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Transforming osteosarcoma care: from historical milestones to precision medicine advances

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Osteosarcoma (OS), one of the earliest recognized cancers in humans, is a rare yet significant malignant bone tumor, diagnosed in 2–6 cases per million annually [1]. It predominantly affects adolescents and young adults, with a second peak in incidence occurring around age 60. Pediatric osteosarcoma typically arises in areas of rapid bone growth, such as the knee and shoulder, and often presents persistent bone pain and progressive mass. While osteosarcoma often has a classic radiographic appearance, diagnosis is ultimately confirmed histologically.

The primary treatment for osteosarcoma is wide surgical resection combined with multi-agent cytotoxic chemotherapy. Historically, amputation was the standard of care, but limb-sparing surgery has been shown to yield statistically equivalent outcomes and has become the preferred strategy in most cases. Limb salvage is occasionally not feasible or is not the patient-preferred approach, though these instances are infrequent. Neoadjuvant chemotherapy, particularly with the MAP regimen (methotrexate, doxorubicin, and cisplatin), allows for the assessment of tumor necrosis, a proxy for chemotherapy efficacy. However, the EURAMOS-1 study demonstrated no value in altering the chemotherapeutic strategy based on poor chemotherapy response, with necrosis rate offering only prognostic value [2]. Despite a five-year survival rate of 60% for localized cases, the prognosis for metastatic disease, especially when spread to the lungs, remains poor, with survival rates dropping to less than 20% [3]. Although survival rates have not significantly improved in the past four decades, advancements in genetic characterization and clinical trial strategies offer new hope.

Precision medicine has started to transform medicine in general, leveraging advances in genomic sequencing, molecular biology, bioinformatics, artificial intelligence (AI), radiomics, reality-enhanced surgery, additive manufacturing-assisted surgical navigation, and personalized implants. These innovations have enhanced diagnostics, enabled targeted therapies, and provided more personalized treatment plans and precise follow-up care. However, widespread adoption faces challenges that include logistical complexities, ethical considerations, and high costs.

This paper reviews current advancements in precision medicine for osteosarcoma, highlighting recent insights into oncogenesis from genomic profiling, evolving diagnostic techniques, targeted treatments, and innovative surgical interventions. Additionally, it addresses the challenges and anticipates future directions in this rapidly evolving field (Fig. 1).

Genetic and molecular profiling: therapeutic targets in precision medicine. In the 1970s, systemic chemotherapy significantly improved overall survival for osteosarcoma patients. However, progress has since plateaued, with survival rates remaining stagnant for the past four decades. This stagnation highlights the limitations of current cytotoxic regimens and the need for more efficient, less toxic therapies targeting novel osteosarcoma-specific agents. Fortunately, advancements in understanding the genetic basis of osteosarcoma and the development of precision medicine approaches are transforming the treatment landscape for this disease (Text S1 online).

Osteosarcoma has long been associated with both a heavy mutational burden and myriad mutational variation, most commonly involving TP53 and RB1. Conditions like Li-Fraumeni syndrome (*TP53* mutation) and hereditary retinoblastoma (*RB1* mutation) increase the risk of developing other tumors, including osteosarcomas. New sequencing techniques have revealed that osteosarcoma genomes are highly chaotic, characterized by widespread chromothripsis (extensive genomic rearrangements), kataegis (localized hypermutation), and breakage-fusion-bridge cycles (unstable chromosomes) [4].

Germline mutations are common in osteosarcoma. Studies indicate that approximately one-quarter of osteosarcoma patients carry pathogenic germline mutations in cancer-predisposing genes, with *TP53* mutations being the most frequent, followed by *RB1*. Additionally, rare pathogenic variants are often found in DNA repair genes (e.g., *BRCA1, BRCA2, BRIP1, CHEK2, RAD51, ATM, WRN*, and *RECQL4*), suggesting a genetic predisposition to genomic instability and homologous recombination deficiency (HRD) [5].

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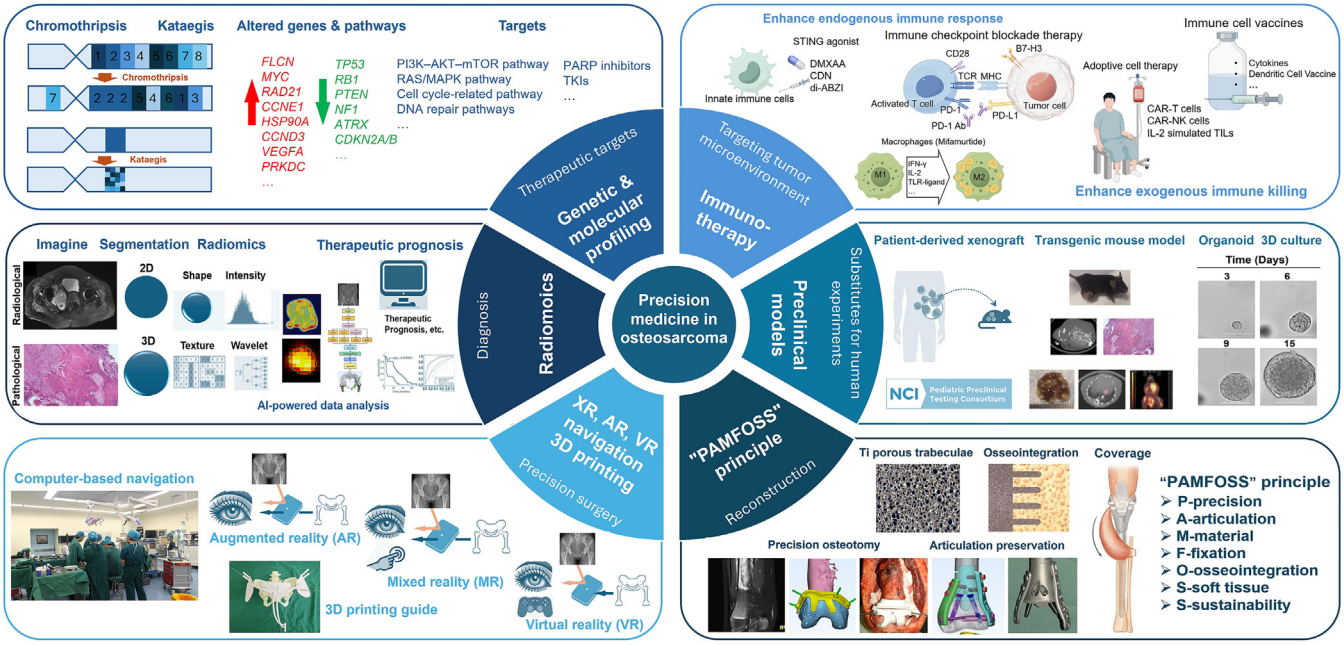


Fig. 1. Overview of the precision medicine in osteosarcoma (partly created by Figdraw).

Somatic mutations, significant genetic variability, and extensive copy-number aberrations are hallmarks of osteosarcoma. These genetic features often result in a *TP53* null state in most tumors, further enhanced by *MDM2* amplification. Loss-of-function mutations in the cell-cycle regulator *RB1* are also common. Combined with mutations in *CDKN2A/B*, these changes contribute to the loss of normal cell-cycle control and the accumulation of DNA damage. Integrated expression data show frequent copy number losses of tumor suppressors like *PTEN*, resulting in the activation of the PI3K-AKT-mTOR pathways. While direct mutations in RAS genes are less common, the RAS/MAPK pathway can be activated through upstream alterations. Additionally, amplifications of oncogenes such as *ATRX, MYC, VEGFA, IGF1R, TGFBR2*, and *CCNE1* have been reported in osteosarcoma, leading to abnormal expression of the IGF, VEGF, PDGF, KIT, and MYC pathways. Many of these pathways offer targets using existing therapeutic agents [6].

These genetic complexities have prompted extensive investigation to identify actionable targets within tumorigenic pathways. While there is no osteosarcoma-specific targeted agent yet, some pathway regulators have shown value and have entered clinical trials. Several pathways have been identified for potential therapeutic regulation. Cell cycle-related pathway regulators (e.g., CDK2, CDK4/6, Aurora kinase) are being explored, and preclinical studies suggest these inhibitors can enhance the efficacy of DNA-damaging agents and other chemotherapies. The impaired DNA repair pathways (e.g., WEE1, PARP) and HRD signature suggest that PARP inhibitors like Olaparib could be applicable. While direct mutations in kinases are less common, the overexpression or amplification of kinase genes can be more frequent. Pan-tyrosine kinase inhibitors (TKIs), such as Regorafenib, Cabozantinib, and Pazopanib, have shown potential and tolerable toxicity profiles in patients with relapsed and unresectable osteosarcoma, demonstrating progression-free survival benefits in clinical trials [7].

Despite these advances, current treatments generally only slow or delay disease progression and often do not significantly improve survival outcomes. Therefore, identifying vulnerable relevant genetic events and drivers remains crucial for developing more effective strategies. Large, gene-dense regions often contain multiple important drivers, requiring accurate assessment through the identification of both small mutations and structural rearrangements. Third-generation, long-read genetic sequencing technologies offer significant advancements in mapping complex genomes that traditional methods often fail to capture. Single-cell sequencing enhances our understanding of tumor heterogeneity and metastasis. Additionally, a multi-omics approach holds great potential for achieving a holistic understanding of cancer and enabling personalized treatment by providing a more comprehensive molecular picture (Text S2 online). Besides, high-throughput technologies like CRISPR-Cas9 knockout libraries might offer the ability to prioritize targets beyond gene amplification, identifying drug targets influenced by epigenetic processes. The future of osteosarcoma treatment lies in sophisticated genetic assessments and innovative clinical trial strategies. Testing targeted therapy in identified patient subgroups based on genetic drivers or other biological factors could be the most efficient way to identify novel agents.

Immunotherapy: tumor microenvironment in precision medicine. Immunotherapy nowadays is appealing in many cancers because it leverages the body's own immune system to specifically target and destroy cancer cells, offering a potentially more precise treatment with fewer side effects compared to traditional cytotoxic therapies [8]. It holds promise for long-term remission by enabling the immune system to remember and continuously fight cancer cells, and it offers the potential to impact tumor growth, independent of any specific genomic complexity. Osteosarcomas exhibit unique and diverse immune profiles, ranging from "hot" tumors with substantial immune cell infiltration to "cold" tumors with minimal immune presence. Additionally, osteosarcoma shows a modest rate of neoantigen-generating missense mutations and occasionally expresses immunotherapeutic targets such as cancer-testis antigens (Text S3 online).

Current immunotherapy strategies involve either activating the innate immune system or enhancing exogenous immune killing. Activation of the innate immune system recruits macrophages, monocytes, and dendritic cells, leading to the production of anti-tumor cytokines and chemokines, thereby enhancing the immune response. One example in osteosarcoma, postoperative infections seem to be associated with improved overall survival, which led to the development of immune regulator mifamurtide (muramyl

tripeptide). It was evaluated in several randomized clinical trials and showed potential in improving survival. While it remains controversial, the treatment was deemed valuable enough to gain approval in some countries.

Antibody-based immune checkpoint inhibitors, which release the inhibition of an immune response to allow immune control of tumors, have shown efficacy in many solid tumors. However, studies of the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab demonstrated minimal activity in recurrent osteosarcoma. Given the current findings regarding genomic complexity, selecting the subgroup of patients potentially sensitive to immune checkpoint inhibitors (ICIs) is crucial for future trials (Text S4 online).

T cells modified to express chimeric antigen receptors (CAR-T cells) have demonstrated efficacy in hematologic cancers. However, their performance in osteosarcoma has been disappointing due to tumor heterogeneity and the lack of efficient targets. Another potential approach is the use of antibody-drug conjugates, which also require targeting tumor-specific surface molecules. Recently reported potential targets, such as B7H3, GD2, and cell-surface protein LRRC15, are awaiting further validation (Text S4 online).

To further enhance the exogenous immune killing, adoptive cell therapy (ACT), which involves extracting tumor-infiltrating lymphocytes (TILs) from a patient's tumor and expanding them with interleukin-2 (IL-2) stimulation, shows promise. ACT offers advantages such as T-cell receptor (TCR) diversification, strong tumor targeting, and low off-target toxicity, making it potentially suitable for osteosarcoma. However, challenges remain in the TIL expansion protocol and the efficacy of IL-2 stimulation. A receptor-biased IL-2 design has been proven to consistently stimulate TILs without causing exhaustion, presenting a potential strategy for immune therapy in osteosarcoma (unpublished data). In general, while many approaches have been studied to date, very few have proven to be of clinical utility, illustrating the challenge and ongoing need for effective immunotherapy treatments in osteosarcoma.

Preclinical models: substitutes for precision medicine experiments. Preclinical models have been used for decades as a bridge between *in vitro* research and clinical trials. They remain essential for advancing osteosarcoma research by providing platforms to gain improved insight into disease biology and test new therapies. Patient-derived xenograft (PDX) models, utilized by the Pediatric Preclinical Testing Consortium (PPTC) and other teams, replicate the molecular alterations and heterogeneity observed in human osteosarcomas, making them valuable for drug testing. However, since PDX models use immunodeficient mice, they do not entirely replicate the human condition. These immune deficient models make it challenging to study the impact of host immunity on osteosarcoma or the effect of immunotherapies on osteosarcoma.

Humanized mice, developed by implanting human hematopoietic stem cells into immunodeficient mice, create a human-like immune system, useful for evaluating immune responses and testing immunotherapies. Despite their advantages, high costs, experimental complexity, and mixed hematopoietic stem cell donors currently limit their application. Additionally, transgenic mouse models, achieved by knocking out tumor suppressors like *Tp53* and *Rb1* in the mesenchymal stem cell to osteoblast differentiation lineages, result in almost full penetrance of osteosarcoma [9]. Canine models are also valuable due to the relatively high frequency of developing osteosarcoma naturally. However, disadvantages also include high costs, ethical concerns, and the complexities of involving pet owners.

In vitro three-dimensional (3D) culturing, using patient-derived tumor and microenvironment components, is emerging as a convenient alternative to animal models. Unlike traditional two-dimensional (2D) adherent cultures, 3D cultures use a scaffold-like structure provided by matrix gel or microprinting, exhibiting a more natural morphology and organization similar to what is found *in vivo*. This spatial arrangement allows for proper cell polarity, differentiation, and interaction with the extracellular matrix, which are crucial for maintaining cellular functions and secretions. These cultures are also suitable for high-throughput drug screening. One example is patient-derived organoids (PDOs), which have been successfully developed using various carcinomas. However, developing organoids for osteosarcoma is challenging due to the biological nature of producing the bony matrix. Few studies have succeeded in creating human or transgenic osteosarcoma organoids for therapeutic screening. Nonetheless, PDOs hold potential and promise for precision medicine, although the protocols require further refinement. In general, all preclinical models exhibit both value and inherent limitations. There is always a concern that results within a more artificial model may not translate into the *in vivo* human context, making it important to leverage more than one approach and validate findings in the clinical setting.

Radiomics: osteosarcoma diagnosis in precision medicine. Imaging has been crucial in diagnosing osteosarcoma since Ernest Codman's 1909 description of the tumor on X-ray. Techniques like computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans are essential throughout treatment, providing vital information for diagnosis, prognosis, and response evaluation. However, the personal learning curve and increasing volume of imaging data pose challenges for radiologists and other providers, increasing the risk of misdiagnosis, especially for rare tumors like osteosarcoma. Radiomics enhances image analysis by automatically extracting numerous quantitative features from medical images, storing information in databases, and mining data for clinical insights (Text S5 online). Radiomics supports screening, diagnosis, follow-up, prognosis, and pharmacokinetic research, offering powerful tools for precision oncology. Additionally, AI enhances radiomics by automating analysis, while deep learning uses neural networks to automatically identify and quantify features, recognize data patterns, and make decisions through algorithms. AI programs integrate functional images like PET or functional MRI with metabolic activity and structural information like CT images to extract radiomic features reflecting anatomical and functional lesion characteristics, akin to genomic data analysis [10].

Histopathological diagnosis of osteosarcoma remains challenging in certain cases. To enhance diagnostic accuracy, studies have developed deep learning-based automated osteosarcoma classification systems using medical images. Additionally, convolutional neural networks (CNNs) have been used to determine osteosarcoma histological subtypes, demonstrating higher efficiency than human evaluation [11].

Predicting a patient's response to neoadjuvant chemotherapy for osteosarcoma typically relies on assessing tumor necrosis in postoperative specimens. Preoperative predictions often depend on radiological changes in tumor volume, edema, and metabolic markers, which can vary due to reader-dependent factors and tumor heterogeneity. AI-assisted radiomics shows promise in this area. Studies utilizing MRI or CT-based deep learning models, such as U-Net, have developed nomograms that effectively predict chemotherapy response in osteosarcoma [12].

Radiomics has also shown promise in predicting the prognosis of osteosarcoma. For instance, a nomogram combining CT image-derived radiomics signatures with clinical variables outperformed a model based on clinical variables alone in predicting survival for high-grade osteosarcoma patients [13]. Additionally, random forest CT radiomics model and LASSO regression-derived radiomics nomogram model have been tested for predicting lung metastasis risk and early relapse in osteosarcoma patients [14].

Radiological and histopathological image evaluation remains fundamental in osteosarcoma treatment. As technology evolves, the collaboration between radiomics and AI promises a transformative approach and significant breakthroughs in osteosarcoma management. Several challenges need to be addressed, including standardization, data quality, segmentation, interpretability, integration with clinical data, regulatory approval, privacy concerns, computational resources, and clinical implementation. Addressing these challenges will be critical to realizing the full potential of radiomics in osteosarcoma evaluation.

Computer-based navigation and additive manufacturing: *osteosarcoma surgery in precision medicine*. Accurate negative surgical margins are crucial for prognosis. Extensive research has focused on preoperative planning and intraoperative guidance. Initially used in neurosurgery, computer-navigated surgery was adopted in orthopedic spinal surgery in the early 2000 s. Today, intraoperative navigation systems based on fluoroscopy or CT are widely utilized globally. Modern techniques enhance surgery by integrating radiological modalities, additive manufacturing, and AI-enhanced augmented reality (AR) or virtual reality (VR), advancing musculoskeletal tumor surgeries.

In preoperative navigation planning, CT scans provide detailed visualization of bone anatomy, while MRI offers supplementary information on soft tissue. These images can be overlaid to combine their strengths. PET scans help differentiate between malignant and benign tissues, guiding resection sites. After planning resection levels, 3D printing allows the creation of models of the tumor and surrounding anatomy, aiding surgical planning and patient education. Additionally, patient-specific instruments (PSI), such as osteotomy guides manufactured through 3D printing, can be sterilized for intraoperative application, enhancing the precision of osteotomies (Text S6 online).

During surgery, extended reality (XR), which includes AR, VR, and mixed reality (MR), further augments surgical accuracy and reproducibility. AR overlays digital images onto the real world in real-time, using systems comprising position tracking, display, and control software. These systems integrate traditional imaging modalities like fluoroscopy or preoperative CT scans to accurately position objects within the surgical field. Some studies have developed an AR system for bone tumor resection using a low-cost tablet PC, achieving greater accuracy than conventional methods. For MR, it offers a transformative approach to visualizing and sharing medical information in real-time. As a cost-effective alternative to traditional computer navigation and 3D printing, MR enhances image visualization and interaction with holograms. Surgeons can access on-demand information and remote assistance through MR head-mounted displays (HMDs) and hands-free control, improving clinical efficiency and patient safety (Text S7 online).

Despite its potential to facilitate surgery, several issues need to be addressed. For example, PSI design must fully consider the surgical approach and placement of the guide plate, as a lack of flexibility for soft tissue variations can compromise resection accuracy, with additional risks from surgeon error and infection. In navigated surgery, inaccuracies in linking therapeutic or holographic objects to virtual objects can lead to resection errors. Besides, delays in planning and jig manufacture can cause mismatches and intralesional resections. Additionally, adopting new techniques requires a learning curve; studies reported planning and tracker setup times as long as 60 min, and navigation was abandoned in 5% of cases due to technical errors [15]. Indeed, computer-based navigation and additive manufacturing hold great promise for improving precision in osteosarcoma surgery. Overcoming the current challenges will be essential for fully realizing the potential of these advanced technologies in clinical practice.

Back to custom-made: musculoskeletal defect reconstruction in precision medicine. Traditional orthopedic oncological implants are either custom-made using subtractive machining or modular, off-the-shelf implants, which are readily available. The former requires extensive manufacturing time, while the latter is associated with higher failure rates than non-modular components. Additive manufacturing offers a potential hybrid solution, allowing for the creation of personalized custom-made prostheses that fit perfectly and are produced without time delays, leveraging the benefits of both.

Additive manufacturing addresses challenges like mechanical complications with precise, customized implants that enhance osseointegration and reduce complications. Current metal 3D printing technologies, such as selective laser melting (SLM) or electron beam melting (EBM), have been shown to be effective for fabricating titanium alloy components with intricate shapes and porous structures, providing advanced mechanical strength and biocompatibility. Clinical studies have shown promising results, including reduced surgical times and complications using 3D-printed guides and implants. For example, Ji et al. [16] reported successful reconstructions using 3D-printed custom implants in 80 pelvic tumor patients, with observed bone ingrowth at the prosthesis-bone interface and reduced long-term complications compared to historical controls.

Precision reconstruction and long-term reliable implants with fewer complications and affordable prices are the goals of patient-centered care. Additive manufacturing and 3D printing offer potential advantages in terms of customization and precision. However, at the current stage, there are still limitations that need to be addressed. Not all materials used in 3D printing are biocompatible, and some 3D-printed materials may not have the necessary strength or durability required for certain types of implants. For example, 3D-printed titanium alloy prosthetic stems for lower limb reconstruction have witnessed higher breakage rates in the early postoperative stage. Several reasons could contribute to this, including the lack of biomechanical testing, as customization makes each implant unique, leaving validation largely to the surgeon's expertise. The long-term performance and durability of 3D-printed implants are still being studied, and there may be concerns about their longevity and potential for wear or degradation over time.

As a rapidly developing technology, additive manufacturing should maximize patient benefits while mitigating potential risks associated with new manufacturing methods. The "PAMFOSS" principle guides the design and application of 3D-printed prostheses through medical-engineering collaboration and aims to reduce reconstruction failure, safeguard patients, and enhance the overall efficacy and safety of the technology [17]. The principle includes: (1) Precision: accurate osteotomy planning with CT/MRI data and 3D-printed guides ensures precise prosthesis fitting. (2) Articulation: the tumor's nature and location determine the preservation of adjacent joints, as 3D printing can provide either intercalary or joint reconstruction. (3) Materials: Ti6Al4V alloy offers strength, stability, and biocompatibility, with porous structures enhancing bone conduction. (4) Fixation: intramedullary, extramedullary, or composite fixation methods ensure stability, with 3D printing enabling custom designs for complex anatomical fits. (5) Osseointegration: 3D-printed porous titanium interfaces improve bone integration, essential for long-term prosthesis stability. (6) Soft tissue coverage: prosthesis design focuses on functional reconstruction, minimizing volume for better soft tissue coverage, and incorporating features for tissue attachment. (7) Sustainability: for children and future revisions, modular designs accommodate growth and simplify surgical updates, with data retention for prosthesis refurbishment.

Conclusion and outlook: the future of osteosarcoma in precision medicine. We are in the era of precision medicine, which holds pro-

mise for improved osteosarcoma management through targeted approaches, patient-tailored solutions, and customizable therapies and implants. Decades of similar conventional treatment approaches have proven unlikely to yield significantly improved outcomes, highlighting the need for innovative approaches to reimagine osteosarcoma treatment, especially where conventional therapy is ineffective. The top priority remains improving the survival rate.

Despite numerous clinical trials, there has been limited progress in improving long-term survival rates for osteosarcoma patients, particularly those with relapse or metastasis. While advances in understanding the genetic and molecular bases of osteosarcoma are significant, overcoming resistance mechanisms to current therapies is essential for improving treatment efficacy. Discovering novel therapeutic targets or mechanisms, developing targeted therapies for common genetic alterations, and enhancing the efficacy of immune-based therapies are critical areas for future research.

Additionally, developing reliable biomarkers to stratify patients and tailor treatments is crucial. Biomarker-driven clinical trials could enhance the precision of osteosarcoma therapy. The rarity of osteosarcoma necessitates new clinical trial designs, including adaptive trials and international collaborations, to evaluate new therapies effectively. Furthermore, the challenges of early detection and screening complicate osteosarcoma management, often resulting in late-stage diagnoses. Utilizing preclinical models and continuing comprehensive genomic profiling are essential strategies for advancing treatment.

The path to precision medicine lies in integrating genetic, molecular, and clinical data to provide a holistic understanding of the cancer. Identifying emerging therapeutic targets and potential new treatment strategies will be vital in improving outcomes for osteosarcoma patients. By focusing on these innovative approaches, we can hope to achieve better survival rates and quality of life for those affected by this challenging disease.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2024.11.027.

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