

Artificial intelligence in bone biology: Transforming basic research into advanced therapeutics

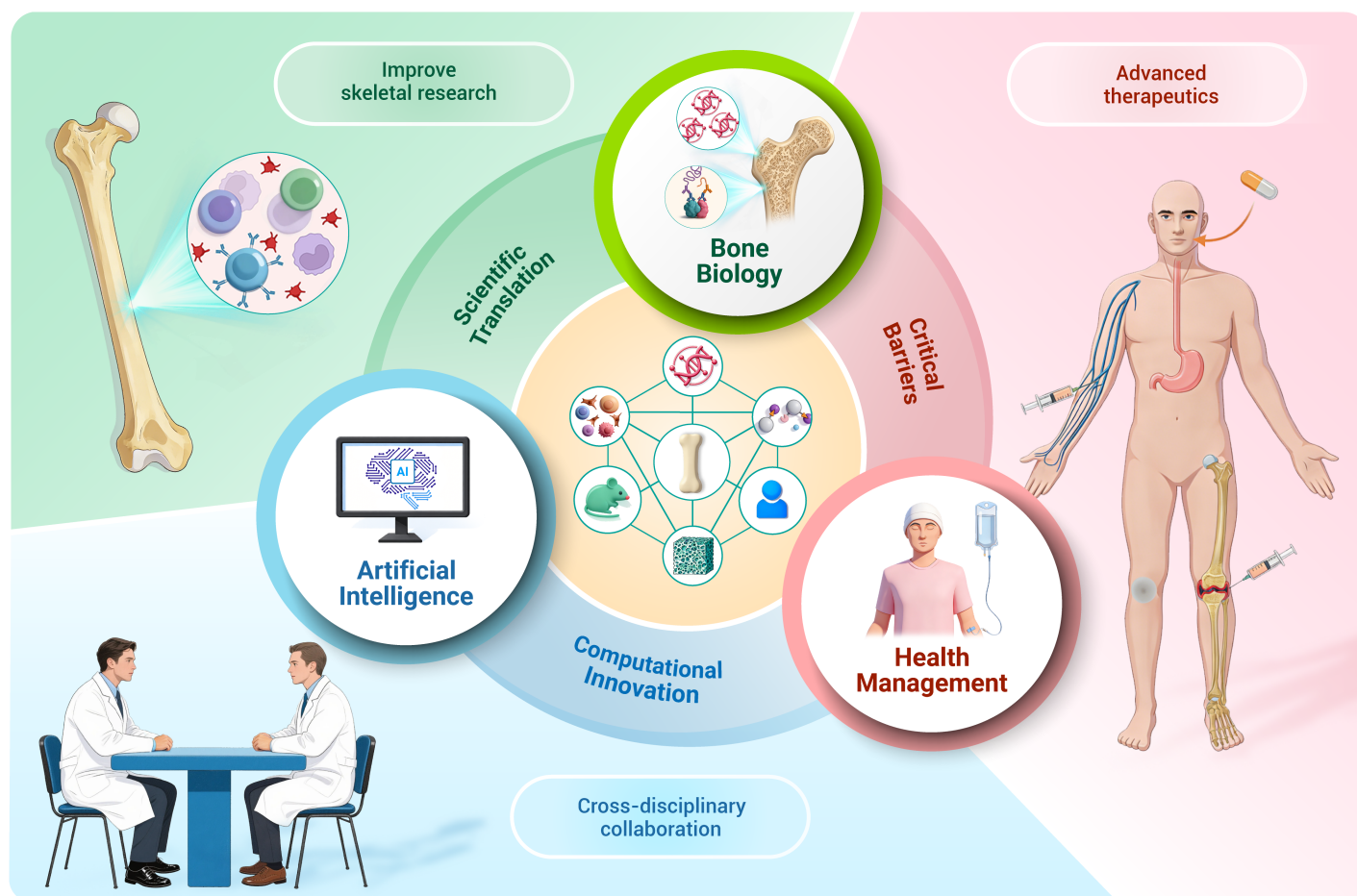
Cheng Li,¹ Zheng Zhong,¹ Ning Zhang,¹ Shuai Yuan,¹ Ruifeng Fang,¹ Fengjun Ge,¹ Weibin Yan,¹ Di Zhang,^{2,*} and Denghui Xie^{1,*}

*Correspondence: xiedenghui221122@smu.edu.cn(D.X.); skintchenzhang@gmail.com(D.Z.)

Received: July 26, 2025; Accepted: December 29, 2025; Published Online: January 7, 2026; <https://doi.org/10.59717/j.xinn-life.2026.100186>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Artificial Intelligence (AI) accelerates the translation of bone biology into advanced therapeutics.
- Computational innovation integrates complex data to overcome critical barriers in skeletal research.
- Cross-disciplinary collaboration is vital to bridge research findings with therapeutic applications.

Artificial intelligence in bone biology: Transforming basic research into advanced therapeutics

Cheng Li,¹ Zheng Zhong,¹ Ning Zhang,¹ Shuai Yuan,¹ Ruifeng Fang,¹ Fengjun Ge,¹ Weibin Yan,¹ Di Zhang,^{2,*} and Denghui Xie^{1,*}

¹Department of Orthopedic Surgery, Center for Orthopedic Surgery, The Third Affiliated Hospital, Southern Medical University, Guangzhou 510515, China

²Radiological Science, University of California, Los Angeles, Los Angeles, CA 90024, USA

*Correspondence: xiedenghui221122@smu.edu.cn(D.X.); skintchenzhang@gmail.com(D.Z.)

Received: July 26, 2025; Accepted: December 29, 2025; Published Online: January 7, 2026; <https://doi.org/10.59717/j.xinn-life.2026.100186>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Li C., Zhong Z., Zhang N., et al. (2026). Artificial intelligence in bone biology: Transforming basic research into advanced therapeutics. *The Innovation Life* 4:100186.

Bone biology orchestrates complex interactions at cellular, molecular, and systemic levels, maintaining skeletal homeostasis and systemic physiology. While significant progress has been made in understanding bone pathophysiology, traditional research methods face challenges in deconvoluting the intricate bone microenvironment and translating findings into effective therapeutic strategies. Artificial intelligence (AI) directly addresses these limitations with its exceptional capacity for analyzing vast, complex datasets and identifying subtle patterns that are often missed by conventional approaches. This review explores how AI is revolutionizing bone biology research and accelerating its translation into therapeutic applications. We categorize AI techniques, including machine learning (ML), deep learning (DL), and natural language processing (NLP), and systematically assess their applications in bone biology. AI shows remarkable potential in decoding complex cellular signaling networks, identifying novel biomarkers, enhancing diagnostic accuracy, and enabling personalized therapeutic approaches for bone disorders. We critically evaluate current implementations and delineate challenges related to data quality, model interpretability, and ethical considerations. Finally, we propose future directions focusing on data standardization, multi-omics integration, and cross-disciplinary collaboration to unlock the full potential of AI in advancing bone health management and developing novel therapies.

INTRODUCTION

A comprehensive understanding of bone biology is essential for managing not only skeletal pathologies but also the many systemic diseases linked to skeletal dysfunction.¹⁻³ To appreciate this translational relevance, it is crucial to recognize that bone biology is a multifaceted discipline encompassing anatomy, physiology, biomechanics, developmental biology, and molecular genetics.⁴⁻⁶ Far from being a static structural framework, bone is a dynamic and metabolically active organ (Figure 1).^{7,8} It acts as a mineral reservoir for calcium and phosphorus, houses the bone marrow niches critical for producing all hematopoietic lineages and immune cells, and functions as the body's largest endocrine organ, modulating systemic metabolism by secreting hormones like osteocalcin.^{6,8-10} This deep integration with the body's essential physiological processes is maintained by bone remodeling that a continuous process of renewal precisely controlled by boneforming osteoblasts, bone-resorbing osteoclasts, and mechanosensing osteocytes.¹¹ When the delicate balance of this process is disturbed by aging, hormonal changes, or other stressors, debilitating conditions such as osteoporosis and osteoarthritis can emerge, severely impacting quality of life for millions and imposing a substantial socioeconomic burden worldwide.^{12,13}

Despite the clear therapeutic need, both fundamental research and practical application face significant hurdles. In the laboratory, conventional in vitro models fail to fully recapitulate the complex bone microenvironment, and imaging cellular events within dense, mineralized tissue remains a profound challenge.¹⁴⁻¹⁶ In current practice, traditional diagnostic tools like X-rays and DXA scans often detect degenerative diseases only after significant and potentially irreversible damage has occurred.^{17,18} Furthermore, the sheer volume and complexity of modern multi-omics and imaging datasets have begun to outpace the capabilities of traditional statistical analysis.^{19,20} This creates a critical gap between biological discovery and effective health management, highlighting an urgent necessity for more powerful analytical tools. AI presents a unique opportunity to shift the management paradigm from treatment to prevention. By analyzing complex datasets to identify

predictive biomarkers and subtle early-stage patterns, AI models have the potential to enable proactive interventions long before significant structural damage occurs (Figure 1).

AI has emerged as a transformative technology capable of bridging this gap.^{21,22} With its power to interrogate vast, high-dimensional datasets and identify subtle patterns invisible to the human eye, AI can accelerate the translation of basic biological findings into therapeutic applications.^{23,24} AI models hold the potential to decode the intricate signaling pathways, genetic regulations, and biomechanical interactions that govern bone health, thereby enabling predictive biomarkers long before structural damage occurs. Simultaneously, AI is propelling the development of innovative diagnostic tools, allowing for more precise and early detection of bone diseases through image analysis and biomarker identification.^{25,26} Additionally, AI aids in creating tailored therapeutic approaches by integrating comprehensive patient data to forecast treatment responses and refine interventions.^{27,28} AI also demonstrates remarkable potential in decoding cellular signaling pathways, genetic regulation, biomechanical interactions, and systemic cross-talk within bone biology, especially when applied to multi-omics datasets.^{19,29} While several reviews have discussed AI in broader fields like orthopedics or radiology, this review provides a focused synthesis on the application of specific AI methodologies directly to bone biology, uniquely bridging the gap from fundamental molecular and cellular research to its eventual advanced therapeutics.³⁰⁻³² By systematically categorizing the techniques and highlighting this translational pathway, we aim to offer a comprehensive roadmap for both basic scientists and clinicians interested in this emerging field.

This review provides a comprehensive examination of AI's diverse applications in bone biology research, spanning from fundamental scientific investigations to potential therapeutic applications. We classify the different types of AI models commonly used in biomedical research and explore novel or emerging AI techniques applied in basic bone biology research. Through a critical analysis of current implementations, we aim to elucidate AI's transformative role in bone biology and offer insights into how and why AI can be harnessed to advance our understanding and management of bone health and disorders. Furthermore, we discuss present limitations and suggest solutions to enhance this innovative approach.

The imperative for AI in bone biology

This review will explore the multifaceted applications of AI in advancing bone biology from basic research to therapeutic practice, as conceptually outlined in Figure 2. We delineate how specific AI domains are leveraged to analyze complex biological data. For instance, Machine Learning (ML) models are increasingly used to analyze patient biomarkers and 'omics' data, enabling robust patient stratification and the prediction of treatment outcomes.^{32,33} Concurrently, Deep Learning (DL) frameworks are proving indispensable for automating the interpretation of medical imagery like radiographs and digital histopathology, as well as accelerating therapeutic development through drug discovery and the computational design of novel biomaterials.³⁴ Furthermore, Natural Language Processing (NLP) is employed to systematically mine vast archives of scientific literature and electronic health records, uncovering hidden patterns and generating new hypotheses.³⁵ Beyond these established domains, emerging techniques such as Protein Language Models are revolutionizing our ability to engineer bespoke therapeutics and understand the molecular machinery governing bone physiology.³⁶ This integrated computational framework, which relies on the synthesis of large-scale, diverse datasets, is critical for building predictive

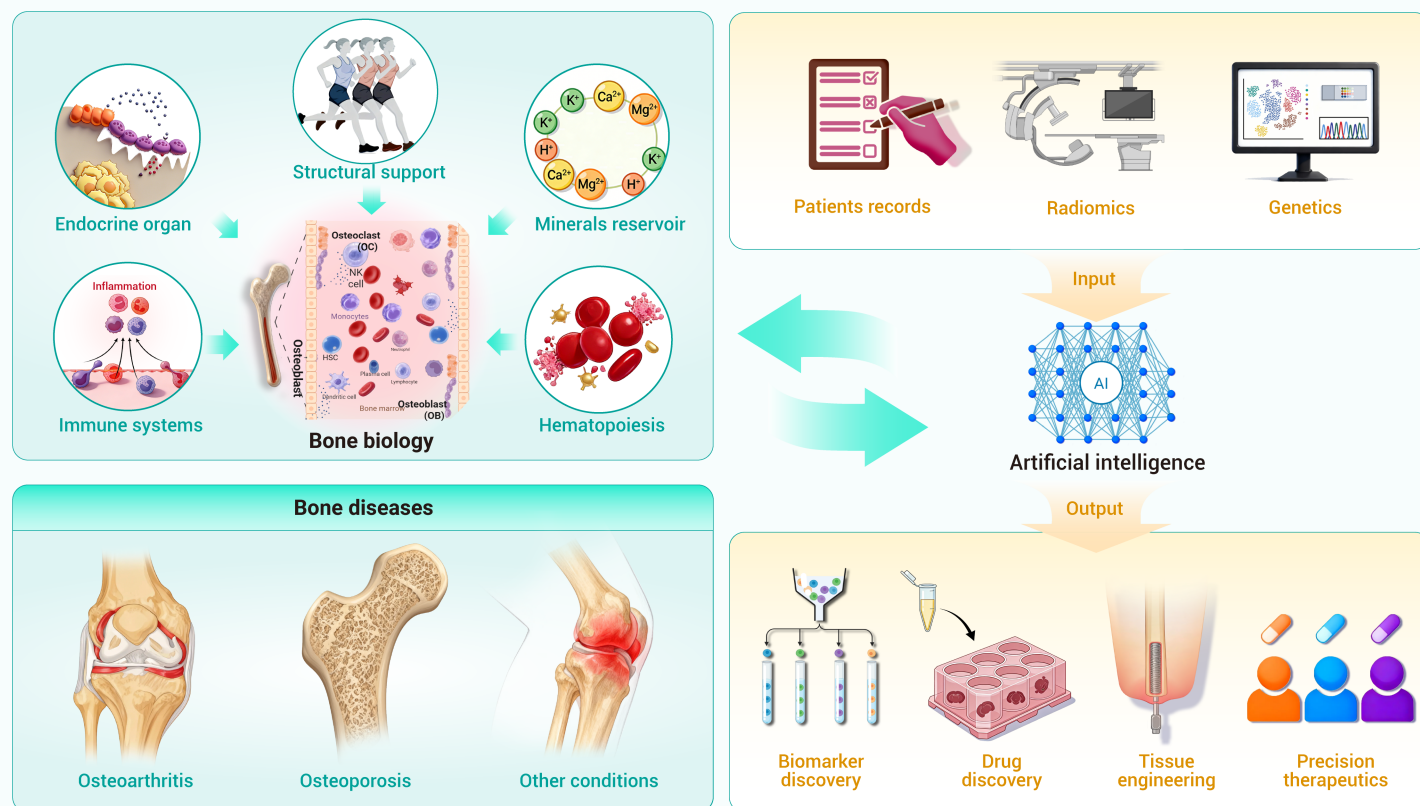


Figure 1. The intersection of bone biology, disease, and Artificial Intelligence (AI) The diagram illustrates the multifaceted nature of bone biology (left panel), encompassing its roles in structural support, mineral storage, hematopoiesis, immune function, and endocrine regulation. Pathological conditions like osteoarthritis and osteoporosis arise when these functions are disrupted. Artificial intelligence (right panel) offers a powerful paradigm for advancing bone health by integrating diverse data inputs, such as patient records, radiomics, and genetics to drive outputs in biomarker and drug discovery, tissue engineering, and precision medicine.

models of biological processes. Finally, we showcase tangible examples of translational success, identify key obstacles to implementation, and discuss the future of AI in reshaping the therapeutic management of bone health.

CLASSIFICATION OF AI TECHNIQUES IN BONE BIOLOGY

Machine learning in bone biology

Machine Learning, a core subset of AI, encompasses algorithms that learn from data to make predictions or decisions without being explicitly programmed for specific tasks.³⁷⁻³⁹ Within bone biology research, ML techniques are instrumental in distilling actionable insights from the complex and high-dimensional datasets generated by modern research.

Supervised learning. Supervised learning algorithms, trained on labeled datasets with predefined input-output relationships, enable models to accurately classify new data or predict outcomes.⁴⁰ In bone biology, this machine learning approach has proven highly beneficial, notably in classifying diseases, predicting risks, and assessing therapeutic responses using high-dimensional biological data like genomics, proteomics, and transcriptomics.

One notable application is identifying diagnostic and prognostic biomarkers for skeletal diseases, such as OA.⁴¹⁻⁴³ Researchers have successfully leveraged supervised learning techniques, including LASSO logistic regression and SVM-RFE, to scrutinize microarray datasets and therapeutic samples.^{44,45} These methods have aided in discovering potential OA biomarkers like SEH1L and BIRC2, highlighting AI's ability to scour complex genomic datasets for molecules relevant to diagnostics and therapeutic advancements.⁴⁶ Furthermore, focusing on specific gene sets, such as mitochondria-related genes, has pinpointed GRPEL1 as a novel diagnostic indicator for OA, showcasing how targeted analyses can reveal biomarkers linked to specific cellular pathways involved in OA pathogenesis.⁴⁷

Beyond biomarker discovery, supervised learning frameworks significantly contribute to stratifying disease risks.^{48,49} For example, a comprehensive machine learning model, devised Feature retrospective therapeutic, lifestyle, and biomarker data from over 19,000 individuals, effectively forecasted five-

year OA risk.²⁷ This model pinpointed established risk factors and categorized patients into 14 distinct OA risk profiles. Validation in an independent cohort attested to the model's robustness and potential to unveil personalized biomarkers tied to underlying disease mechanisms, like disruptions in GDF5 and TGF- β signaling pathways. Such predictive models pave the way for early OA detection and tailored prevention strategies based on individual risk profiles.

Moreover, supervised learning is increasingly employed in rheumatology to anticipate treatment responses for conditions profoundly affecting bone health, such as Rheumatoid Arthritis (RA) and Spondyloarthritis (SpA), often characterized by bone erosion and inflammation.⁵⁰⁻⁵² In RA, where biologic therapies exhibit varying efficacy, machine learning methods have analyzed molecular signatures from synovial biopsies.^{51,53} Data from the R4RA clinical trial showed that algorithms analyzing these signatures could predict therapeutic response, with Area Under Curve (AUC) values of 0.74 for rituximab and 0.68 for tocilizumab, and also identified multidrug resistance patterns (AUC 0.69).⁵⁴ These findings underscore the potential of combining molecular profiling with machine learning to steer personalized treatment choices and optimize therapeutic outcomes in inflammatory bone diseases.

In regenerative medicine and biomaterial science, supervised learning aids in the rational design of materials for bone tissue engineering.^{55,56} By constructing and analyzing comprehensive databases, ML algorithms can foretell the osteoinductive potential of biomaterials based on their physicochemical properties.¹⁴ A recent study exemplified this, achieving high predictive performance (Area Under Curve AUC=0.921) and identifying key factors influencing bone formation, such as material porosity and the incorporation ratio of BMP-2. This ML-guided optimization led to the creation of biomaterials that significantly boosted new bone formation in preclinical models, surpassing average database performance. This illustrates how supervised learning can expedite the design and refinement of biomaterials for superior bone regeneration.

Unsupervised learning. Unsupervised learning algorithms explore unla-

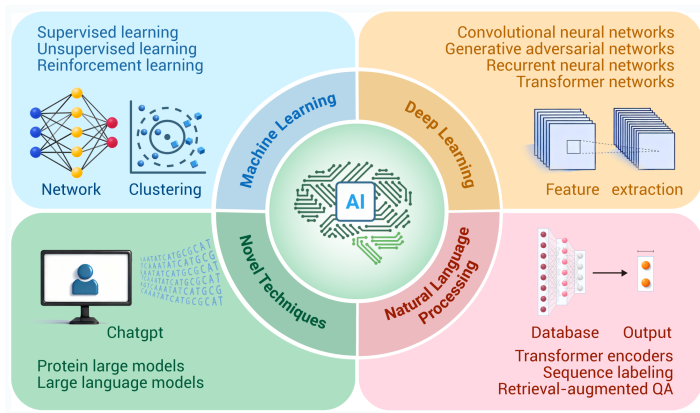


Figure 2. A schematic of the landscape of Artificial Intelligence The central AI concept branches into four interconnected disciplines. Machine Learning encompasses foundational methods like Supervised, Unsupervised, and Reinforcement Learning. Deep Learning represents a class of machine learning algorithms using deep neural networks, including Convolutional Neural Networks (CNNs), Generative Adversarial Networks (GANs), and Transformers. Natural Language Processing (NLP) involves techniques that enable machines to understand and generate human language, such as Transformer encoders and retrieval-augmented question answering. Finally, Novel Techniques highlights emerging and highly impactful models, exemplified by Large Language Models (LLMs) and specialized Protein Language Models.

beled datasets, discerning latent patterns and intrinsic structures without any prior knowledge of outcome variables.⁵⁷ These techniques are particularly valuable in bone biology, as they elucidate heterogeneity within complex biological data, facilitate data-driven patient stratification, and aid in the identification of novel molecular signatures or cell populations.⁵⁸⁻⁶⁰

A prime application of these algorithms lies in patient stratification, especially in heterogeneous conditions such as osteoporosis.^{61,62} Unsupervised methods, including clustering algorithms and Principal Component Analysis (PCA), are applied to multi-omics data from patient cohorts.⁶³ By reducing data dimensionality and revealing inherent groupings, these techniques unveil distinct molecular profiles among individuals with osteoporosis.⁶² This stratification surpasses traditional clinical classifications, offering a more nuanced understanding of disease subtypes and potentially guiding the development of precise, targeted therapeutic strategies.⁴⁸

Beyond patient stratification, unsupervised learning plays a pivotal role in extracting novel biological insights from high-dimensional omics datasets, such as genomics, transcriptomics, proteomics, and metabolomics.⁵⁹ These analyses contribute to pipelines aimed at identifying regulators and markers of skeletal cell function and differentiation. For example, studies utilizing machine learning for analyzing complex biological data related to osteoclast activity have highlighted molecules like the G-protein coupled receptors SSTR2 and FFAR4, as well as FLNB and LOX-1, facilitating the discovery of potential diagnostic and prognostic biomarkers, and therapeutic targets.⁶⁴

Moreover, unsupervised approaches have proven effective in identifying novel secreted factors involved in bone homeostasis.^{65,66} Through sophisticated analysis of multi-omics data, researchers have identified 375 candidate osteokines that are potentially responsive to stimuli such as aging and mechanical loading.⁶⁷ Subsequent integrated secretion prediction (ISP) analysis, utilizing Gene Ontology (GO) annotations, has pinpointed 107 potential bone-secreted genes (BSGs). Notably, this approach has implicated fatty acid-binding protein 3 (FABP3), secreted by senescent osteoblasts, in crosstalk with vascular smooth muscle cells, thus demonstrating the ability of unsupervised learning to uncover previously unknown intercellular communication networks relevant to bone health and associated pathologies.

Reinforcement learning (RL). RL involves training an agent to make sequential decisions by interacting with an environment.^{68,69} The agent learns through trial and error, receiving feedback in the form of rewards or penalties for its actions, aiming to maximize a cumulative reward over time. This paradigm is well-suited for optimizing strategies in dynamic and complex systems.

When applied to bone biology, RL offers promise in addressing intricate optimization tasks, particularly those encountered in bone tissue engineering (BTE).^{55,70} BTE is a multidisciplinary field that focuses on regenerating bone

through a combination of scaffolds, cells, and growth factors. The success of BTE relies heavily on the precise adjustment of multiple interrelated factors, such as scaffold material traits (e.g., composition, porosity, pore size distribution, mechanical features) and the timed release of bioactive molecules to guide cellular behavior. This creates a highly complex, dynamic system where optimizing one parameter can affect others, presenting a formidable obstacle for traditional methods.^{71,72} To handle this intricacy, RL techniques, including Q-learning, have been suggested for automatically generating optimized three-dimensional vascular networks tailored to individual bone defect geometries in bioprinting. Here, the RL agent systematically explores and improves potential vascular designs within anatomical limits, guided by rewards that prioritize structures likely to boost bioprinting feasibility and subsequent graft survival (for instance, by minimizing vessel tortuosity). The ultimate objective is the automated creation of vascular designs optimized for the successful production and performance of vascularized bone grafts.

The selection of the appropriate ML paradigm is intrinsically linked to the specific research question being addressed in bone biology. Supervised learning is employed when the goal is prediction or classification based on known examples. Unsupervised learning is utilized for discovering underlying structures and patterns in unlabeled data, often as a first step in understanding complex datasets like omics. Reinforcement learning offers a framework for modeling and optimizing interventions within dynamic, multi-parameter biological systems where sequential decision-making is key.

Deep learning in bone biology

Deep Learning represents a more advanced subfield of Machine Learning that utilizes artificial neural networks with multiple layers to interrogate complex data and learn hierarchical representations.^{73,74} The ability of deep learning models to automatically extract intricate features from raw data has led to significant advancements in bone biology research.

Convolutional neural networks (CNNs). CNNs excel in processing grid-like data, particularly images, making them invaluable for analyzing medical imaging modalities common in bone biology, such as X-rays, CT scans, and MRI.^{75,76} Their application has transformed the analysis of microscopy images of bone tissue and cells, facilitating the extraction of quantitative data and revealing new morphological insights.^{77,78}

Within the field of bone histopathology, CNNs are significantly enhancing the analysis of digitized whole-slide images (WSIs) from biopsies.⁷⁹ These models automate complex analytical tasks traditionally reliant on manual interpretation by pathologists, offering remarkable potential for improving diagnostic efficiency, consistency, and objectivity. Applications include classifying primary and metastatic bone tumors based on cellular morphology, tissue architecture, and matrix composition;^{80,81} quantifying specific cell populations, such as osteoclasts in culture assays, to aid drug screening and mechanistic studies;⁸² rapidly assessing bone marrow cellularity;⁸³ detecting hematopoietic disorders within bone marrow biopsies;⁸⁴ and identifying prognostically significant microenvironmental features.^{85,86} Various CNN architectures, sometimes integrated into larger analytical platforms, enable these capabilities, exhibiting a profound ability to learn subtle and complex morphological patterns, aiding in challenging differential diagnoses and reducing inter-observer variability.

A compelling example of CNNs' power is found in osteosarcoma research, where deep learning models applied to post-neoadjuvant therapy histology slides predict patient prognosis. One neural network accurately automated tumor necrosis quantification, achieving an excellent correlation with expert pathologist assessments ($R^2 = 0.899$; $P < 0.0001$). Importantly, this morphology-based supervised approach also predicted overall survival, demonstrating significant predictive value (Hazard Ratio [HR] = 2.43, 95% CI 1.10-5.38; $P = 0.0028$).⁸⁷ Furthermore, Features like certain types of necrosis, fibroblastic stroma, and osteoblastic morphology correlated with better survival, while viable tumor and fat necrosis indicated worse outcomes, demonstrating how neural networks can automate assessment and identify new morphological biomarkers for prognosis.

In the field of medical image analysis, advanced architectures such as Swin-UNetR are being investigated for image segmentation duties, particularly in analyzing the complex osteocyte networks within bone tissue.⁸⁸ A recent study examining the automation of osteocyte connectomics segmen-

tation and measurement, which is pivotal for comprehending bone physiology, revealed the limitations of traditional techniques: they are time-consuming and prone to human error.⁸⁹ By deploying U-Nets and Vision Transformers, the study achieved notable segmentation accuracy, reaching 81.8% for osteocytes and 42.1% for dendritic processes when benchmarked against manual labeling. Furthermore, the model accurately distinguished between the bones of young (2-month-old) and aged (36-month-old) mice, and even detected degenerative changes arising from genetic modifications. Such progress has the potential to significantly advance bone health research by facilitating a more efficient and detailed exploration of osteocyte networks.

Recurrent neural networks (RNNs). RNNs have the capacity to retain information from preceding time steps through their recurrent connections, thus enabling them to model temporal dependencies within sequential data.^{90,91} This characteristic makes them ideal for investigating dynamic biological processes. For example, in bone biology, RNNs can be applied to model the sequential stages of bone development, and predict patient-specific bone density changes from time-series data.⁹² In a groundbreaking application, an RNN-based architecture was successfully used as the final classifier in an image processing pipeline. After extracting key features from a potential fracture site, the RNN model processes this information to make a highly accurate prediction. This method serves as a clear example of how RNNs can be applied to solve challenging pattern-recognition problems in clinical bone analysis. In addition, another key application is in automated Bone Age Assessment (BAA), a crucial diagnostic process in pediatrics.⁹¹ One advanced model utilizes a multi-stage approach based on the Tanner-Whitehouse 3 (TW3) method. After segmenting key regions of a hand X-ray, a Faster R-CNN is used to learn and extract deep feature sets. Finally, an Optimally trained RNN models processes these sequential features to predict the final bone age. The model's performance was enhanced by optimizing the RNN's training weights with a novel algorithm, demonstrating a sophisticated fusion of AI techniques to solve a classic radiological problem.

Generative adversarial networks (GANs). GANs constitute a notable category of deep learning models, recognized for their proficiency in generating synthetic data.⁹³ In the domain of bone biology research, GANs have emerged as invaluable tools, especially for expanding limited datasets and simulating a range of bone conditions.

GANs operate by comprehending the inherent patterns within real datasets, enabling them to produce novel synthetic samples that mirror the original data.⁹⁴ This capability effectively bolts down the size and variety of datasets available for training other AI models, a crucial aspect in medical imaging where acquiring extensive, meticulously annotated datasets can pose challenges due to privacy restrictions and the infrequency of specific conditions.⁹⁵ Beyond their utility in data augmentation, GANs are finding their footing in various other aspects of bone biology research. A prime example is their use in virtual staining of label-free microscopy images of bone tissue. This technique allows researchers to generate images that appear histologically stained (e.g., with H&E) from unstained samples, reducing sample preparation time and cost while preserving the tissue for other analyses.⁹⁶ Another powerful application is in facilitating the segmentation of intricate bone structures within medical images. GANs can be trained to translate sparse or low-resolution medical images into high-resolution, clearly delineated images, making it easier for other AI models to accurately identify and measure features like trabecular bone microarchitecture or osteocyte lacunae.⁹⁷

Transformer networks. Transformer networks, originally developed for natural language processing, have exhibited remarkable performance in a range of sequence-based tasks.^{97,98} Their capacity to capture long-range dependencies through self-attention mechanisms has propelled their widespread use in computer vision and bone biology investigations. A significant application is in the early prediction of bone metastasis in lung cancer patients, a critical step for improving patient outcomes.⁹⁹ Researchers have developed a multimodal model using two Swin Transformer networks to independently process CT scans and digitized histopathological images. These distinct data streams were then integrated using decision-level fusion, creating a more holistic and accurate predictive tool than single-modality approaches. This model achieved outstanding accuracy (AUC of 0.966), showcasing the power of Transformers to synthesize diverse clinical data for complex risk stratification.

Natural language processing in bone biology

Natural Language Processing, a subset of artificial intelligence, centers on enabling computers to comprehend, interpret, and manipulate human language.^{100,101} In the domain of bone biology research, NLP proves invaluable in sifting through the enormous and continuously expanding scientific literature, extracting pertinent information, identifying relationships, and revealing insights.¹⁰² The overwhelming volume of biomedical publications poses a considerable challenge for researchers striving to stay abreast of the latest developments and discern crucial interconnections between studies. NLP techniques offer automated solutions for processing and analyzing this extensive textual data, equipping researchers with potent tools to expedite the discovery process.^{103,104} This process involves analyzing vast corpora of unstructured text, such as PubMed abstracts, full-text articles, and clinical trial records. The goal is to structure this information using specific NLP tasks. For instance, techniques like Named Entity Recognition (NER) are employed to automatically scan literature and identify key biological entities such as genes (e.g., RUNX2), proteins (e.g., osteocalcin), and diseases (e.g., osteoporosis).^{34,35} Following this, Relation Extraction (RE) models are used to discern the complex relationships between these entities, such as identifying drug-target interactions or gene-disease associations. The integration of deep learning is critical to the success of these tasks. Modern NLP models are often built on deep learning architectures like Transformers (e.g., BioBERT), which analyze the context of words within a sentence to perform NER and RE with far greater accuracy than older methods. This deep learning-powered knowledge extraction is pivotal for building comprehensive interaction maps and accelerating discovery.^{105,106}

The practical applications of NLP in advancing therapeutic innovations for bone-related conditions are exemplified by several recent investigations.¹⁰⁷ One notable study sought safer and more economical alternatives to protein-based cytokine therapies aimed at promoting bone regeneration.¹⁰⁸ Researchers employed a computational approach that integrates Deep Learning and Natural Language Processing to scrutinize protein databases annotated with functional information from scientific literature to find new, short amino acid sequences called bioactive peptides that can promote blood vessel growth. Through this *in silico* screening, they discovered a new pro-angiogenic tripeptide called PSP. Experimental testing revealed that PSP stimulates vascularization in endothelial cells and boosts osteogenic differentiation of bone marrow stem cells in a laboratory setting. Furthermore, *in vivo* studies conducted on mice corroborated its regenerative capabilities. This study highlights an effective method driven by artificial intelligence for identifying and verifying bioactive peptides, opening up avenues for peptide-based treatments for skeletal disorders.

Another key application is the automated extraction of structured data from unstructured clinical notes.³⁵ This is exemplified by the development of "BoneScore," an NLP tool designed to read reports from dual-energy X-ray absorptiometry (DXA) scans and accurately pull out specific data points. BoneScore uses a rule-based algorithm with a set of regular expressions to identify and extract femoral neck T-scores, a critical value used to diagnose osteopenia and osteoporosis. After testing, the tool achieved 98% accuracy. This automation saves significant time and effort, enabling researchers to quickly assemble large datasets for studying bone health, risk factors, and disease prevalence.

Novel and emerging AI in bone biology

While the machine learning and deep learning techniques discussed previously have proven powerful, they often rely on large volumes of well-structured, labeled data for training. However, many challenges in bone biology involve either making predictions from very limited data or synthesizing knowledge from vast, unstructured sources. For instance, determining the three-dimensional structure of a protein from its amino acid sequence alone, or generating novel hypotheses by reading the entire corpus of scientific literature, are tasks that stretch the capabilities of conventional models. The following sections explore novel and emerging AI models, such as advanced protein structure predictors and Large Language Models (LLMs), that have been developed to address these complex, knowledge-intensive challenges, showcasing their unique advantages over previous approaches.^{109,110}

Protein structure models in bone research. AI is transforming molecular

Table 1. Overview of AI techniques and their applications in bone biology.

Technique Family	Typical Inputs	Representative Algorithm	Representative Bone Tasks
Machine Learning (ML) ^{33,120}	Structured/tabular data (patient demographics, labs, DXA/BMD, FRAX factors, imaging-derived measurements, genotypes/omics)	Supervised Learning Unsupervised Learning Reinforcement Learning	Risk Prediction Biomarker Discovery Treatment Response Patient Phenotyping Data Compression
Deep Learning (DL) ^{121,122}	Raw/unstructured data (X-rays/CT/MRI/histology; time series like accelerometry/gait; genomic/protein sequences; waveforms)	Convolutional Neural Networks Generative Adversarial Networks Recurrent Neural Networks Transformer Networks	Image Analysis Fracture Detection / Classification Image Segmentation 3D Modeling
Natural Language Processing (NLP) ^{34,35}	Unstructured text (EHRs, clinical notes, radiology/pathology reports, literature, trial registries, forums)	Transformer encoders Sequence labeling Retrieval-augmented QA	Information Extraction Phenotyping Literature Review / Knowledge Discovery Clinical Decision Support
Novel and Emerging Models ^{36,123}	Large text/code corpora; protein/compound sequences/ structures; knowledge graphs; paired image–text	Protein LMs Large Language Models	Protein Structure Prediction Drug Design Scientific Literature Synthesis Clinical Documentation Knowledge Base Querying Educational Tools

biology, particularly through the highly precise prediction of protein structures using tools such as AlphaFold and through innovative protein design, thereby greatly influencing bone biology research.¹¹¹ Reliable 3D structures of bone-related proteins, including previously elusive therapeutic targets linked to osteoporosis (e.g., in TP53, EGFR pathways), can now be accurately predicted. These structural models form the basis for structure-based drug design.¹¹² Moreover, AI-predicted structures are essential inputs for integrated computational pipelines that combine network pharmacology and molecular docking to identify and prioritize potential drug candidates.¹¹³ For example, this method uncovered resveratrol's possible interaction with targets involved in ferroptosis-related osteoporosis, leading to testable therapeutic hypotheses.¹¹⁴

Beyond mere prediction, AI facilitates the de novo design of customized proteins with new functions tailored for bone applications. This could involve creating optimized osteogenic growth factors with enhanced specificity, enzymes for biomaterial modification, or targeted peptides for skeletal therapy or imaging.^{115,116}

Large language models in bone research. Advanced Large Language Models (LLMs), such as DeepSeek and ChatGPT, are robust AI systems renowned for their sophisticated reasoning derived from vast text and code datasets.¹¹⁷ Originating in natural language processing, their proficiency in complex pattern recognition, information synthesis, and contextual understanding is driving exploration in scientific fields, with significant potential emerging in bone biology.¹¹⁸ A prime example is in accelerating drug repurposing. For instance, a fine-tuned Large Language Model (GPT-4) was tasked with identifying promising anti-osteosarcoma compounds from a library of polyphenols. The LLM identified gossypol as a top candidate by evaluating the complex correlations between the compounds' multiplexed chemical properties and known experimental anti-osteosarcoma activity data. This approach showcases the power of LLMs to synthesize and reason over diverse data types to generate novel, testable hypotheses for drug discovery in bone oncology.¹¹⁹ Furthermore, In a groundbreaking study comparing various machine learning approaches, LLMs processing molecular representations of drug compounds exhibited remarkable predictive power, achieving high accuracy (Accuracy (ACC) 0.87–0.88). This notable finding underscores that, despite their primary training on language, LLMs can effectively learn from non-textual molecular data to make biologically relevant predictions about bone health impacts.

In summary, these powerful AI tools expedite the generation of molecular insights into skeletal health and disease. They streamline the identification and optimization of therapeutic targets and drug candidates, paving the way for the development of advanced biologics, diagnostics, and biomaterials to combat bone disorders.

Key application domains of AI in bone research

The transformative power of Artificial Intelligence extends across a broad spectrum of bone biology, from fundamental mechanistic studies to direct therapeutic applications. To provide a clear framework, we have summarized the key AI methodologies, their typical data inputs, and their representative applications in bone-related research and therapeutic practice in Table 1. Beyond advanced analytical techniques and multi-omics integration, AI is proving invaluable in specific contexts research, improving diagnostics, and personalizing treatment strategies. To illustrate this translational pipeline, Figure 3 provides a conceptual map of the key application domains where AI is proving invaluable. These core areas including biomarker discovery, drug discovery, precision medicine, and advanced tissue engineering, form the framework for the subsequent sections of this report and underscore AI's versatile role in advancing bone health. There highlight several distinct applications that underscore AI's versatile role in bone research.

One of the most promising and rapidly expanding areas is AI in bone tissue engineering. Building on the multi-omics integration discussed earlier, AI offers unprecedented precision in designing biomaterials and controlling stem cell differentiation. AI models can predict optimal scaffold architectures and compositions that best support osteointegration and bone regeneration, moving beyond trial-and-error approaches.¹²⁴ Furthermore, by analyzing complex molecular profiles from patient-derived stem cells, AI can guide their differentiation towards specific bone or cartilage lineages, enhancing the success rates of regenerative therapies for critical bone defects or osteochondral lesions.¹²⁵ This predictive capability accelerates the development of personalized implants and bio-scaffolds tailored to individual patient needs and biological responses.

Another significant application lies automated Bone Age Assessment (BAA) using radiographs.^{126,127} Bone age assessment is a routine pediatric therapeutic procedure used to evaluate a child's skeletal maturity, which is crucial for diagnosing growth disorders, predicting adult height, and timing pubertal interventions. Traditionally, this involves comparing a child's hand-wrist radiograph against standardized atlases (e.g., Greulich-Pyle or Tanner-Whitehouse), a process that is time-consuming, subjective, and prone to inter-observer variability. AI, particularly Convolutional Neural Networks (CNNs), has revolutionized this field. Trained on vast datasets of annotated radiographs, CNNs can automatically analyze bone morphology (e.g., epiphyseal fusion, carpal bone development) and predict bone age with remarkable accuracy and speed, often surpassing human experts. This not only standardizes the assessment process and reduces diagnostic variability but also significantly lightens the workload for radiologists, allowing for more efficient therapeutic workflows and timely patient management.

Artificial Intelligence is also fundamentally transforming bone and biomechanical research by enhancing finite element analysis (FEA), a powerful



Figure 3. The integrated application of AI across the research-to-clinic pipeline in bone biology This figure illustrates the four key areas discussed in this report. Biomarker discovery leverages molecular data (e.g., genetic, proteomic) to predict treatment response and stratify patients. AI-driven drug discovery accelerates the identification of new therapeutics and predicts their toxicity. Tissue engineering utilizes computational models informed by histopathology and databases to design and fabricate implants and hydrogels via 3D printing. Finally, precision medicine synthesizes high-dimensional 'omics' data to perform subtype analysis and tailor interventions to individual patients.

computational method used to simulate the physical behavior of materials.¹²⁸ Traditionally, FEA has been indispensable for modeling how bone structures respond to mechanical forces, predicting stress, strain, and potential fracture points.¹²⁹ However, conventional FEA is computationally intensive and labor-demanding, requiring meticulous manual effort that has made it impractical for rapid, patient-specific therapeutic use. The integration of AI, particularly deep learning, addresses these limitations by automating and personalizing the entire workflow. AI algorithms can autonomously segment complex bone structures from medical images and generate high-quality, patient-specific meshes with minimal manual intervention. Furthermore, AI excels at creating more physiologically accurate simulations by inferring an individual's unique

bone material properties from a combination of imaging data and clinical records. This fusion of technologies provides a scalable solution for personalized biomechanical analysis with profound therapeutic implications. This transformative approach is already being applied to complex clinical problems. For instance, in analyzing knee joint dysfunction linked to meniscal extrusion (ME), where traditional FEA is too computationally expensive for real-time assessment, a geometric deep learning (GDL) model trained on FEA data can now predict biomechanical responses almost instantaneously.¹³⁰ This enables clinicians to gain rapid insights into joint mechanics, which is invaluable for improving surgical planning and designing personalized rehabilitation strategies. Beyond joint mechanics, this synergy is also revolution-

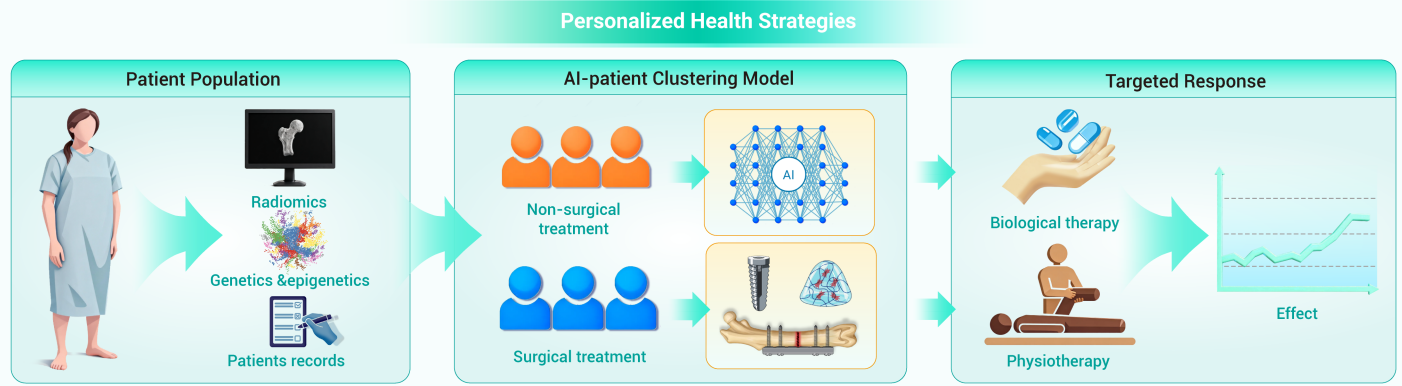


Figure 4. AI-driven personalization of medicine for musculoskeletal conditions This diagram illustrates a workflow for leveraging artificial intelligence to achieve personalized medicine. It begins with data acquisition from an individual patient, encompassing diverse inputs such as radiomics (quantitative features extracted from medical images like X-rays or CT scans), genetics & epigenetics (molecular data unique to the patient), and comprehensive patient records (clinical history, lab results, demographics). An AI-Patient clustering model then processes this rich, multi-modal data to stratify patients into distinct subgroups. Based on the characteristics of these clusters, the AI guides decision-making toward either non-surgical treatment pathways (e.g., leading to personalized biological therapy and tailored physiotherapy) or surgical treatment pathways (e.g., involving specific implants or procedures, followed by personalized biological therapy and tailored physiotherapy). This personalized approach aims to achieve a targeted response, optimizing treatment efficacy and leading to a desired effect in patient outcomes.

izing the design and validation of medical devices. In the development of vertebral implants, AI-driven optimization FEA is used to evaluate the performance of novel materials like Magnesium-Rare Earth-Zirconium (Mg-RE-Zr) alloys.¹³¹ By simulating dynamic physiological loads, engineers can precisely predict stress distribution (up to 0.160 GPa) and deformation patterns (0.015 mm to 0.01875 mm), validating implant performance with high accuracy (under 5% error) before clinical use. This provides a robust, predictive method for enhancing the biomechanical efficacy and safety of spinal implants, ultimately improving patient outcomes.

Furthermore, AI is making substantial inroads into the analysis of bone metastasis. Bone is a common site for metastasis from various primary cancers (e.g., breast, prostate, lung), leading to severe pain, pathological fractures, and reduced quality of life.^{33,132} Early and accurate detection of bone metastasis is critical for guiding treatment decisions and improving patient prognosis. However, identifying subtle metastatic lesions on routine imaging (X-rays, CT, MRI, bone scintigraphy) can be challenging, especially in complex anatomical regions or at early stages. AI algorithms, particularly deep learning models, are being developed to automatically detect, localize, and even characterize metastatic lesions. By learning intricate patterns associated with metastatic disease from large image datasets, AI can assist radiologists in identifying suspicious areas, quantifying tumor burden, and tracking treatment response more objectively than manual methods. This enhances diagnostic accuracy, reduces false negatives, and facilitates more timely and effective oncology management, ultimately impacting patient survival and well-being.

In summary, AI's role in bone research is multifaceted (Figure 4). Its ability to process vast, complex datasets, automate intricate tasks, and uncover subtle patterns makes it an indispensable tool for advancing bone tissue engineering, standardizing diagnostic assessments, and improving the detection and management of challenging conditions like bone metastasis. These diverse applications collectively underscore AI's transformative potential to accelerate discoveries and improve patient outcomes in musculoskeletal health.

CHALLENGES AND LIMITATIONS

While artificial intelligence presents a powerful toolkit for advancing bone biology, several challenges and limitations must be acknowledged to ensure its responsible and effective implementation in both research and clinical settings. The transition of AI from a promising research tool to a reliable therapeutic application necessitates careful consideration of factors such as data quality, model interpretability, ethical implications, and integration into existing healthcare systems (Figure 5).

Data quality and availability

The efficacy of AI models in bone biology relies heavily on access to high-

quality, comprehensively annotated datasets for training purposes.¹³³ Yet, acquiring such datasets is often challenging due to their scarcity and high acquisition costs. Moreover, ensuring data diversity is essential for AI models to achieve broad applicability and precise performance in various clinical contexts and patient demographics.¹³⁴

The success and adaptability of AI models are directly tied to the richness and variety of the datasets they are trained on.¹³⁵ Inadequate, poorly labeled, or skewed datasets may result in models with compromised accuracy or biased results against specific patient subpopulations.¹³⁶ Additionally, bone biology investigations frequently yield diverse data types, stemming from distinct imaging techniques, multiple omics platforms, and disparate clinical data gathering methods.^{56,70} This diversity creates a significant hurdle in crafting resilient and widely applicable AI models, given AI algorithms' sensitivity to input variations. Disparities in image clarity, contrast, or omics data processing can influence model outcomes and limit their use across datasets of different provenances. For example, in bone imaging, the high density of mineralized tissue can create artifacts in micro-computed tomography (μCT) scans, leading to inconsistencies that affect model training. Furthermore, standardizing image acquisition protocols (e.g., resolution, scanner settings) across different research centers is a major challenge, making it difficult to pool datasets for large-scale analysis. Similarly, in multi-omics, integrating transcriptomic data from bone biopsies with proteomic data from blood samples requires sophisticated alignment, as these data types are often collected at different times and measure different aspects of the biological system. Also, the absence of uniform bone biology datasets, encompassing imaging, omics, and clinical details, complicates the training and assessment of AI models. The lack of standard data formats and annotation criteria obstructs data sharing and integration among research teams, thus impeding the progress of AI in bone biology.^{137,138}

Representing the complexity of bone biology

Bone tissue is characterized by its intricate complexity and dynamic nature, encompassing a web of cellular interactions, vascular networks, innervation, and continuous remodeling.⁶ Present-day AI models frequently encounter difficulties in fully grasping this complexity, thereby hindering their capacity to precisely simulate biological processes and foretell treatment outcomes in clinically pertinent situations.¹³⁹

In fact, prevalent *in vitro* models often fall short of replicating the intricate bone microenvironment, adding another layer of complexity to the development of AI models that aim to bridge the divide between *in vitro* observations and *in vivo* results.¹³⁸ Additionally, capturing and analyzing cellular and molecular events within the dense, mineralized matrix of bone tissue at a subcellular level remains a substantial undertaking, posing obstacles for AI-driven analysis.^{88,140} The inherent density and mineral content of bone tissue pose challenges to acquiring high-resolution imaging data at the cellular and

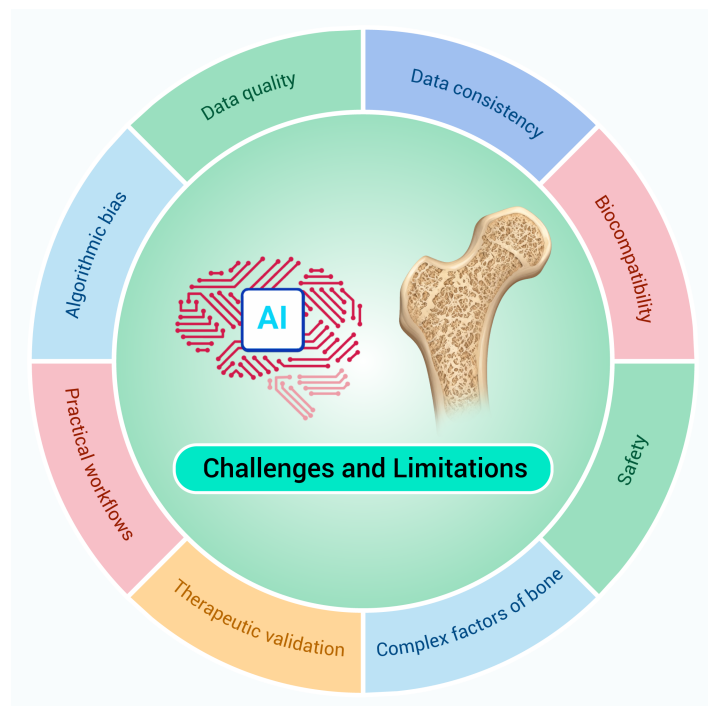


Figure 5. Challenges and limitations in integrating AI into bone biology research and advanced therapeutics These hurdles span multiple domains: Data and Algorithms (ensuring high data quality, data consistency, and mitigating algorithmic bias); Clinical Implementation (the need for robust clinical validation and seamless integration into clinical workflows); and Biological and Safety Concerns (addressing the complex factors of bone biology while ensuring the biocompatibility and safety of AI-guided applications). Overcoming these multifaceted challenges is essential for the successful and responsible deployment of AI in bone health.

molecular scales, thereby restricting the informational pool available for training AI models to scrutinize these fine details.

Moreover, the task of modeling bone's perpetual remodeling process between osteoblasts, osteoclasts, and osteocytes, presents a notable challenge for contemporary AI methods.¹³⁸ To accurately simulate bone remodeling, AI models must adeptly capture the temporal shifts and the intricate interplay among these diverse cell types, often demanding longitudinal datasets and advanced modeling techniques.

Ethical considerations and biases

The integration of AI into bone biology research and therapeutic applications raises several ethical considerations that must be carefully addressed.^{140,141} These include concerns related to patient privacy, data security, and the transparency of AI algorithms. The use of AI in healthcare necessitates adherence to ethical guidelines to safeguard patient rights and ensure fair and equitable outcomes.

A critical challenge lies in the potential for biases within AI algorithms used for diagnosis and treatment in bone diseases. These biases can originate from the training data and may inadvertently lead to disparities in healthcare outcomes for different demographic groups.^{142,143} Examples of such biases related to race, gender, age, and socioeconomic status have been reported. If the training data for an AI model underrepresents certain demographic groups or reflects existing biases in healthcare practices, the model's performance and recommendations may be unfair or inaccurate for those groups. Another significant limitation is the "black-box" nature of some deep learning models, where the decision-making processes are opaque and difficult for humans to understand.¹⁴⁴ This lack of transparency can hinder the adoption of AI in therapeutic practice, as clinicians may be reluctant to trust decisions without understanding the underlying reasoning.

Integration and workflow challenges

The translation of AI applications in bone biology into therapeutic practice hinges on their smooth integration within prevalent healthcare workflows and IT frameworks, including Picture Archiving and Communications Systems

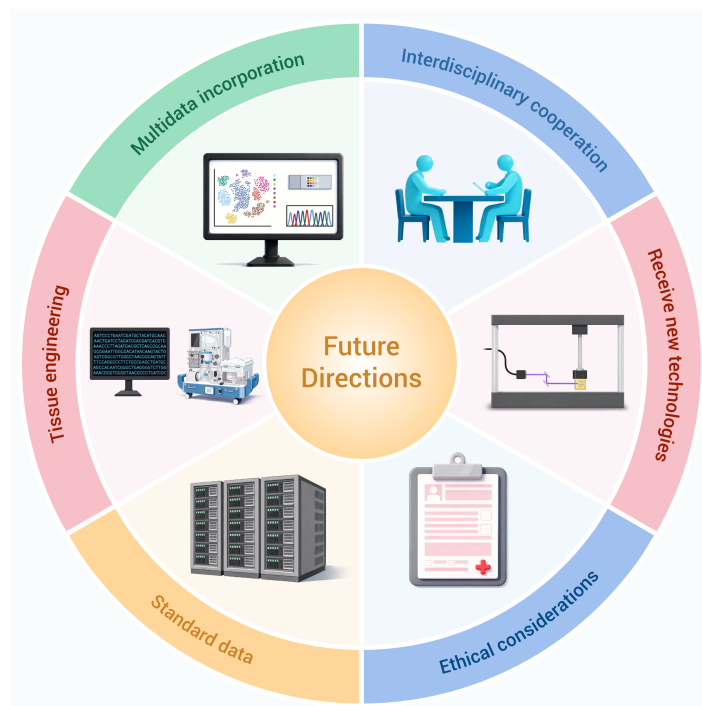


Figure 6. A strategic roadmap for future directions in bridge AI and bone biology The key directions include: (1) Multidata Incorporation, integrating diverse datasets for comprehensive analysis; (2) Interdisciplinary Cooperation, fostering collaboration between experts in medicine, engineering, and data science; (3) Receiving New Technologies, embracing innovation to enhance capabilities; (4) Ethical Considerations, ensuring responsible development and application; (5) Standard Data, establishing uniform data protocols for reproducibility and large-scale analysis; and (6) Tissue Engineering, a primary application target for these advanced approaches. Together, these pillars represent a comprehensive strategy for driving innovation.

(PACS) and Radiological Information Systems (RIS).^{145,146} Nevertheless, introducing AI solutions into the intricate and frequently dispersed healthcare IT landscape can pose significant technical challenges, often demanding considerable adaptations to existing systems. Additionally, healthcare practitioners require comprehensive training to proficiently operate AI tools and establish trust in their results.^{134,147} Resistance to change and limited exposure to AI among medical providers can further hinder their widespread acceptance.

FUTURE DIRECTIONS

AI has shown transformative potential in driving innovative advancements and paradigm shifts in bone biology research. However, significant challenges remain, necessitating targeted efforts to unlock AI's full translational impact. In what follows, we outline key future directions to enhance AI's role in advancing skeletal science and therapeutic translation (Figure 6).

Standardization and data

Standard datasets, particularly large ones, are crucial for building robust AI models.¹⁴⁸ To ensure the dependability of AI applications, researchers must follow established best practices for digital and data-driven health technologies. These include guidelines like the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) and those set by the National Health Service (NHS), which underscore transparent methodologies and exacting standards, thereby bolstering the reproducibility and trustworthiness of AI models.^{147,148}

Moving forward, research efforts should prioritize the creation of expansive, diverse datasets incorporating high-quality data from multiple sources. Furthermore, to facilitate the progress and reproducibility of future models, international bone biology associations should establish open communication platforms hosting diverse data and source codes, akin to GitHub or the GEO database. Such platforms would enable researchers to test and validate their models using external datasets, while also fostering the development of shared core codes for AI model optimization.

Multidata incorporation

The evolving omics technologies have shifted the spotlight to the integration of multi-omics data, encompassing genomics, proteomics, transcriptomics, and epigenomics. Future initiatives will concentrate on merging these diverse datasets and devising refined algorithms to scrutinize heterogeneous data from various origins.^{149,150} This approach promises deeper insights into the intricate interplay of genes, proteins, environmental stimuli, and mechanical forces.

Moreover, the escalating significance of digital clinical archives in forging predictive models and facilitating drug discovery cannot be understated. Forthcoming AI frameworks ought to strive for the assimilation of extensive real-world clinical information, such as electronic health records and patient-reported outcomes. This integration will bolster the pertinence and utility of prognostic outputs, enabling AI instruments to generate more tailored forecasts on treatment reactions, disease progression, and potential drug synergies.

Ethical considerations

Although there is a pressing need to advance AI applications in bone biology, ethical considerations are paramount in shaping their future progress.¹⁵¹ Common challenges in medical AI deployment include algorithmic bias, data privacy concerns, and the need for informed consent. It is imperative for researchers to guarantee that upcoming AI applications are fair, transparent, and adhere to ethical norms, thereby fostering trust and promoting equitable results for a wide range of patients.

Integration with emerging technologies

As new technologies arise, artificial intelligence must adapt to harness these innovations. Organoids, which are three-dimensional organ models crafted from stem cells have demonstrated remarkable promise in pharmaceutical research.^{152,153} AI can refine the development and cultivation parameters for bone organoids, thus speeding up the screening process among thousands of potential drug candidates. Future research efforts should concentrate on integrating organoids and AI in the field of bone biology, aiming to investigate bone disorders and facilitate drug discovery.

With the cost of sequencing and multi-omics data gathering steadily declining, AI will be pivotal in amalgamating these intricate datasets.¹⁵⁴ This will aid in pinpointing novel therapeutic targets, anticipating patient outcomes, and tracking disease advancement. Precision medicine, driven by AI, is destined to expand towards tailored therapies. This will empower clinicians to fine-tune treatments for individuals suffering from bone ailments, simultaneously enriching multi-omics data repositories to refine AI-powered models continuously.

AI-guided tissue engineering

AI-guided tissue engineering offers considerable potential in driving advancements in bone regeneration and tailored therapies.¹⁵⁵ Forthcoming research ought to prioritize the incorporation of patient-specific data, including imaging and mechanical loading conditions, into the design phase of tissue engineering. Such an approach is likely to enhance the integration of engineered tissue with its surrounding environment and diminish complications often encountered with conventional implants. Furthermore, AI's capability to monitor the progression of bone tissue formation and adjust treatment protocols in real-time through AI-guided systems promises more flexible and responsive treatment plans. These plans can be tailored to each patient's unique healing trajectory, potentially leading to improved outcomes and expedited recovery periods.

Cross-disciplinary collaboration

Addressing the aforementioned challenges demands concerted efforts. Future endeavors should focus on creating standardized, top-quality datasets, enhancing model interpretability, building resilient validation structures, outlining unequivocal ethical standards, reducing prejudices, and promoting collaborative efforts among computational scientists, biologists, and clinicians. This will align innovative practices with clinical demands.

The progress of AI in bone biology hinges on solid collaborations across fields. Computer scientists and AI researchers offer invaluable technical proficiency in shaping and deploying algorithms, whereas bone biologists

impart vital domain understanding for substantial model advancement and interpretation. Clinicians impart pivotal perspectives on practical necessities and factors for effective therapeutic application. This interdisciplinary method guarantees that AI resolutions tackle genuine obstacles in bone biology investigations and therapeutic practices. Collaborative systems that enable the exchange of knowledge and resources among these diverse parties will prove essential in forging AI solutions that truly elevate bone health management.

CONCLUSIONS

Artificial intelligence represents a paradigm shift, promising to revolutionize our understanding and approach to bone biology and its associated pathologies. Its diverse capabilities span from decoding complex molecular networks and accelerating tissue engineering research to enhancing precision detection and enabling precision therapeutic strategies. This technology opens up exciting new opportunities for addressing critical unmet needs in bone health management. Nevertheless, alongside these advancements, substantial challenges persist, such as concerns regarding data quality, model transparency, ethical considerations, and workflow integration. Surmounting these obstacles requires a collaborative effort to standardize data sets, enhance model explainability, and ensure equitable implementation. The advancement of AI in bone biology relies on its integration with cutting-edge technologies, the exploration of multi-omics approaches, and the establishment of ethical guidelines. Through cross-disciplinary collaboration and a patient-centered focus, AI has the potential to deepen our understanding of skeletal biology and improve bone health globally. As methodologies evolve, AI is positioned to deliver increasingly personalized and efficient skeletal health strategies, while also expanding our fundamental understanding of bone biology.

REFERENCES

1. Ilen K. D., Thoma L. M. and Golightly Y. M. (2022). Epidemiology of osteoarthritis. *Osteoarthritis Cartilage* **30**:184–195. DOI:10.1016/j.joca.2021.04.020
2. Buttgerit F., Palmowski A., Bond M., et al. (2024). Osteoporosis and fracture risk are multifactorial in patients with inflammatory rheumatic diseases. *Nat. Rev. Rheumatol.* **20**:417–431. DOI:10.1038/s41584-024-01120-w
3. Yu S. and Yao X. (2024). Advances on immunotherapy for osteosarcoma. *Mol. Cancer* **23**:192. DOI:10.1186/s12943-024-02105-9
4. Florencio-Silva R., Sasso G. R., Sasso-Cerri E., et al. (2015). Biology of bone tissue: Structure, function, and factors that influence bone cells. *Biomed. Res. Int.* **2015**:421746. DOI:10.1155/2015/421746
5. Su N., Yang J., Xie Y., et al. (2019). Bone function, dysfunction and its role in diseases including critical illness. *Int. J. Biol. Sci.* **15**:776–787. DOI:10.7150/ijbs.27063
6. Iaquinia M. R., Montesi M. and Mazzoni E. (2024). Advances in bone biology. *Int. J. Mol. Sci.* **25**. DOI:10.3390/ijms25136892
7. Zaidi M., Kim S. M., Mathew M., et al. (2023). Bone circuitry and interorgan skeletal crosstalk. *Elife* **12**:e83142. DOI:10.7554/eLife.83142
8. Besio R., Chow C. W., Tonelli F., et al. (2019). Bone biology: Insights from osteogenesis imperfecta and related rare fragility syndromes. *FEBS J.* **286**:3033–3056. DOI:10.1111/febs.14963
9. Starling S. (2019). A role for autophagy in bone biology. *Nat. Rev. Endocrinol.* **15**:438–439. DOI:10.1038/s41574-019-0223-5
10. Li Q., Cheng J. C., Jiang Q., et al. (2021). Role of sirtuins in bone biology: Potential implications for novel therapeutic strategies for osteoporosis. *Aging Cell* **20**:e13301. DOI:10.1111/ace1.13301
11. Fotiou D. and Katodritou E. (2025). From biology to clinical practice: The bone marrow microenvironment in multiple myeloma. *J. Clin. Med.* **14**. DOI:10.3390/jcm14020327
12. Yang D., Xu J., Xu K., et al. (2024). Skeletal interoception in osteoarthritis. *Bone Res.* **12**:22. DOI:10.1038/s41413-024-00328-6
13. Misseri G., Gregoretti C. and Lo Bianco G. (2024). Review of evaluation and treatment of knee pain. *JAMA* **331**:706–707. DOI:10.1001/jama.2023.27754
14. Lin S., Zhuang Y., Chen K., et al. (2024). Osteoinductive biomaterials: Machine learning for prediction and interpretation. *Acta Biomater.* **187**:422–433. DOI:10.1016/j.actbio.2024.08.017
15. Stegen S. and Carmeliet G. (2024). Metabolic regulation of skeletal cell fate and function. *Nat. Rev. Endocrinol.* **20**:399–413. DOI:10.1038/s41574-024-00969-x
16. Wang Y., Liu S., Spiteri A. G., et al. (2024). Understanding machine learning applications in dementia research and clinical practice: A review for biomedical scientists and clinicians. *Alzheimers Res. Ther.* **16**:175. DOI:10.1186/s13195-024-01540-6
17. Cao F., Xu Z., Li X. X., et al. (2024). Trends and cross-country inequalities in the global burden of osteoarthritis, 1990–2019: A population-based study. *Ageing Res. Rev.* **99**:102382. DOI:10.1016/j.arr.2024.102382

18. Huang K. and Cai H. (2024). The interplay between osteoarthritis and osteoporosis: Mechanisms, implications, and treatment considerations - a narrative review. *Exp. Gerontol.* **197**:112614. DOI:10.1016/j.exger.2024.112614
19. Li M. M., Huang Y., Sumathipala M., et al. (2024). Contextual AI models for single-cell protein biology. *Nat. Methods* **21**:1546–1557. DOI:10.1038/s41592-024-02341-3
20. He X., Li Y., Zou D., et al. (2024). An overview of magnesium-based implants in orthopaedics and a prospect of its application in spine fusion. *Bioact. Mater.* **39**:456–478. DOI:10.1016/j.bioactmat.2024.04.026
21. Varghese C., Harrison E. M., O'Grady G., et al. (2024). Artificial intelligence in surgery. *Nat. Med.* **30**:1257–1268. DOI:10.1038/s41591-024-02970-3
22. Matsubara S. (2024). Medical artificial intelligence and human values. *N. Engl. J. Med.* **391**:1167. DOI:10.1056/NEJMc2408971
23. Hao M., Gong J., Zeng X., et al. (2024). Large-scale foundation model on single-cell transcriptomics. *Nat. Methods* **21**:1481–1491. DOI:10.1038/s41592-024-02305-7
24. Yang K. N., Yeo J. G., Kumar P., et al. (2023). Artificial intelligence and high-dimensional technologies in the theragnosis of systemic lupus erythematosus. *Lancet Rheumatol.* **5**:e151–e165. DOI:10.1016/S2665-9913(23)00010-3
25. Wojtara M., Rana E., Rahman T., et al. (2023). Artificial intelligence in rare disease diagnosis and treatment. *Clin. Transl. Sci.* **16**:2106–2111. DOI:10.1111/cts.13619
26. Sharif N., Gilani S. Z., Suter D., et al. (2023). Machine learning for abdominal aortic calcification assessment from bone density machine-derived lateral spine images. *EBioMedicine* **94**:104676. DOI:10.1016/j.ebiom.2023.104676
27. Nielsen R. L., Monfeuga T., Kitchen R. R., et al. (2024). Data-driven identification of predictive risk biomarkers for subgroups of osteoarthritis using interpretable machine learning. *Nat. Commun.* **15**:2817. DOI:10.1038/s41467-024-46663-4
28. Al Turkestani N., Li T., Bianchi J., et al. (2024). A comprehensive patient-specific prediction model for temporomandibular joint osteoarthritis progression. *Proc. Natl. Acad. Sci. U S A* **121**:e2306132121. DOI:10.1073/pnas.2306132121
29. Khanal S. K., Tarafdar A. and You S. (2023). Artificial intelligence and machine learning for smart bioprocesses. *Bioresour. Technol.* **375**:128826. DOI:10.1016/j.biortech.2023.128826
30. Zhang Y., Li J., Yang Q., et al. (2025). A clinically applicable AI system for detection and diagnosis of bone metastases using CT scans. *Nat. Commun.* **16**:4444. DOI:10.1038/s41467-025-59433-7
31. Tieu A., Kroen E., Kadish Y., et al. (2024). The role of artificial intelligence in the Identification and evaluation of bone fractures. *Bioengineering (Basel)* **11**. DOI:10.3390/bioengineering11040338
32. Papalia G. F., Brigato P., Sisco L., et al. (2024). Artificial intelligence in detection, management, and prognosis of bone metastasis: A systematic review. *Cancers (Basel)* **16**. DOI:10.3390/cancers16152700
33. Bowes M. A., Kacena K., Alabas O. A., et al. (2021). Machine-learning, MRI bone shape and important clinical outcomes in osteoarthritis: Data from the osteoarthritis initiative. *Ann. Rheum. Dis.* **80**:502–508. DOI:10.1136/annrheumdis-2020-217160
34. Yadalam P. K. and Ardila C. M. (2025). Deep neural networks based on sp7 protein sequence prediction in peri-Implant bone formation. *Int. J. Dent.* **2025**:7583275. DOI:10.1155/ijod/7583275
35. Fodeh S., Wang R., Murphy T. E., et al. (2024). BoneScore: A natural language processing algorithm to extract bone mineral density data from DXA scans. *Health Informatics J.* **30**:14604582241295930. DOI:10.1177/14604582241295930
36. Desai D., Kantliwala S. V., Vybhavi J., et al. (2024). Review of AlphaFold 3: Transformative advances in drug design and therapeutics. *Cureus* **16**:e63646. DOI:10.7759/cureus.63646
37. Xia J., Zhang Y. and Jiang B. (2025). The evolution of machine learning potentials for molecules, reactions and materials. *Chem. Soc. Rev.* **54**:4790–4821. DOI:10.1039/d5cs00104h
38. ordan M. I. and Mitchell T. M. (2015). Machine learning: Trends, perspectives, and prospects. *Science* **349**:255–260. DOI:10.1126/science.aaa8415
39. Mahesh B. (2020). Machine learning algorithms-a review. *Int. J. Sci. Res.* **9**:381–386. DOI: https://dx.doiorg/10.21275/SR22815163219
40. Nasteski V. (2017). An overview of the supervised machine learning methods. *Horizons. b* **4**:56. DOI:10.20544/HORIZONS.B.04.1.17.P05
41. Kokkoti S., Moustakidis S., Papageorgiou E., et al. (2020). Machine learning in knee osteoarthritis: A review. *Osteoarthr. Cartil. Open.* **2**:100069. DOI:10.1016/j.ocarto.2020.100069
42. Parisi L., RaviChandran N. and Lanzillotta M. (2023). Supervised machine learning for aiding diagnosis of knee osteoarthritis: A systematic review and meta-analysis. *TechRxiv.* **26**:2020. DOI:10.36227/techrxiv.13132931.v1
43. Pruneski J. A., Pareek A., Kunze K. N., et al. (2023). Supervised machine learning and associated algorithms: applications in orthopedic surgery. *Knee Surg. Sports Traumatol. Arthrosc.* **31**:1196–1202. DOI:10.1007/s00167-022-07181-2
44. Xuan A., Chen H., Chen T., et al. (2023). The application of machine learning in early diagnosis of osteoarthritis: A narrative review. *Ther. Adv. Musculoskelet. Dis.* **15**:1759720X231158198. DOI:10.1177/1759720X231158198
45. Castagno S., Gompels B., Strangmark E., et al. (2024). Understanding the role of machine learning in predicting progression of osteoarthritis. *Bone Joint J.* **106-B**:1216–1222. DOI:10.1302/0301-620X.106B11.BJJ-2024-0453.R1
46. Wang X., Liu T., Sheng Y., et al. (2025). Exploration and verification of circulating diagnostic biomarkers in osteoarthritis based on machine learning. *Front Genet* **16**:1513675. DOI:10.3389/fgene.2025.1513675
47. Wang H., Zhang Z., Cheng X., et al. (2024). Machine learning algorithm-based biomarker exploration and validation of mitochondria-related diagnostic genes in osteoarthritis. *PeerJ.* **12**:e17963. DOI:10.7717/peerj.17963
48. Anam M., Hussain M., Nadeem M. W., et al. (2021). Osteoporosis prediction for trabecular bone using machine learning: A review. *Computers, Materials & Continua.* **67**:89–105. DOI:10.32604/cmc.2021.013159
49. Smets J., Shevroja E., Hügler T., et al. (2020). Machine learning solutions for osteoporosis—a review. *J. Bone Miner. Res.* **36**: 833–851. DOI: 10.1002/jbmr.4292
50. Hugle M., Omoumi P., van Laar J. M., et al. (2020). Applied machine learning and artificial intelligence in rheumatology. *Rheumatol. Adv. Pract.* **4**:rkaa005. DOI:10.1093/rap/rkaa005
51. Shi Y., Zhou M., Chang C., et al. (2024). Advancing precision rheumatology: Applications of machine learning for rheumatoid arthritis management. *Front. Immunol.* **15**:1409555. DOI:10.3389/fimmu.2024.1409555
52. Chen Y., Liu H., Yu Q., et al. (2024). Entry point of machine learning in axial spondyloarthritis. *RMD Open* **10**:e003832. DOI:10.1136/rmdopen-2023-003832
53. Momtazmanesh S., Nowroozi A. and Rezaei N. (2022). Artificial intelligence in rheumatoid arthritis: Current status and future perspectives: A state-of-the-art review. *Rheumatol. Ther.* **9**:1249–1304. DOI:10.1007/s40744-022-00475-4
54. Rivellesse F., Surace A. E. A., Goldmann K., et al. (2022). Rituximab versus tocilizumab in rheumatoid arthritis: Synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial. *Nat. Med.* **28**:1256–1268. DOI:10.1038/s41591-022-01789-0
55. Guo J. L., Januszyk M. and Longaker M. T. (2023). Machine learning in tissue engineering. *Tissue Eng. Part A* **29**:2–19. DOI:10.1089/ten.tea.2022.012
56. Kolomenskaya E., Butova V., Poltavskiy A., et al. (2023). Application of artificial intelligence at all stages of bone tissue engineering. *Biomedicine* **12**:76. DOI:10.3390/biomedicine12010076
57. Naeem S., Ali A., Anam S., et al. (2023). An unsupervised machine learning algorithms: Comprehensive review. *Int. J. Com. Dig. Sys.* **13**No.1. DOI:10.12785/ijcds/130172
58. Kong S. H. and Shin C. S. (2021). Applications of machine learning in bone and mineral research. *Endocrinol. Metab.* **36**:928–937. DOI:10.3803/EnM.2021.1111
59. Trezza A., Visibelli A., Roncaglia B., et al. (2024). Unsupervised learning in precision medicine: Unlocking personalized healthcare through AI. *Appl. Sci.* **14**:9305. DOI:10.3390/app14209305
60. Obeagu E. I., Ezeanya C. U., Ogenyi F. C., et al. (2025). Big data analytics and machine learning in hematology: Transformative insights, applications and challenges. *Medicine* **104**:e41766. DOI:10.1097/MD.00000000000041766
61. Li Q., Wang J. and Zhao C. (2024). From genomics to metabolomics: Molecular insights into osteoporosis for enhanced diagnostic and therapeutic approaches. *Biomedicine* **12**:2389. DOI:10.3390/biomedicine12102389
62. Yang J. and Wu J. (2023). Discovery of potential biomarkers for osteoporosis diagnosis by individual omics and multi-omics technologies. *Expert Rev. Mol. Diagn.* **23**:505–520. DOI:10.1080/14737159.2023.2208750
63. Yang T. L., Shen H., Liu A., et al. (2020). A road map for understanding molecular and genetic determinants of osteoporosis. *Nat. Rev. Endocrinol.* **16**:91–103. DOI:10.1038/s41574-019-0282-7
64. Hansen M. S., Madsen K., Price M., et al. (2024). Transcriptional reprogramming during human osteoclast differentiation identifies regulators of osteoclast activity. *Bone Res.* **12**:5. DOI:10.1038/s41413-023-00312-6
65. Gaweda A. E., Lederer E. D. and Brier M. E. (2022). Use of artificial intelligence to identify new mechanisms and approaches to therapy of bone disorders associated with chronic kidney disease. *Front. Med.* **9**:807994. DOI:10.3389/fmed.2022.807994
66. Wang H., Joshi P., Hong S. H., et al. (2022). Predicting the targets of IRF8 and NFATc1 during osteoclast differentiation using the machine learning method framework cTAP. *BMC Genomics* **23**:14. DOI:10.1186/s12864-021-08159-z
67. Liang W., Wei T., Hu L., et al. (2024). An integrated multi-omics analysis reveals osteokines involved in global regulation. *Cell Metab.* **36**:1144–1163 e1147. DOI:10.1016/j.cmet.2024.03.006
68. Yu C., Liu J., Nemati S., et al. (2021). Reinforcement learning in healthcare: A survey. *ACM Comput. Surv.* **55**:1–36. DOI:10.1145/347760
69. Thompson E., Tashman A. and Scialla J. J. (2025). Chronic kidney disease-mineral and bone disorder management in 4D: The case for dynamic treatment regime methods to optimize care. *Curr.Osteoporos. Rep.* **23**:16. DOI:10.1007/s11914-025-00911-8
70. Mackay B. S., Marshall K., Grant-Jacob J. A., et al. (2021). The future of bone regeneration: Integrating AI into tissue engineering. *Biomed. Phys. Eng. Express.* **7**:052002. DOI:10.1088/2057-1976/ac154f
71. Hoveidae A. H., Sadat-Shojai M., Nabavizadeh S. S., et al. (2025). Clinical challenges in bone tissue engineering - A narrative review. *Bone* **192**:117363. DOI:10.1016/j.bone.2024.117363
72. Aslam Khan M. U., Aslam M. A., Bin Abdullah M. F., et al. (2024). Current perspectives of protein in bone tissue engineering: Bone structure, ideal scaffolds, fabrication techniques, applications, scopes, and future advances. *ACS Appl. Bio. Mater.* **7**:5082–5106. DOI:10.1021/acsabm.4c00362
73. Mohammed A. and Kora R. (2023). A comprehensive review on ensemble deep learning: Opportunities and challenges. *J. King Saud Univ. Comput. Inf. Sci.*

- 35:757–774. DOI:10.1016/j.jksuci.2023.01.014
74. Sharifani K. and Amini M. (2023). Machine learning and deep learning: A review of methods and applications. *World Inf. Technol. Eng. J.* **10**:3897–3904. DOI:10.2139/ssrn.4458723
 75. Sistaninejad B., Rasi H. and Nayeri P. (2023). A Review paper about deep learning for medical image analysis. *Comput. Math. Methods Med.* **2023**:7091301. DOI:10.1155/2023/7091301
 76. Wang Y., Lin Q., Zhao S., et al. (2024). Automated diagnosis of bone metastasis by classifying bone scintigrams using a self-defined deep learning model. *Curr. Med. Imaging* **20**:e15734056281578. DOI:10.2174/0115734056281578231212104108
 77. Shen S. C., Pena Fernandez M., Tozzi G., et al. (2021). Deep learning approach to assess damage mechanics of bone tissue. *J. Mech. Behav. Biomed. Mater.* **123**:104761. DOI:10.1016/j.jmbbm.2021.104761
 78. van Eekelen L., Pinckaers H., van den Brand M., et al. (2022). Using deep learning for quantification of cellularity and cell lineages in bone marrow biopsies and comparison to normal age-related variation. *Pathology* **54**:318–327. DOI:10.1016/j.pathol.2021.07.011
 79. Cao R., Nelson S. D., Davis S., et al. (2023). Label-free intraoperative histology of bone tissue via deep-learning-assisted ultraviolet photoacoustic microscopy. *Nat. Biomed. Eng.* **7**:124–134. DOI:10.1038/s41551-022-00940-z
 80. He Y., Pan I., Bao B., et al. (2020). Deep learning-based classification of primary bone tumors on radiographs: A preliminary study. *EBioMedicine* **62**:103121. DOI:10.1016/j.ebiom.2020.103121
 81. Tao Y., Huang X., Tan Y., et al. (2021). Qualitative histopathological classification of primary bone tumors using deep learning: A pilot study. *Front. Oncol.* **11**:735739. DOI:10.3389/fonc.2021.735739
 82. Cohen-Karlik E., Awida Z., Bergman A., et al. (2021). Quantification of osteoclasts in culture, powered by machine learning. *Front. Cell Dev. Biol.* **9**:674710. DOI:10.3389/fcell.2021.674710
 83. Shiffman S., Rios Piedra E. A., Adediji A. O., et al. (2023). Analysis of cellularity in H&E-stained rat bone marrow tissue via deep learning. *J. Pathol. Inform.* **14**:100333. DOI:10.1016/j.jpi.2023.100333
 84. Irshaid L., Bleiberg J., Weinberger E., et al. (2022). Histopathologic and machine deep learning criteria to predict lymphoma transformation in bone marrow biopsies. *Arch. Pathol. Lab. Med.* **146**:182–193. DOI:10.5858/arpa.2020-0510-OA
 85. Chen D., Sarkar S., Candia J., et al. (2016). Machine learning based methodology to identify cell shape phenotypes associated with microenvironmental cues. *Biomaterials* **104**:104–118. DOI:10.1016/j.biomaterials.2016.06.040
 86. Krichevsky S., Ouseph M. M., Zhang Y., et al. (2023). A deep learning-based pathomics methodology for quantifying and characterizing nucleated cells in the bone marrow microenvironment. *Blood* **142**:2294. DOI:10.1182/blood-2023-191272
 87. Coudray N., Occidental M. A., Mantilla J. G., et al. (2025). Quantitative and morphology-based deep convolutional neural network approaches for osteosarcoma survival prediction in the neoadjuvant and metastatic settings. *Clin. Cancer. Res.* **31**:365–375. DOI:10.1158/1078-0432.CCR-24-2599
 88. Lu L., Ono N. and Welch J. D. (2025). Linking transcriptome and morphology in bone cells at cellular resolution with generative AI. *J. Bone Miner. Res.* **40**:20–26. DOI:10.1093/jbmr/zjae151
 89. Jothi R. and Jayanthi K. (2024). A deep multi-filtering network based on dilated mask RCNN framework with self-attention RNN model for segmenting and classifying bone fracture. *Multimed. Tools Appl.* **84**:29815–29841. DOI:10.1007/s11042-024-20245-4
 90. Deshmukh S. and Khaparde A. (2022). Faster region-convolutional neural network oriented feature learning with optimal trained recurrent neural network for bone age assessment for pediatrics. *Biomed. Signal. Process. Control.* **71**:103016. DOI:10.1016/j.bspc.2021.103016
 91. Chen H., Dreizin D., Gomez C., et al. (2025). Interpretable severity scoring of pelvic trauma through automated fracture detection and bayesian inference. *IEEE Trans. Med. Imaging* **44**:130–141. DOI:10.1109/TMI.2024.3428836
 92. Thomsen F. S. L., Iarussi E., Borggreve J., et al. (2023). Bone-GAN: Generation of virtual bone microstructure of high resolution peripheral quantitative computed tomography. *Med. Phys.* **50**:6943–6954. DOI:10.1002/mp.16482
 93. Ali M., Ali M., Hussain M., et al. (2024). Generative adversarial networks (gans) for medical image processing: Recent advancements. *Arch. Comput. Methods Eng.* **32**:1185–1198. DOI:10.1007/s11831-024-10174-8
 94. Ahmad Z., Jaffri Z. u. A., Chen M., et al. (2024). Understanding GANs: Fundamentals, variants, training challenges, applications, and open problems. *Multimed. Tools. Appl.* **84**:10347–10423. DOI:10.1007/s11042-024-19361-y
 95. Jin L., Tang Y., Coole J. B., et al. (2024). DeepDOF-SE: Affordable deep-learning microscopy platform for slide-free histology. *Nat. Commun.* **15**:2935. DOI:10.1038/s41467-024-47065-2
 96. Mao X., Hui Q., Zhu S., et al. (2023). Automated skeletal bone age assessment with two-stage convolutional transformer network based on X-ray images. *Diagnostics* **13**:1837. DOI:10.3390/diagnostics13111837
 97. Liu J., Wang H., Shan X., et al. (2024). Hybrid transformer convolutional neural network-based radiomics models for osteoporosis screening in routine CT. *BMC Med. Imaging* **24**:62. DOI:10.1186/s12880-024-01240-5
 98. Li W., Zou X., Zhang J., et al. (2025). Predicting lung cancer bone metastasis using CT and pathological imaging with a Swin Transformer model. *J. Bone Oncol.* **52**:100681. DOI:10.1016/j.jbo.2025.100681
 99. Casey A., Davidson E., Poon M., et al. (2021). A systematic review of natural language processing applied to radiology reports. *BMC Med. Inform. Decis. Mak.* **21**:179. DOI:10.1186/s12911-021-01533-7
 100. AlShehri Y., Sidhu A., Lakshmanan L. V. S., et al. (2024). Applications of natural language processing for automated clinical data analysis in orthopaedics. *J. Am. Acad. Orthop. Surg.* **32**:439–446. DOI:10.5435/JAAOS-D-23-00839
 101. Cai J., Han R., Li J., et al. (2024). Exploring mechanobiology network of bone and dental tissue based on Natural Language Processing. *J. Biomech.* **174**:112271. DOI:10.1016/j.jbiomech.2024.112271
 102. Raza S., Garg M., Reji D. J., et al. (2024). Nbias: A natural language processing framework for BIAS identification in text. *Expert Syst. Appl.* **237**:121542. DOI:10.1016/j.eswa.2023.121542
 103. Maree M., Al-Qasem R. and Tantour B. (2024). Transforming legal text interactions: Leveraging natural language processing and large language models for legal support in Palestinian cooperatives. *Int. J. Inf. Technol.* **16**:551–558. DOI:10.1007/s41870-023-01584-1
 104. Yadalam P. K., Pawar A. R., Natarajan P. M., et al. (2025). A novel dual embedding few-shot learning approach for classifying bone loss using orthopantomogram radiographic notes. *Head Face Med.* **21**:49. DOI:10.1186/s13005-025-00528-3
 105. Gill J. K., Chetty M., Lim S., et al. (2025). BioBERT based text mining for incorporating prior knowledge in the inference of genetic network models. *Comput. Biol. Med.* **186**:109623. DOI:10.1016/j.compbimed.2024.109623
 106. Cung M., Sosa B., Yang H. S., et al. (2024). The performance of artificial intelligence chatbot large language models to address skeletal biology and bone health queries. *J. Bone Miner. Res.* **39**:106–115. DOI:10.1093/jbmr/zjad007
 107. Chen Y., Chen L., Wu J., et al. (2025). Throw out an oligopeptide to catch a protein: Deep learning and natural language processing-screened tripeptide PSP promotes Osteoclast-mediated vascularized bone regeneration. *Bioact. Mater.* **46**:37–54. DOI:10.1016/j.bioactmat.2024.11.011
 108. Gill S. S., Golec M., Hu J., et al. (2025). Edge AI: A taxonomy, systematic review and future directions. *Cluster Comput.* **28**:1–53. DOI:10.1007/s10586-024-04686-y
 109. Razavi-Termeh S. V., Sadeghi-Niaraki A., Ali F., et al. (2025). Cutting-Edge strategies for absence data identification in natural hazards: Leveraging voronoi-entropy in flood susceptibility mapping with advanced AI techniques. *J. Hyd.* **648**:132337. DOI:10.1016/j.jhydrol.2024.132337
 110. Dessay M., Couture E., Maaroufi H., et al. (2022). Attenuated clinical and osteoclastic phenotypes of Paget's disease of bone linked to the p.Pro392Leu/SQSTM1 mutation by a rare variant in the DOCK6 gene. *BMC Med. Genomics* **15**:41. DOI:10.1186/s12920-022-01198-9.
 111. Huo K., Yang Y., Yang T., et al. (2024). Identification of drug targets and agents associated with ferroptosis-related osteoporosis through integrated network pharmacology and molecular docking technology. *Curr. Pharm. Des.* **30**:1103–1114. DOI:10.2174/0113816128288225240318045050
 112. Xu J., Wen X., Sun L., et al. (2025). Large model era: Deep learning in osteoporosis drug discovery. *J. Chem. Inf. Model.* **65**:2232–2244. DOI:10.1021/acs.jcim.4c02264
 113. Zeng P., Huang H. and Li D. (2024). Combining bioinformatics, network pharmacology, and artificial intelligence to predict the mechanism of resveratrol in the treatment of rheumatoid arthritis. *Heliyon* **10**:e37371. DOI:10.1016/j.heliyon.2024.e37371
 114. Zhong J., Hu X., Dong J., et al. (2024). Bisphosphonates activated keratin assembled nanoparticle targeting bone fracture for enhanced immunomodulatory and osteoinductivity. *Chem. Eng. J.* **489**:151265. DOI:10.1016/j.cej.2024.151265
 115. Lee S. B., Abdal Dayem A., Kmiecik S., et al. (2024). Efficient improvement of the proliferation, differentiation, and anti-arthritis capacity of mesenchymal stem cells by simply culturing on the immobilized FGF2 derived peptide, 44-ERGVSIVKGV-53. *J. Adv. Res.* **62**:119–141. DOI:10.1016/j.jare.2023.09.041
 116. Kanemaru N., Yasaka K., Fujita N., et al. (2025). The fine-tuned large language model for extracting the progressive bone metastasis from unstructured radiology reports. *J. Imaging Inform. Med.* **38**:865–872. DOI:10.1007/s10278-024-01242-3
 117. kumar Yadalam P. (2023). Pre-trained language models based sequence prediction of wnt-sclerostin protein sequences in alveolar bone formation. *J. Pioneering Med. Sci.* **12**:55–60. DOI:10.61091/jpms202312311
 118. Chen Y. Q., Yu T., Song Z. Q., et al. (2025). Application of large language models in drug-induced osteotoxicity prediction. *J. Chem. Inf. Model.* **65**:3370–3379. DOI:10.1021/acs.jcim.5c00275
 119. Arbeeve L., Minnig M. C., Yates K. A., et al. (2023). Machine learning approaches to the prediction of osteoarthritis phenotypes and outcomes. *Curr. Rheumatol. Rep.* **25**:213–225. DOI:10.1007/s11926-023-01114-9
 120. Wang R., Wang Y., Niu Y., et al. (2023). Deep learning-predicted dihydroartemisinin rescues osteoporosis by maintaining mesenchymal stem cell stemness through activating histone 3 lys 9 acetylation. *ACS. Cent. Sci.* **9**:1927–1943. DOI:10.1021/acscentsci.3c00794
 121. Wang P. and Ho D. (2023). Deep learning and drug discovery for healthy aging. *ACS. Cent. Sci.* **9**:1860–1863. DOI:10.1021/acscentsci.3c01212
 122. Cui H., Wang C., Maan H., et al. (2024). scGPT: Toward building a foundation model for single-cell multi-omics using generative AI. *Nat. Methods* **21**:1470–1480. DOI:10.

- 1038/s41592-024-02201-0
123. Vickram A. S., Infant S. S., Manikandan S., et al. (2025). 3D bio-printed scaffolds and smart implants: evaluating functional performance in animal surgery models. *Ann. Med. Surg.* **87**:3618–3634. DOI:10.1097/MS9.0000000000003333
124. Bai L., Zhou D., Li G., et al. (2024). Engineering bone/cartilage organoids: Strategy, progress, and application. *Bone Res.* **12**:66. DOI:10.1038/s41413-024-00376-y
125. van Leeuwen K. G., Schalekamp S., Rutten M., et al. (2024). Comparison of commercial AI software performance for aadiograph lung nodule detection and bone age prediction. *Radiology* **310**:e230981. DOI:10.1148/radiol.230981
126. Jeong S., Han K., Kang Y., et al. (2025). The impact of artificial intelligence on radiologists' reading time in bone age radiograph assessment: A preliminary retrospective observational study. *J. Imaging Inform. Med.* **38**:1915–1923. DOI:10.1007/s10278-024-01323-3
127. Guo H., Li Q., Zreikat H., et al. (2026). Emerging technologies for personalised oro-maxillofacial bone regeneration: Design strategies and fabrication techniques. *Biomaterials* **326**:123709. DOI:10.1016/j.biomaterials.2025.123709
128. Yan M., Liang T., Zhao H., et al. (2024). Model properties and clinical application in the finite element analysis of knee joint: A review. *Orthop. Surg.* **16**:289–302. DOI:10.1111/os.13980
129. Ma X., Xu J., Fu J., et al. (2025). A geometric deep learning model for real-time prediction of knee joint biomechanics under meniscal extrusion. *Ann. Biomed. Eng.* **53**:2503–2512. DOI:10.1007/s10439-025-03798-9
130. Malachi I. O., Olawumi A. O. and Oladapo B. I. (2025). AI-driven optimization of spinal implant design using parametric modelling. *Colloids Surf. B. Biointerfaces* **253**:114753. DOI:10.1016/j.colsurfb.2025.114753
131. Luo M., Yang W., Bai L., et al. (2024). Artificial intelligence for life sciences: A comprehensive guide and future trends. *Innov. Life* **2**:100105. DOI:10.59717/j.xinn-life.2024.100105
132. Enshaei N. and Naderkhani F. (2024). The role of data quality for reliable AI performance in medical applications. *IEEE Reliability Magazine*. 1:24–28. DOI:10.1109/MRL.2024.3430192
133. Esmaeilzadeh P. (2024). Challenges and strategies for wide-scale artificial intelligence (AI) deployment in healthcare practices: A perspective for healthcare organizations. *Artif. Intell. Med.* **151**:102861. DOI:10.1016/j.artmed.2024.102861
134. Tripathi S., Gabriel K., Dheer S., et al. (2023). Understanding biases and disparities in radiology AI datasets: A review. *J. Am. Coll. Radiol.* **20**:836–841. DOI:10.1016/j.jacr.2023.06.015
135. Siddiqui I. A., Littlefield N., Carlson L. A., et al. (2024). Fair AI-powered orthopedic image segmentation: Addressing bias and promoting equitable healthcare. *Sci. Rep.* **14**:16105. DOI:10.1038/s41598-024-66873-6
136. Asim M. N., Ibrahim M. A., Asif T., et al. (2025). RNA sequence analysis landscape: A comprehensive review of task types, databases, datasets, word embedding methods, and language models. *Heliyon* **11**:e41488. DOI:10.1016/j.heliyon.2024.e41488
137. Tong L., van Wijnen A. J., Wang H., et al. (2024). Advancing bone biology: The mutual promotion of biology and pioneering technologies. *Innov. Life* **2**:100078. DOI:10.59717/j.xinn-life.2024.100078
138. Cook C. V., Lighty A. M., Smith B. J., et al. (2024). A review of mathematical modeling of bone remodeling from a systems biology perspective. *Front. Syst. Biol.* **4**:1368555. DOI:10.3389/fsysb.2024.1368555
139. Papalia G. F., Brigato P., Sisca L., et al. (2024). Artificial intelligence in detection, management, and prognosis of bone metastasis: A systematic review. *Cancers* **16**:2700. DOI:10.3390/cancers16152700
140. Panahi O. and Farrokhi S. (2025). Ethical considerations of AI in implant dentistry: A clinical perspective. *J. Clin. Rev. Case. Rep.* **10**:01–05. DOI:10.33140/JCRC20250105
141. Shi M., Gong Z., Zeng P., et al. (2024). Multi-quantifying maxillofacial traits via a demographic parity-based AI model. *BME Front* **5**:0054. DOI:10.34133/bmef.0054
142. Khosravi B., Rouzrokh P., Erickson B. J., et al. (2024). Analyzing racial differences in imaging joint replacement registries using generative artificial intelligence: Advancing orthopaedic data equity. *Arthroplast. Today* **29**:101503. DOI:10.1016/j.artd.2024.101503
143. Toy T. (2024). Transparency in AI. *AI & SOCIETY* **39**:2841–2851. DOI:10.1007/s00146-023-01786-y
144. Lili S., Xiujun Y., Guangjun Y., et al. (2020). Technical realization of integrating bone age artificial intelligence assessment system with hospital RIS-PACS network. *Chin. J. Med. Instrum.* **44**:415–419. DOI:10.3969/j.issn.1671-7104.2020.05.008
145. Kutbi M. (2024). Artificial intelligence-based applications for bone fracture detection using medical images: A systematic review. *Diagnostics* **14**:1879. DOI:10.3390/diagnostics14171879
146. Russell R. G., Lovett Novak L., Patel M., et al. (2023). Competencies for the use of artificial intelligence-based tools by health care professionals. *Acad. Med.* **98**:348–356. DOI:10.1097/ACM.0000000000004963
147. Arora A., Alderman J. E., Palmer J., et al. (2023). The value of standards for health datasets in artificial intelligence-based applications. *Nat. Med.* **29**:2929–2938. DOI:10.1038/s41591-023-02608-w
148. Tong L., Shi W., Isgut M., et al. (2023). Integrating multi-omics data with EHR for precision medicine using advanced artificial intelligence. *IEEE Rev. Biomed. Eng.* **17**:80–97. DOI:10.1109/RBME.2023.3324264
149. Yetgin A. (2025). Revolutionizing multi - omics analysis with artificial intelligence and data processing. *Quant. Biol.* **13**:e70002. DOI:10.1002/qub2.70002
150. Prem E. (2023). From ethical AI frameworks to tools: A review of approaches. *AI and Ethics* **3**:699–716. DOI:10.1007/s43681-023-00258-9
151. Bai L., Wu Y., Li G., et al. (2024). AI-enabled organoids: Construction, analysis, and application. *Bioact. Mater.* **31**:525–548. DOI:10.1016/j.bioactmat.2023.09.005
152. Zhou L., Huang J., Li C., et al. (2025). Organoids and organs-on-chips: Recent advances, applications in drug development, and regulatory challenges. *Med.* **6**:100667. DOI:10.1016/j.medj.2025.100667
153. Tanaka M. (2025). From Serendipity to precision: Integrating AI, multi-omics, and human-specific models for personalized neuropsychiatric care. *Biomedicines* **13**:167. DOI:10.3390/biomedicines13010167
154. Fan J., Xu J., Wen X., et al. (2024). The Future of bone regeneration: Artificial intelligence in biomaterials discovery. *Mater. Today Commun.* **40**:109982. DOI:https://doi.org/10.1016/j.mtcomm.2024.109982
155. Vaishya R., Dhali S. and Vaish A. (2024). Artificial intelligence (AI): A potential game changer in regenerative orthopedics-a scoping review. *Indian J. Orthop.* **58**:1362–1374. DOI:10.1007/s43465-024-01189-1

FUNDING AND ACKNOWLEDGMENTS

This work was supported by grants from Natural Science Foundation of Guangdong Province for Distinguished Young Scholars(2022B1515020044) and the National Natural Science Foundation of China (Grant No. 82372358)). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

D.X. conceived the manuscript. D.Z. provide critical revision for intellectual content and structure. C.L. wrote the manuscript from the comments of Z.Z., N.Z., A.Z., S.Y., L.L. and R.F. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare that they have no conflicts of interest.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Not applicable.