PTOA Question 8: Do current preclinical models have the appropriate features and outcome measures to appropriately evaluate therapeutic interventions for PTOA?

Yuwei Zhang, Zhilong Zhou, Qiongjiao Zeng, Ning Wang, Hang Lin, Stuart B. Goodman, David J. Hunter, Rocky S. Tuan, Zhong Alan Li

---

RESPONSE/RECOMMENDATION: Partially

To rigorously evaluate therapeutic interventions for post-traumatic osteoarthritis (PTOA), experimental models should be reproducible and clinically relevant; recapitulate key features of PTOA pathophysiology (low-grade synovitis, cartilage degradation, and subchondral bone remodeling); and mirror clinical manifestations (pain and joint dysfunction) as well as disease progression from acute to chronic. Models should also capture critical influencing factors, including injury type, mechanical load, and individual susceptibility. Model selection should be tailored to the therapeutic target: for example, anterior cruciate ligament transection (ACLT) for biomechanical imbalance, destabilization of the medial meniscus (DMM) for chronic, insidious progression, and medial meniscal tear (MMT) for local inflammation. A comprehensive assessment toolkit is available: the modified Osteoarthritis Research Society International (OARSI) histopathology score as the core readout, supplemented by osteophyte and synovitis grading for tissue changes; magnetic resonance imaging (MRI) and micro-CT for noninvasive whole-joint structural monitoring; functional measures (e.g., gait analysis, pain assessment, and range-of-motion tests) for outcome evaluation; and biomarker assays, preferably multiplexed panels, for detecting early molecular alterations. Integrating artificial intelligence (AI) to automate quantification and better align preclinical and clinical datasets is strongly encouraged.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE:

RATIONALE:

What would be the features of a model needed to appropriately evaluate therapeutic interventions for PTOA?

PTOA refers to osteoarthritis (OA) that occurs after a definite joint trauma, such as intra-articular fracture, ligament and meniscus injury, joint dislocation, or cartilage impact. PTOA is more common in younger populations [1,2]. PTOA has several core characteristics. It is initially triggered by mechanical tissue damage and acute inflammation, and then driven by persistent low-grade synovitis, chondrocyte death and phenotypic changes, as well as cartilage matrix degradation, which gradually leads to diffuse thinning, fissures and defects of cartilage. These events are accompanied by subchondral bone sclerosis, osteophyte formation, and bone marrow lesions, and often accompanied by joint instability, alignment abnormalities, and changes in load redistribution, which collectively accelerate the degeneration process [3-5]. Clinically, PTOA mainly manifests as activity-related pain, that gradually progresses to persistent pain, joint swelling, stiffness, limited movement, and decreased joint function [6]. Radiologically, X-ray imaging can show joint space narrowing,

osteophytes, and subchondral bone changes, while MRI further reveals cartilage defects, bone marrow lesions, synovitis/effusion, and meniscus and ligament lesions [7]. The occurrence of PTOA is driven by the combined influence of multiple factors, including the type and severity of the initial injury, the quality of treatment, the subsequent mechanical environment (alignment and load conditions), systemic metabolic/inflammatory status, and individual susceptibility.

Main Modeling Methods, Characteristics and Simulated Features of PTOA.

To understand PTOA pathogenesis and develop disease-modifying therapies, it is essential to establish reproducible, clinically relevant animal models. The mainstream modeling methods are predominantly surgical-induced approaches, among which ACLT [8], DMM [9], and MMT [10] are the most used in basic research. Each of these models has its unique characteristics and strengths in replicating specific clinical features of PTOA (Table 1). Notably, although these animal models partially mimic key features of traumatic osteoarthritis, they do not fully recapitulate the complex etiology, progressive pathology, and clinical heterogeneity of PTOA encountered in orthopaedic practice [11]. Other approaches, such as non-invasive injury and compression models, are attracting growing interest for their ability to better recapitulate physiological loading and minimize surgical artifacts [12,13]. Furthermore, while rodent ACLT, DMM, and MMT models are invaluable for early mechanistic studies and therapeutic screening, larger animal species (e.g., sheep, cattle, dogs, and nonhuman primates) are often required to rigorously evaluate disease-modifying osteoarthritis drugs because their knee anatomy and biomechanics more closely resemble those of humans[14-18].

What tools would we need to assess this?

The current PTOA management is primarily palliative, aiming to alleviate symptoms, restore function, and delay joint replacement. OA pharmacotherapy commonly relies on non-steroidal anti-inflammatory drugs and, for short-term symptom relief, intra-articular corticosteroid injections; however, prolonged or frequent use is limited by the risk of adverse effects [25,26]. Non-pharmacological approaches, especially structured physical therapy for muscle strengthening and gait retraining, are foundational for improving joint stability [27,28]. When these conservative measures fail, surgical interventions become necessary, including joint-preserving techniques (such as cartilage restoration or osteotomy) and, when indicated, arthroplasty [29]. Critically evaluating treatment efficacy requires comprehensive outcome measures that include structural, functional, and pain-related behavioral endpoints. The OARSI histopathology scoring system is a widely used tool for grading severity in animal models; however, it has recognized limitations and continues to be refined, as shown in Table 2 [30].

Table 1. Main modeling methods, characteristics and simulated clinical features of PTOA.

Modeling Method	Core Surgical Operation	Key Characteristics	Simulated Clinical PTOA Features	Model validity and establishing criteria	Recommendation
ACLT [8,19,20]	Surgically transect the ACL of rodent knee joints (rats/mice)	1. Directly impairs joint biomechanical stability, causing tibial anterior translation and rotational instability 2. Rapid disease progression (osteoarthritic changes evident at 4–6 weeks post-operation) 3. Severe pathological manifestations: obvious articular cartilage erosion, chondrocyte apoptosis, subchondral bone sclerosis, osteophyte formation 4. Easy to establish with high reproducibility	ACL rupture-induced PTOA (common in young people/athletes); progressive joint degeneration due to long-term abnormal post-trauma biomechanical loading	Validate outcomes with OARSI histological scoring at 4–6 weeks; include age/sex-matched rodents; confirm ACL transection via biomechanical instability tests.	First choice for studying PTOA pathogenesis driven by joint instability; preferable for efficient evaluation of disease-modifying therapies targeting biomechanical imbalance
DMM [9,21-23]	Cut the medial meniscotibial ligament (no damage to the meniscus	1. Induces chronic medial meniscal instability during joint movement 2. Slow disease progression (moderate changes at 6–8 weeks post-operation)	Occult PTOA caused by chronic meniscal instability (e.g., meniscal injury healing disorders, long-term occupational strain);	Validate outcomes with meniscal displacement imaging at 6–8 weeks; include consistent age/sex cohorts; confirm	Preferred for studying chronic, insidious PTOA progression; suitable for evaluating long-term efficacy of therapies targeting meniscal

	itself), leading to abnormal meniscal displacement/ dysfunction	3. Mild intraoperative cartilage damage, minimizing interference from unintentional surgical injury 4. Moderate pathological manifestations: cartilage surface irregularity, proteoglycan loss, meniscal fibrosis 5. Insidious disease onset with progressive cartilage degeneration	cartilage damage driven by abnormal meniscus-articular surface contact	ligament transection via post-mortem dissection.	instability and mild cartilage degeneration
MMT [10,24]	Surgically create a tear in the medial meniscus	1. Induces localized cartilage damage adjacent to the meniscal tear site 2. Triggers prominent local inflammatory post-injury responses 3. Pathological changes are regionally concentrated (not diffuse joint degeneration) 4. Recapitulates acute traumatic meniscal injury in humans	Acute meniscal tear-induced secondary PTOA; clinical scenarios of localized joint damage and inflammation from traumatic meniscal injury	Validate outcomes via cartilage loss quantification at 2–4 weeks; use balanced sex/age groups; confirm meniscus transection via post-operative imaging.	Preferable for investigating the role of meniscal injury and local inflammation in PTOA initiation; suitable for developing targeted anti-inflammatory therapies or meniscal repair strategies

Table 2: Tools for PTOA model assessment: characteristics, pros/cons and recommendations.

Assessment Tool	Core characteristics	Advantages	Limitations	Improvements	Recommendation
OARSI Histopathology Scoring [30-35]	Semi-quantitative scale (0–6) for cartilage lesions; focuses on articular cartilage; validated in surgical models.	High standardization/ reproducibility; widely recognized; adaptable to common staining (Safranin O, H&E, Toluidine Blue).	1. Low sensitivity in non-surgical models 2. Ignores whole-joint features (osteophytes, synovitis) 3. Original protocol is inefficient	1. Use single mid-coronal section 2. Supplement with osteophyte and synovitis scores	Core histopathological tool; use with modifications and supplements for whole-joint assessment.
Imaging (MRI, Micro-CT) [36]	Non-invasive, holistic monitoring: MRI assesses cartilage/synovitis/bone; micro-CT reveals s detailed bone morphology.	Holistic tissue coverage	1. MRI: high cost, needs professional operation 2. Micro-CT: preclinical-only 3. No cellular-level details	1. Combine with OARSI histopathology scoring 2. Standardize imaging parameters	Use as an essential supplement for whole-joint structural assessment and longitudinal monitoring.
Functional Tools (Gait analysis, ROM test) [37,38]	1. Evaluates joint function (core endpoint) 2. Gait analysis: Assesses joint instability and pain-related functional	1. Direct functional assessment 2. Objective, quantifiable 3. Easy integration with other tools	1. Requires specialized equipment/standardization 2. Affected by non-PTOA factors	1. Standardize testing conditions 2. Combine with pain assessment/behavioral assays	Necessary for preclinical translation; include for functional outcome evaluation.

	limitations; ROM test: Evaluates knee joint mobility and range of motion 3. Aligns with clinical goals				
Biomarker Assays (ELISA, etc.) [39]	1. Detects synovial/serum biomarkers 2. Enables early, minimally invasive monitoring of disease progression 3. Reflects molecular changes prior to structural damage	High sensitivity for early diagnosis	1. Lack of specific biomarkers 2. Affected by systemic factors	1. Use biomarker panels 2. Combine with OARSI histopathology scoring	Critical for clinical relevance; integrate with functional/structural tools to capture full disease spectrum.
Pain Assay (Pressure Application Measurement [PAM]) [40,41]	Applies graded, localized pressure directly to the affected joint to measure withdrawal threshold, specifically evaluating joint-associated mechanical allodynia or hyperalgesia.	High specificity for joint-derived pain; sensitive to PTOA-related nociception; minimally influenced by general animal stress or handling.	Not suitable for assessing widespread or spontaneous pain; requires precise probe placement and operator training; may not fully capture pain-related functional impairment.	Standardize probe size, pressure ramp rate, and pre-test acclimation; combine with gait or weight-bearing analysis for comprehensive pain phenotyping.	Preferred primary endpoint for quantifying joint-specific mechanical pain in PTOA models; critical for linking structural damage to localized nociceptive behavior.

Future Directions in PTOA Evaluation: Integration, Quantification, and Regulatory Alignment

Future evaluation systems increasingly emphasize integration, quantification, automation, and regulatory alignment. The trend is to combine semi-quantitative OARSI grades with fully quantitative histomorphometric measures (e.g., cartilage area and thickness) and standardized scores of other joint features, yielding multi-parametric analyses with richer, more reproducible data [31]. The most transformative development is the integration of AI and machine learning [42,43]. AI-driven radiomics can convert standard medical images into quantitative biomarkers, while advanced algorithms show promise for automating and objectively grading histopathological or imaging data, potentially creating "digital biomarkers" of PTOA severity that bridge preclinical and clinical research [42]. This technological shift aligns with regulatory guidelines, specifically the U.S. Food and Drug Administration draft guidance, which prioritizes structural endpoints to measure OA progression. This guidance aims to evaluate treatments that modify the underlying pathophysiology of the disease, rather than merely managing symptoms. Key structural endpoints include radiographic joint space narrowing and MRI-assessed changes in cartilage, bone, and soft tissues [44]. Accordingly, preclinical PTOA models should adopt methods that mirror these clinical endpoints, ensuring that research findings are both scientifically robust and translationally relevant.

References

1. Thomas, A.C., Hubbard-Turner, T., Wikstrom, E.A. & Palmieri-Smith, R.M. Epidemiology of Posttraumatic Osteoarthritis. *Journal of Athletic Training* **52**, 491-496 (2017).
2. Riordan, E.A., Little, C. & Hunter, D. Pathogenesis of post-traumatic OA with a view to intervention. *Best Practice & Research Clinical Rheumatology* **28**, 17-30 (2014).
3. Dilley, J.E., Bello, M.A., Roman, N., McKinley, T. & Sankar, U. Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation. *Bone Rep* **18**, 101658 (2023).
4. Punzi, L.*, et al.* Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. *RMD Open* **2**, e000279 (2016).
5. Kramer, W.C., Hendricks, K.J. & Wang, J. Pathogenetic mechanisms of posttraumatic osteoarthritis: opportunities for early intervention. *Int J Clin Exp Med* **4**, 285-298 (2011).
6. Takase, K., McCulloch, P.C., Yik, J.H.N. & Haudenschild, D.R. Clinical and molecular landscape of post-traumatic osteoarthritis. *Connective Tissue Research* **66**, 373-379 (2025).
7. Martel-Pelletier, J., Tardif, G., Paiement, P. & Pelletier, J.P. Common Biochemical and Magnetic Resonance Imaging Biomarkers of Early Knee Osteoarthritis and of Exercise/Training in Athletes: A Narrative Review. *Diagnostics (Basel)* **11**(2021).
8. Zhao, Z.*, et al.* Days 7 to 14 May Represent an Optimal Window for Stem Cell-Based Treatment in a Rat Model of Anterior Cruciate Ligament Transection-Induced Posttraumatic Osteoarthritis. *Am J Sports Med* **53**, 1629-1640 (2025).
9. Mével, E.*, et al.* Systemic inhibition or global deletion of CaMKK2 protects against

post-traumatic osteoarthritis. *Osteoarthritis Cartilage* **30**, 124-136 (2022).
10. Zhi, Z.Y. & Wang, P.C. The Mitochondrial Targeting Drug SkQ1 Attenuates the Progression of Post- Traumatic Osteoarthritis through Suppression of Mitochondrial Oxidative Stress. *Curr Mol Pharmacol* **17**, e18761429383749 (2024).
11. Riewruja, K.*, et al.* Experimental models to study osteoarthritis pain and develop therapeutics. *Osteoarthr Cartil Open* **4**, 100306 (2022).
12. Sangsuwan, R.*, et al.* Intra-articular injection of flavopiridol-loaded microparticles for treatment of post-traumatic osteoarthritis. *Acta Biomater* **149**, 347-358 (2022).
13. Gui, T.*, et al.* Activating EGFR Signaling Attenuates Osteoarthritis Development Following Loading Injury in Mice. *J Bone Miner Res* **37**, 2498-2511 (2022).
14. Xu, L.*, et al.* Early zoledronate treatment inhibits subchondral bone microstructural changes in skeletally-mature, ACL-transected canine knees. *Bone* **167**, 116638 (2023).
15. Hetrick, K., Harkin, K.R. & Roush, J.K. Evaluation of Fortetropin in geriatric and senior dogs with reduced mobility. *Can Vet J* **63**, 1057-1060 (2022).
16. Zhou, X.*, et al.* [Shaoyangzhugu Formula regulates p19(Arf)-p53-p21(Cip1) signaling pathway to ameliorate cartilage degeneration in aged cynomolgus monkeys with knee osteoarthritis]. *Nan Fang Yi Ke Da Xue Xue Bao* **38**, 346-352 (2018).
17. Bartell, L.R.*, et al.* Mitoprotective therapy prevents rapid, strain-dependent mitochondrial dysfunction after articular cartilage injury. *J Orthop Res* **38**, 1257-1267 (2020).
18. Acevedo Rua, L.*, et al.* Engineered nasal cartilage for the repair of osteoarthritic knee cartilage defects. *Sci Transl Med* **13**, eaaz4499 (2021).
19. Wang, X.*, et al.* Improving the symptoms of post-traumatic osteoarthritis by α2-macroglobulin-rich serum. *Connect Tissue Res* **63**, 615-624 (2022).
20. Sutton, K.M. & Bullock, J.M. Anterior cruciate ligament rupture: differences between males and females. *J Am Acad Orthop Surg* **21**, 41-50 (2013).
21. Tang, Y.Z.*, et al.* 4-Octyl itaconate inhibits synovitis in the mouse model of post-traumatic osteoarthritis and alleviates pain. *Chin J Traumatol* **28**, 50-61 (2025).
22. Thomas, N.P.*, et al.* Attenuation of cartilage pathogenesis in post-traumatic osteoarthritis (PTOA) in mice by blocking the stromal derived factor 1 receptor (CXCR4) with the specific inhibitor, AMD3100. *J Orthop Res* **33**, 1071-1078 (2015).
23. Wu, X.*, et al.* Kindlin-2 preserves integrity of the articular cartilage to protect against osteoarthritis. *Nat Aging* **2**, 332-347 (2022).
24. Beaufils, P. & Pujol, N. Management of traumatic meniscal tear and degenerative meniscal lesions. Save the meniscus. *Orthop Traumatol Surg Res* **103**, S237-s244 (2017).
25. Magni, A.*, et al.* Management of Osteoarthritis: Expert Opinion on NSAIDs. *Pain and Therapy* **10**, 783-808 (2021).
26. Grodzinsky, A.J., Wang, Y., Kakar, S., Vrahas, M.S. & Evans, C.H. Intra-articular dexamethasone to inhibit the development of post-traumatic osteoarthritis. *J Orthop Res* **35**, 406-411 (2017).
27. Wang, W., Niu, Y. & Jia, Q. Physical therapy as a promising treatment for osteoarthritis: A narrative review. *Frontiers in Physiology* **Volume 13 - 2022**(2022).
28. Lim, J.*, et al.* Pharmacopuncture and joint movement manual therapy for post-

traumatic phalangeal osteoarthritis: A case report. *Medicine (Baltimore)* **100**, e27081 (2021).
29. Daher, M., Nassar, J.E., Liu, J., Daniels, A.H. & El-Othmani, M. Total knee arthroplasty in post-traumatic versus degenerative osteoarthritis: a meta-analysis of outcomes. *European Journal of Orthopaedic Surgery & Traumatology* **35**, 325 (2025).
30. Kraus, V.B., Huebner, J.L., DeGroot, J. & Bendele, A. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the guinea pig. *Osteoarthritis and Cartilage* **18**, S35-S52 (2010).
31. Armstrong, A.R., Carlson, C.S., Rendahl, A.K. & Loeser, R.F. Optimization of histologic grading schemes in spontaneous and surgically-induced murine models of osteoarthritis. *Osteoarthritis and Cartilage* **29**, 536-546 (2021).
32. Glasson, S.S., Chambers, M.G., Van Den Berg, W.B. & Little, C.B. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the mouse. *Osteoarthritis and Cartilage* **18**, S17-S23 (2010).
33. Du, G.*, et al.* Abnormal Mechanical Loading Induces Cartilage Degeneration by Accelerating Meniscus Hypertrophy and Mineralization After ACL Injuries In Vivo. *The American Journal of Sports Medicine* **44**, 652-663 (2016).
34. Wang, S., Liu, P., Chen, K., Zhang, H. & Yu, J. Mouse model of subtalar post-traumatic osteoarthritis caused by subtalar joint instability. *Journal of Orthopaedic Surgery and Research* **17**, 537 (2022).
35. Bedingfield, S.K.*, et al.* Top-Down Fabricated microPlates for Prolonged, Intra-articular Matrix Metalloproteinase 13 siRNA Nanocarrier Delivery to Reduce Post-traumatic Osteoarthritis. *ACS Nano* **15**, 14475-14491 (2021).
36. O'Neill, T.W. & Felson, D.T. Mechanisms of Osteoarthritis (OA) Pain. *Curr Osteoporos Rep* **16**, 611-616 (2018).
37. Chan, K.M., Bowe, M.T. & Allen, K.D. Recommendations for the analysis of rodent gait data to evaluate osteoarthritis treatments. *Osteoarthritis Cartilage* **31**, 425-434 (2023).
38. Soucie, J.M.*, et al.* Range of motion measurements: reference values and a database for comparison studies. *Haemophilia* **17**, 500-507 (2011).
39. Kalogera, S.*, et al.* Relevance of Biomarkers in Serum vs. Synovial Fluid in Patients with Knee Osteoarthritis. *Int J Mol Sci* **24**(2023).
40. Ishihara, S., Miller, R.E. & Malfait, A.M. Assessment of Knee Hyperalgesia in Mice using Pressure Application Measurement. *J Vis Exp* (2025).
41. Tamai, H.*, et al.* Transient receptor potential ankyrin 1 in the knee is involved in osteoarthritis pain. *Biochem Biophys Rep* **34**, 101470 (2023).
42. Harkey, M.S.*, et al.* Artificial intelligence in osteoarthritis research: summary of the 2025 OARSI pre-congress workshop. *Osteoarthritis and Cartilage Open* **7**, 100687 (2025).
43. Ashinsky, B.G.*, et al.* Machine learning classification of OARSI-scored human articular cartilage using magnetic resonance imaging. *Osteoarthritis and Cartilage* **23**, 1704-1712 (2015).
44. (FDA), U.S.F.a.D.A. Osteoarthritis: Structural Endpoints for the Development of

Drugs, Devices, and Biological Products for Treatment. Draft Guidance for Industry. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/osteoarthritis-structural-endpoints-development-drugs, 2018).

Supplementary Information

Literature Search Strategy

PubMed, Web of Science, Cochrane Library, Google Scholar, and Scopus were searched for potentially eligible studies from database inception to February 2026. The search strategy was designed to address these research questions: "What would be the features of a model needed to appropriately evaluate therapeutic interventions for PTOA? What tools would we need to assess this?" and included terms related to PTOA, surgical modeling, therapeutic interventions, and assessment tools. In our initial literature review, 223 PTOA-related records were retrieved; the titles and abstracts of all 223 studies were screened, followed by full-text review of 216 studies. Ultimately, a total of 133 studies were included in the analysis.

1. Search Keywords

((“Osteoarthritis”[MeSH Terms] OR osteoarthritis[tiab] OR osteoarthrosis[tiab] OR osteoarthritic[tiab]) AND (surg*[tiab] OR “surgically induced”[tiab] OR “surgically-induced”[tiab] OR “destabilization of the medial meniscus”[tiab] OR DMM[tiab] OR “anterior cruciate ligament transection”[tiab] OR ACLT[tiab] OR meniscectomy[tiab] OR “partial meniscectomy”[tiab] OR “medial meniscectomy”[tiab] OR “meniscal tear”[tiab] OR “meniscal injury”[tiab] OR “joint destabilization”[tiab] OR transection[tiab] OR “post-traumatic”[tiab] OR “posttraumatic”[tiab] OR PTOA[tiab] OR “post-traumatic osteoarthritis”[tiab] OR “posttraumatic osteoarthritis”[tiab]) AND (intervention[tiab] OR therapeutic*[tiab] OR treatment[tiab] OR “drug therapy”[tiab] OR “physical therapy”[tiab] OR “surgical intervention”[tiab] OR “cartilage restoration”[tiab]) AND (assessment[tiab] OR “evaluation tool”[tiab] OR “OARSI”[tiab] OR “MRI”[tiab] OR “micro-CT”[tiab] OR “gait analysis”[tiab] OR “biomarker”[tiab] OR “ELISA”[tiab] OR “histopathology”[tiab])) AND (Animals[Mesh] NOT Humans[Mesh])

2. Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Studies focused on PTOA (post-traumatic osteoarthritis); (2) Studies involving surgical PTOA models (e.g., ACLT, DMM, MMT); (3) Studies evaluating therapeutic interventions for PTOA; (4) Studies reporting PTOA model features or assessment tools; (5) Preclinical studies using animal models (Animals[Mesh], excluding humans); (6) Full-text articles with available data on model features or assessment tools.
Exclusion Criteria: (1) Studies on naturally occurring osteoarthritis or age-related osteoarthritis (without traumatic/surgical induction), including those induced by ovariectomy (OVX); (2) Studies without therapeutic intervention or assessment tool evaluation; (3) Human clinical studies; (4) Reviews, meta-analyses, case reports, letters, or abstracts without full data; (5) Studies with incomplete or unreproducible data on model features or assessment tools.