis Challenge to Predict Incident Symptomatic Radiographic Knee Osteoarthritis From MRI and X-Ray Images,"*Osteoarthritis and Cartilage* 31, no. 1 (2023): 115–125.

128. S. Kundu, B. G. Ashinsky, M. Bouhrara, et al., "Enabling Early Detection of Osteoarthritis From Presymptomatic Cartilage Texture Maps via Transport-Based Learning," *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 40 (2020): 24709–24719.

129. T. Han, J. N. Kather, F. Pedersoli, et al., "Image Prediction of Disease Progression for Osteoarthritis by Style-Based Manifold Extrapolation," *Nature Machine Intelligence* 4 (2022): 1029–1039.

130. S. Castagno, M. Birch, M. van der Schaar, et al., "Predicting Rapid Progression in Knee Osteoarthritis: A Novel and Interpretable Automated Machine Learning Approach, With Specific Focus on Young Patients and Early Disease," *Annals of the Rheumatic Diseases* 84, no. 1 (2025): 124–135.

131. H. H. Nguyen, S. Saarakkala, M. B. Blaschko, and A. Tiulpin, "Semixup: In- and Out-of-Manifold Regularization for Deep Semi-Supervised Knee Osteoarthritis Severity Grading from Plain

Radiographs," *IEEE Transactions on Medical Imaging* 39, no. 12 (2020): 4346–4356.

132. J. Hu, C. Zheng, Q. Yu, et al., "DeepKOA: A Deep-Learning Model for Predicting Progression in Knee Osteoarthritis Using Multimodal Magnetic Resonance Images From the Osteoarthritis Initiative," *Quantitative Imaging in Medicine and Surgery* 13, no. 8 (2023): 4852–4866.

133. R. Yin, H. Chen, T. Tao, et al., "Expanding From Unilateral to Bilateral: A Robust Deep Learning-Based Approach for Predicting Radiographic Osteoarthritis Progression," *Osteoarthritis and Cartilage* 32, no. 3 (2024): 338–347.

134. M. Luo, W. Yang, L. Bai, et al., "Artificial Intelligence for Life Sciences: A Comprehensive Guide and Future Trends," *The Innovation Life* 2, no. 4 (2024): 100105.

135. J. Palma-Chavez, T. J. Pfefer, A. Agrawal, J. V. Jokerst, and W. C. Vogt, "Review of Consensus Test Methods in Medical Imaging and Current Practices in Photoacoustic Image Quality Assessment," *Journal of Biomedical Optics* 26, no. 9 (2021): 090901.

136. O. O. Madandola, R. I. Bjarnadottir, Y. Yao, et al., "The Relationship Between Electronic Health Records User Interface Features and Data Quality of Patient Clinical Information: An Integrative Review," *Journal of the American Medical Informatics Association* 31, no. 1 (2023): 240–255.

137. B. Allen, M. Chatfield, J. Burleson, and W. T. Thorwarth, "Improving Diagnosis in Health Care: Perspectives From the American College of Radiology," *Diagnosis* 4, no. 3 (2017): 113–124.

138. M. Mantri, S. Taran, and G. Sunder, "DICOM Integration Libraries for Medical Image Interoperability: A Technical Review," *IEEE Reviews in Biomedical Engineering* 15 (2022): 247–259.

139. W. Goossen and L. H. Langford, "Exchanging Care Records Using HL7 V3 Care Provision Messages," *Journal of the American Medical Informatics Association* 21, no. e2 (2014): e363–e368.

140. T. Iliou, C. N. Anagnostopoulos, I. M. Stephanakis, et al., "A Novel Data Preprocessing Method for Boosting Neural Network Performance: A Case Study in Osteoporosis Prediction," *Information Sciences* 380 (2017): 92–100.

141. D. Peloquin, M. DiMaio, B. Bierer, and M. Barnes, "Disruptive and Avoidable: GDPR Challenges to Secondary Research Uses of Data," *European Journal of Human Genetics* 28, no. 6 (2020): 697–705.

142. S. T. Rosenbloom, J. R. L. Smith, R. Bowen, J. Burns, L. Riplinger, and T. H. Payne, "Updating HIPAA for the Electronic Medical Record Era," *Journal of the American Medical Informatics Association* 26, no. 10 (2019): 1115–1119.

143. T. Huang, H. Xu, H. Huang, et al., "Artificial Intelligence for Medicine: Progress, Challenges, and Perspectives," *The Innovation Medicine* 1, no. 2 (2023): 100030.

144. D. Truhn, S. Tayebi Arasteh, O. L. Saldanha, et al., "Encrypted Federated Learning for Secure Decentralized Collaboration in Cancer Image Analysis," *Medical Image Analysis* 92 (2024): 103059.

145. L. Min, Q. Tian, X. Lu, and H. Duan, "Modeling EHR With the openEHR Approach: An Exploratory Study in China," *BMC Medical Informatics and Decision Making* 18 (2018): 75.

146. A. Boussadi and E. Zapletal, "A Fast Healthcare Interoperability Resources (FHIR) Layer Implemented Over i2b2," *BMC Medical Informatics and Decision Making* 17 (2017): 120.

147. V. Vimbi, N. Shaffi, and M. Mahmud, "Interpreting Artificial Intelligence Models: A Systematic Review on the Application of LIME and SHAP in Alzheimer's Disease Detection," *Brain Informatics* 11, no. 1 (2024): 10.

148. Z. Miao, T. Tian, W. Chen, et al., "Spatial Resolved Transcriptomics: Computational Insights Into Gene Transcription Across Tissue and Organ Architecture in Diverse Applications," *The Innovation Life* 2, no. 4 (2024): 100097.

149. Y. Hozumi, K. A. Tanemura, G. W. Wei, et al., "Preprocessing of Single Cell RNA Sequencing Data Using Correlated Clustering and Projection," *Journal of Chemical Information and Modeling* 64, no. 7 (2024): 2829–2838.

150. L. Peng, X. He, X. Peng, Z. Li, and L. Zhang, "STGNNks: Identifying Cell Types in Spatial Transcriptomics Data Based on Graph Neural Network, Denoising Auto-Encoder, and k-Sums Clustering," *Computers in Biology and Medicine* 166 (2023): 107440.

151. I. Abedeen, M. A. Rahman, F. Z. Prottyasha, T. Ahmed, T. M. Chowdhury, and S. Shatabda, "FracAtlas: A Dataset for Fracture Classification, Localization and Segmentation of Musculoskeletal Radiographs," *Scientific Data* 10 (2023): 521.

152. K. Leung, B. Zhang, J. Tan, et al., "Prediction of Total Knee Replacement and Diagnosis of Osteoarthritis by Using Deep Learning on Knee Radiographs: Data From the Osteoarthritis Initiative," *Radiology* 296, no. 3 (2020): 584–593.

153. A. Colaprico, T. C. Silva, C. Olsen, et al., "TCGAbiolinks: An R/Bioconductor Package for Integrative Analysis of TCGA Data," *Nucleic Acids Research* 44, no. 8 (2016): e71.

154. F. Prior, K. Smith, A. Sharma, et al., "The Public Cancer Radiology Imaging Collections of the Cancer Imaging Archive," *Scientific Data* 4 (2017): 170124.

155. S. Wilson, M. Fitzsimons, M. Ferguson, et al., "Developing Cancer Informatics Applications and Tools Using the NCI Genomic Data Commons API," *Cancer Research* 77, no. 21 (2017): e15–e18.

156. F. Zanca, C. Brusasco, F. Pesapane, et al., "Regulatory Aspects of the Use of Artificial Intelligence Medical Software," *Seminars in Radiation Oncology* 32, no. 4 (2022): 432–441.

157. S. Polevikov, "Advancing AI in Healthcare: A Comprehensive Review of Best Practices," *Clinica Chimica Acta* 548 (2023): 117519.

158. World Health Organization, Regulatory Considerations on Artificial Intelligence for Health (World Health Organization, 2023), https://iris.who.int/handle/10665/373421.

159. R. Ahmed and A. S. Imran, "Knee Osteoarthritis Analysis Using Deep Learning and XAI on X-Rays," *IEEE Access* 12 (2024): 68870–68879.

160. Q. Zhou, Z-H. Chen, Y-H. Cao, and S. Peng, "Clinical Impact and Quality of Randomized Controlled Trials Involving Interventions Evaluating Artificial Intelligence Prediction Tools: A Systematic Review," *NPJ Digital Medicine* 4, no. 1 (2021): 154.

161. R. Xie, D. Yi, D. Zeng, et al., "Specific Deletion of Axin1 Leads to Activation of β-Catenin/BMP Signaling Resulting in Fibular Hemimelia Phenotype in Mice," *eLife* 11 (2022): e80013

162. J. Huang, L. Zhao, L. Xing, and D. Chen, "MicroRNA-204 Regulates Runx2 Protein Expression and Mesenchymal Progenitor Cell Differentiation," *Stem Cells* 28, no. 2 (2010): 357–364.

163. Y. Huang, Z. Du, K. Li, et al., "ROS-Scavenging Electroactive Polyphosphazene-Based Core-Shell Nanofibers for Bone Regeneration," *Advanced Fiber Materials* 4 (2022): 894–907.

164. K. Lu, T. S. Shi, S. Y. Shen, et al., "Defects in a Liver-Bone Axis Contribute to Hepatic Osteodystrophy Disease Progression," *Cell Metabolism* 34, no. 3 (2022): 441–457.e7.

165. I. Tavassoly, J. Goldfarb, and R. Iyengar, "Systems Biology Primer: The Basic Methods and Approaches," *Essays in Biochemistry* 62, no. 4 (2018): 487–500.

166. J. P. Roussarie, V. Yao, P. Rodriguez-Rodriguez, et al., "Selective Neuronal Vulnerability in Alzheimer's Disease: A Network-Based Analysis," *Neuron* 107, no. 5 (2020): 821–835.e12.

167. T. B. Nguyen, D. N. Do, M-L. Nguyen-Thi, H. Hoang-The, T-T. Tran, and T. Nguyen-Thanh, "Identification of Potential Crucial Genes and Key Pathways Shared in Inflammatory Bowel Disease and Cervical Cancer by Machine Learning and Integrated Bioinformatics," *Computers in Biology and Medicine* 149 (2022): 105996.

168. C. Song, Y. Zhang, H. Huang, et al., "Cis-Cardio: A Comprehensive Analysis Platform for Cardiovascular-Relevant Cis-Regulation in Human and Mouse, Molecular Therapy," *Nucleic Acids* 33 (2023): 655–667.

169. J. Tarum, G. Ball, T. Gustafsson, et al., "Artificial Neural Network Inference Analysis Identified Novel Genes and Gene Interactions Associated With Skeletal Muscle Aging," *Journal of Cachexia, Sarcopenia and Muscle* 15, no. 5 (2024): 2143–2155.

170. J. Meng, H. Du, H. Lv, J. Lu, J. Li, and J. Yao, "Identification of the Osteoarthritis Signature Gene PDK1 by Machine Learning and Its Regulatory Mechanisms on Chondrocyte Autophagy and Apoptosis," *Frontiers in Immunology* 13 (2023): 1072526.

171. H. Dowden and J. Munro, "Trends in Clinical Success Rates and Therapeutic Focus," *Nature Reviews Drug Discovery* 18, no. 7 (2019): 495–496.

172. G. Durant, F. Boyles, K. Birchall, et al., "The Future of Machine Learning for Small-Molecule Drug Discovery Will Be Driven by Data," *Nature Computational Science* 4, no. 10 (2024): 735–743.

173. A. Jamshidi, J. P. Pelletier, and J. Martel-Pelletier, "Machine-Learning-Based Patient-Specific Prediction Models for Knee Osteoarthritis," *Nature Reviews Rheumatology* 15, no. 1 (2019): 49–60.

174. J. Smets, E. Shevroja, T. Hügle, W. D. Leslie, and D. Hans, "Machine Learning Solutions for Osteoporosis—A Review," *Journal of Bone and Mineral Research* 36, no. 5 (2021): 833–851.

175. L. Fasihi, B. Tartibian, R. Eslami, and H. Fasihi, "Artificial Intelligence Used to Diagnose Osteoporosis From Risk Factors in Clinical Data and Proposing Sports Protocols," *Scientific Reports* 12, no. 1 (2022): 18330.

176. M. Y. Lu, B. Chen, D. F. K. Williamson, et al., "A Multimodal Generative AI Copilot for Human Pathology," *Nature* 634, no. 8033 (2024): 466–473.

177. Y. Zhao, Z. Zhu, B. Chen, et al., "Toward Parallel Intelligence: An Interdisciplinary Solution for Complex Systems," *The Innovation* 4, no. 6 (2023): 100521.

178. J. Cheng, G. Novati, J. Pan, et al., "Accurate Proteome-Wide Missense Variant Effect Prediction With AlphaMissense," *Science* 381, no. 6664 (2023): eadg7492.

179. P. P. Fiziev, J. McRae, J. C. Ulirsch, et al., "Rare Penetrant Mutations Confer Severe Risk of Common Diseases," *Science* 380, no. 6648 (2023): eabo1131.

180. X. Hou, Y. He, P. Fang, et al., "Using Artificial Intelligence to Document the Hidden RNA Virosphere," *Cell* 187, no. 24 (2024): 6929–6942.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.