PTOA Question 9: Are there diagnostic or therapeutic interventions that could potentially mitigate or reverse PTOA?

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RESPONSE/RECOMMENDATION: No
***Diagnostic Strategies*:** No diagnostic modalities were identified that mitigate PTOA, but quantitative and biomechanical MRI metrics correlated to worse patient reported outcomes (PRO) after joint injury, potentially improving risk stratification. Progress has been made in identifying molecular biomarkers, although gaps remain in integrating clinical data with adequately powered cohorts. Continued efforts to identify biomarkers for earlier detection are needed.
***Therapeutic Interventions* –** Clinical evidence support symptomatic improvement and structural mitigation with IL-1 blockade, teriparatide treatment, MSC-based therapies, and meniscal surgical intervention in the knee. Evidence for prevention remains inconclusive, potentially due to patient molecular endotype, clinical phenotype, and loading variation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE:

RATIONALE: Post-traumatic OA accounts for ~12% of symptomatic OA patients.[1] In contrast to age-related primary OA, PTOA has a defined initiation point, creating an opportunity for early intervention to address initial and progressive inflammatory effects on cartilage and bone matrix, the onset of cartilage degeneration, and joint instability. The pathophysiology of PTOA following joint injury (*e.g.,* fracture, chondral damage, meniscal or ligamentous injury in the knee) is thought to result from a combination of synovial inflammation, hemarthrosis, pathological mechanical stress, and abnormal joint loading.[2-10] Temporally, the pathogenetic process has been described as 1) an acute phase with prominent inflammation lasting up to ~2 months followed by 2) a chronic phase during which metabolic and biochemical changes in cartilage and other joint structures gradually progress through clinically asymptomatic to symptomatic phases with joint pain and dysfunction.[11]

It is reported that knee injuries such as anterior crutiate ligament (ACL) rupture and meniscal tears lead to PTOA in 25 to 50% of all patients,[2] increasing to 50-80% with 10-year follow-up.[12] Although surgical repair supports a timely return to presurgical activity levels, the incidence of PTOA has not been consistently reduced by surgical interventions depending on the lesion and surgical approach[13-17] Subsequent synovitis, chondrocyte hypertrophy, mitochondrial dysfunction, reactive oxygen species production, and apoptosis, coupled with subchondral bone remodeling leading to sclerosis, all play a role in PTOA pathogenesis.[18] The rationale to advance diagnostic or therapeutic strategies is driven by the need to improve mobility and long-term quality of life after joint injuries typically affecting young, active individuals.

The aims to develop PTOA diagnostics are to 1) identify high-risk patients, 2) evaluate treatment efficacy, and 3) customize targeted treatments to the specific type of injury (*e.g.,* meniscus vs. ACL tear). The goals to advance PTOA disease modifying therapeutics are to 1) target and mitigate early synovitis to inhibit reactive oxygen species and mitigate mitochondrial

dysregulation limiting the inflammatory cascade, 2) prevent irreversible cartilage and bone damage before it occurs, 3) repair or regenerate cartilage and bone structure, and 4) delay the need for total joint replacement (TJR) at young ages, thereby reducing long-term disability and healthcare burden. This consensus statement seeks to review the current 'state of play' of diagnostic and therapeutic investigations to mitigate PTOA.

Diagnostics to improve early detection and risk stratification in PTOA. Strategies currently under investigation to detect PTOA include quantitative imaging metrics and biomarkers in synovial fluid and blood.

Quantitative magnetic resonance imaging (qMRI) and functional MRI-derived biomechanical strains: Systematic review of 11 studies involving 776 participants with ACL injury undergoing knee MRI detected altered bone morphology, tibial position, joint effusion, synovitis, and cartilage/subchondral bone composition at 12 months post-injury. The imaging phenotypes were linked to worse PRO and radiological progression. qMRI relaxation times T1rho and T2, bone morphology, and radiomic modelling were proposed as potential biomarkers.[19]

Review of T2 and T1rho qMRI-based cartilage compositional biomarkers indicated that these markers have been validated for compositional and structural changes in cartilage extracellular matrix, thereby providing potentially valuable information about cartilage structure. However, these measures have not been directly correlated to pain or functional loss and are not routinely applied clinically, potentially limiting their application to treatment.[20]

qMRI (T2, T2*, T1ρ) relaxometry and MRI-derived biomechanical strains were measured concurrently in 35 patients to determine correlation to PROs at six months post unilateral ACL reconstruction. Higher femoral shear and transverse strains, but no relaxometry measures were correlated to worse PROs,[21] and shear strain further differentiated symptomatic, asymptomatic, and healthy knees.[22] These findings suggest that altered strain may represent early biomechanical changes that identify patients at higher risk of developing PTOA.[21]

Nanoparticle-enabled molecular imaging – Biomarker molecule-targeted (*e.g.,* type II collagen, proteoglycans, glycosaminoglycans) nanoparticle-assisted imaging techniques are under preliminary preclinical investigation to provide molecular pathological information in addition to anatomical structure.[23]

Synovial fluid (SF) and serum biomarkers – Review of molecular biomarkers to date (2025) identified 1 genomic analysis, 22 protein, 6 metabolite, 9 inflammatory markers, and 6 biomarkers integrating multiple molecular levels.[24] Prior systematic review (2020) of SF biomarkers of patients with knee OA identified numerous biomarkers, defining the most promising analytes to be C4S, IL-6, IL-8, Leptin, MMP-1/3, TIMP-1, TNF-α, and VEGF, but acknowledging evidence for each was limited and often conflicting.[25]

Evaluation of SF from meniscectomy patients with acute (<6 weeks, n=30) or chronic (>1 year, n=55) symptoms indicated that a more pro-inflammatory profile in chronic (but not acute) patients correlated to worse outcomes.[26] Evaluation of blood biomarkers associated with PTOA after ACL injury suggested potential value in assessing systemic changes but concluded evidence was lacking on clinical utility of these markers to identify individuals who will develop PTOA.[27] Ongoing (2025) systematic review performed across five platforms aims to identify randomized clinical trials, non-randomized prospective or retrospective clinical trials, case-

controls, cohort studies, and case series on SF biomarkers for PTOA after ACL and meniscus injuries.[12]

Summary of Diagnostics. MRI strain and qMRI relaxometry may provide complementary assessments for PROs after joint injury. Standardization of MRI sequences could progress imaging applications for PTOA biomarkers. Advancements have been made in identifying molecular biomarkers for OA across joints, sample types and molecular levels, but gaps remain to validate clinical data with larger sample sizes. Demonstration of the utility of PROs, biomarkers, and imaging outcomes remains an important area for further research.[28]

Therapeutic interventions to mitigate or prevent PTOA. Treatments under investigation for PTOA include:

IL-1 blockade (IL-1Ra or IL-1Ra gene therapy) – IL-1 blockade using IL-1Ra protein or IL-1Ra gene therapy has been evaluated extensively across preclinical and emerging clinical studies. A 2022 systematic review identified 10 preclinical and one clinical study in knee PTOA, showing that early IL-1 inhibition (within two weeks of injury) consistently reduced cartilage damage, lesion size, and synovial IL-1β levels, although these effects declined with time.[29] In addition, recent equine PTOA work demonstrates that AAV-mediated IL-1Ra gene delivery achieves sustained intra-articular IL-1Ra production with reduced lameness, decreased PGE_2, and improved cartilage and subchondral bone histology. Clinically IA IL-1Ra (anakinra) one month after ACL tear reduced knee pain and improved function.[30] Complementing these findings, a first-in-human phase 1 trial of intra-articular sc-AAV2.5-IL-1Ra in knee OA showed the approach to be safe, with synovial IL-1Ra levels elevated for up to one year and associated with improved pain and function scores.

Teriparatide (PTH 1-34) – In a mouse meniscal/ligamentous injury model, teriparatide reduced cartilage degeneration and increased proteoglycan content, even when treatment was delayed. In the murine destabilization of the medial meniscus (DMM) PTOA model, teriparatide preserved cartilage thickness and glycosaminoglycan content while improving subchondral bone remodeling, and reduced synovial inflammation and cartilage degeneration. Pre-publication findings in a human knee OA phase 2 clinical trial, which included a subset of individuals with PTOA, suggest increased cartilage thickness with 6 months of daily teriparatide treatment, but no effect on PROs, including WOMAC and PROMIS (NCT03072147).

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Corticosteroids – A randomized trial indicated IA corticosteroids at 4 days after ACL injury reduced CTX-II associated with collagen type II breakdown; no differences were seen in PRO or other biomarkers assessed.[31]

Hyaluronic-acid (HA) – Review of preclinical models of knee injury indicated mixed results with some evidence for meniscal and cartilage healing.[32] Micrometric HA particles to release fetuin-A decreased joint degeneration, synovial hyperplasia and muscle damage in murine PTOA.[33] Clinical PTOA reports are lacking.

Platelet-rich plasma (PRP) – Preclinical models show inconsistent effects of PRP, with leukocyte-poor PRP (LP-PRP) associated with greater cartilage thickness and surface area,

whereas leukocyte-rich PRP (LR-PRP) tends to produce stronger analgesic responses.[34,35] Clinical evidence remains mixed. A recent clinical trial indicated IA PRP after ACLR did not improve knee symptoms at 12 months.[36] Review and meta-analysis (2025) concluded moderate pain reduction and functional improvement but not long-term structural improvement with either LR- or LP-PRP.[37] Another systematic review (2026) incorporating traumatic OA populations concluded that PRP improves overall function (WOMAC Total), particularly in younger patients, but does not consistently improve pain, stiffness, or other symptom subscales, and findings remain limited by substantial heterogeneity in preparation methods, dosing, and patient selection. Current clinical trial assesses LP-PRP for acute PTOA.[38]

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Mesenchymal stromal cells (MSC) or precursor cells (MPC) – Review of MSC for knee OA indicated delivery of moderate/higher cell numbers mitigate pain and lead to cartilage preservation in select patient clinical phenotypes.[39] Preclinical evidence in PTOA models (murine, rabbit, pig, caprine, ovine) demonstrated anti-inflammatory, immunomodulation, and structural improvement.[40] Few clinical studies exist, one demonstrated reduced pain scores, joint space narrowing, and tibial bone expansion on MRI/radiographs vs. HA.[41,42] Bone marrow aspirate concentrate (BMAC) reports for PTOA are limited; preclinically erythrocyte-depletion improved outcomes.[43]

Senotherapeutics – UBX0101 reduced oxidative protein stress in aging male murine models of PTOA[44] but failed to demonstrate efficacy in Phase II trials with a single IA dose.[45] Evidence for pain relief by reducing peripheral nociceptive signaling without structural modification was reported in human spontaneous OA but not PTOA.[46,47] PIKASO trial (2025) evaluates metformin to slow structural change and pain after ACL injury.[48]

Doxycycline – Doxycycline inhibited synovitis, reduced cartilage damage, and lowered tibial cartilage MMP-13 levels in a murine ACL rupture model.[49] Evidence for doxycycline to limit joint space narrowing and increased pain in primary OA in aged individuals is favorable but clinical reports are lacking for PTOA.[50,51]

Mechanical loading paradigms – Review of mechanotherapy studies investigating impact of exercise and exercise intensity suggest moderate joint loading exercises may be chondroprotective while high intensity exercise accelerates PTOA.[40]

Surgical approaches – Meniscal repair was associated with lower PTOA risk compared to meniscectomy.[52-54] Surgical stabilization reduced PTOA progression in murine ACLR models,[55] but systematic review and meta-analyses of clinical data have not supported ACL reconstruction reduced PTOA risk vs. non-surgical management.[56]

Alternate approaches in *primary* OA – Approaches such as Wnt inhibitors, FGF-18 receptor antagonists, TGF-β, tissue specific peptides, cathepsin inhibitors and mitochondrial ROS inhibition are currently under investigation for primary OA although evidence for PTOA is lacking.

Summary of Therapeutics. Preclinical and clinical reports support symptomatic and structural improvement with IA IL-1 blockade, teriparatide treatment, MSC based therapies, and surgical

approaches for repair of meniscal lesions. Evidence for PTOA prevention remains inconclusive; efficacy may be due to molecular endotype, clinical phenotype, or loading variation.[39]

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