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Guidance for Sponsors
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Medical Imaging of Osteoarthritis of the Knee in Clinical Trials

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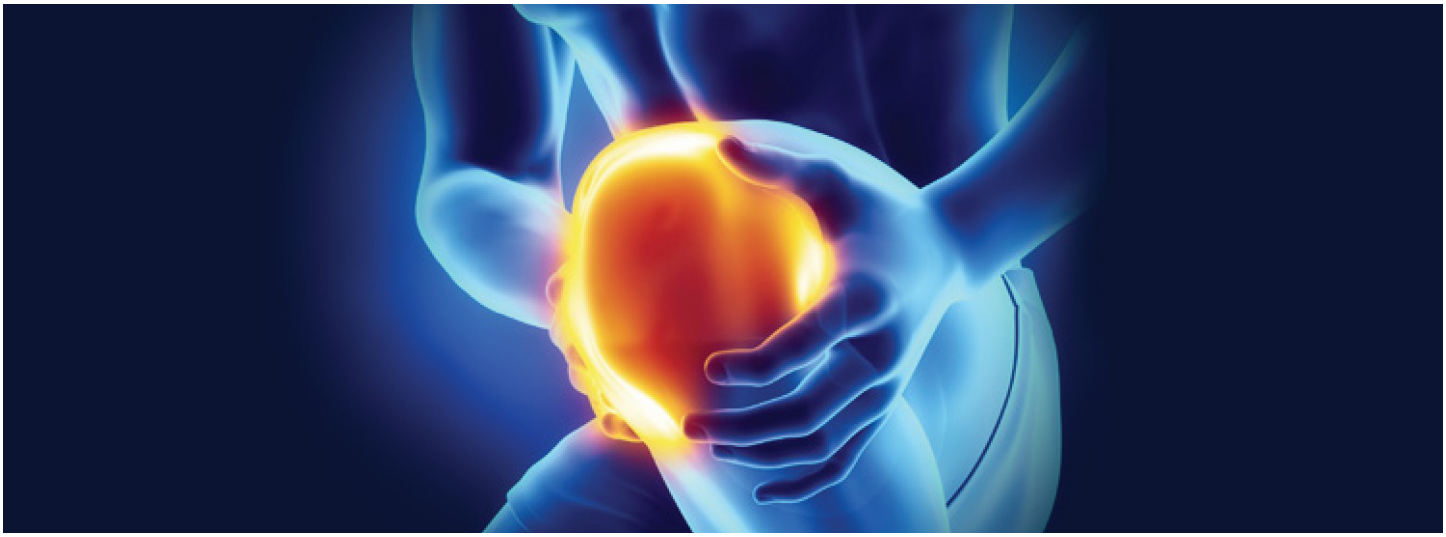

Osteoarthritis of the knee is among the most common causes of disability, and among the most difficult conditions in which to prove that a therapy modifies disease. Radiographic joint space narrowing, the traditional structural endpoint, is slow, indirect and sensitive to positioning. MRI shows cartilage, bone marrow, menisci and synovium directly, and validated semiquantitative scores, quantitative cartilage morphometry and compositional mapping now offer far more sensitive measures of change. This issue reviews the strengths and limitations of each modality and how sponsors should combine them in trials of disease-modifying therapies.

Introduction

Arthritis, inflammation of one or more joints, takes many forms, but the most common is osteoarthritis, or degenerative joint disease. During 2019–2021, an estimated 53.2 million U.S. adults, 21.2% of the adult population, reported a diagnosis of arthritis.[1] As the population ages and obesity rises, the burden of knee osteoarthritis and the number of joint replacements continue to grow. Substantial research is therefore directed at devices, biologics and disease-modifying osteoarthritis drugs (DMOADs), and imaging is central to proving that they work.

Pathophysiology

The common endpoint of osteoarthritis is the destruction of articular cartilage, the smooth, shock-absorbing tissue that covers the ends of bones. Predisposing factors include age, obesity, prior trauma or surgery and genetics. The disease may begin as cartilage damage that slowly erodes the chondral surface and exposes bone, producing joint instability and chronic synovitis with pain, stiffness and swelling. Alternatively, it may begin with injury to stabilizing structures, ligaments and menisci, that creates microinstability and accelerates cartilage loss. Both processes likely operate together, to different degrees in each patient. Osteoarthritis is a disease of the whole joint, and imaging must evaluate the whole joint.

Radiography

The knee is the joint most often studied in osteoarthritis trials: it is commonly affected, and its cartilage is the thickest and most easily imaged in the body. The frontal radiograph has long been the standard examination, graded by joint space narrowing and osteophyte formation. Cartilage itself is invisible on radiographs; its thickness is inferred from the space between the femur and tibia. That space also depends on the menisci and on positioning. Standardized fixed-flexion views improve reproducibility, but radiographic narrowing remains a late finding that correlates poorly with symptoms, and detecting it typically requires large samples and years of follow-up. FDA's draft guidance on structural endpoints for osteoarthritis addresses radiographic joint space width while recognizing the potential of other imaging measures.[2]

Magnetic Resonance Imaging

MRI shows cartilage directly, along with the bone marrow lesions, meniscal damage, synovitis and effusion that contribute to pain and progression. Two validated semiquantitative scoring systems dominate clinical research. The Whole-Organ Magnetic Resonance Imaging Score (WORMS) grades features across subregions of the knee,[3] and the MRI Osteoarthritis Knee Score (MOAKS) refined that approach to improve the scoring of bone marrow lesions and menisci.[4] These scores require trained musculoskeletal radiologists and benefit from central reading with calibrated readers.

Quantitative morphometry goes further, measuring cartilage thickness and volume in three dimensions by segmentation of high-resolution sequences. It has proven its value in trials. In the FORWARD study of intra-articular sprifermin, MRI-measured cartilage thickness was the primary structural endpoint, and five-year follow-up showed sustained structural modification of the treated knee.[5]

Compositional MRI

Before cartilage thins, its composition changes. T2 mapping reflects collagen organization and water content, and T1ρ is sensitive to proteoglycan loss. In 2021, the Quantitative Imaging Biomarkers Alliance (QIBA) published a profile defining hardware, software, acquisition and processing practices for reliable quantification of knee cartilage composition.[6] Compositional measures may identify early disease and earlier treatment response, but they demand rigorous harmonization across scanners and sites.

Ultrasound

Ultrasound evaluates effusion, synovitis, osteophytes and the superficial femoral trochlear cartilage at low cost and without radiation. It cannot visualize most weight-bearing cartilage and depends on the operator, but it is useful for inflammatory features and for guiding injection.

Guidance for Sponsors

Imaging a knee osteoarthritis trial

- **Discuss endpoints early.** Align structural endpoints with FDA before the pivotal trial.[2]
- **Standardize positioning.** Use fixed-flexion radiography with positioning frames and technologist training.
- **Harmonize MRI.** Specify sequences, scanner field strength and quality control at every site.[6]
- **Use validated scores.** Apply MOAKS or WORMS and quantitative morphometry with calibrated central readers.[3,4,5]
- **Read centrally.** Use blinded, independent analysis under a documented imaging charter.[7]

Summary

Knee osteoarthritis demands imaging that sees the whole joint and detects change earlier than radiographs can. Radiography remains the regulatory foundation, but MRI, through validated semiquantitative scores, quantitative morphometry and compositional mapping, offers the sensitivity that disease-modifying therapies require. Standardized acquisition and expert central analysis turn that sensitivity into evidence.

About the Author

Dr. Jack Clement wrote the original edition of this issue as Medical Director, Musculoskeletal Imaging, at Intrinsic Imaging. A graduate of Tulane University in New Orleans, he completed M.D. and Ph.D. degrees at Baylor College of Medicine in Houston, where his training was sponsored by the National Institutes of Health. He has coauthored peer-reviewed original research in *Science*, the *New England Journal of Medicine* and *Neuron*. He completed a diagnostic radiology residency at Baylor College of Medicine and subspecialized in musculoskeletal radiology at Harvard Medical School's Massachusetts General Hospital in Boston. He is a board-certified radiologist with specialized training in orthopedic radiology and interventional pain management.

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