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Guidance for Sponsors
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# Advances in High-Field MRI for the Assessment of Arthritis

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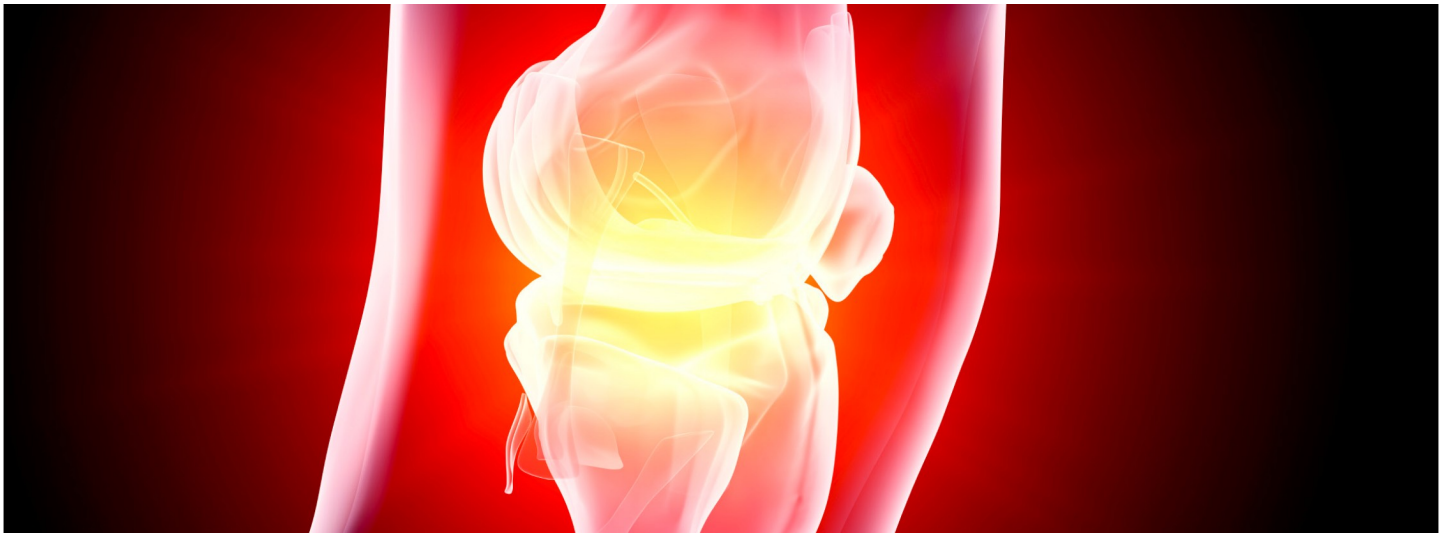

**Arthritis is a leading cause of disability, affecting about 53 million U.S. adults. Its central feature is loss of hyaline cartilage, which has little capacity to repair. Radiographs show only late damage; high-field 3.0 Tesla MRI shows cartilage morphology in fine detail, and compositional techniques such as T2 mapping reveal degeneration before visible loss. For sponsors, the challenge is regulatory as well as technical: FDA has not yet accepted a structural endpoint for osteoarthritis approval, so imaging must be precise, reproducible and linked to how patients feel and function.**

## Assessment of Arthritis

Arthritis is joint inflammation followed by joint destruction, and it is a leading cause of disability in the United States. During 2019 to 2021, an estimated 53.2 million U.S. adults, 21.2% of the adult population, reported diagnosed arthritis.[1] Substantial research, including drugs, biologics and devices, aims to prevent and slow the disease and relieve arthritic pain. Imaging is central to assessing cartilage integrity and whether these interventions succeed.

The central feature of arthritis is loss of hyaline cartilage, an avascular tissue covering the articulating bone of synovial joints. Cartilage has very little capacity for regeneration; once fractured, fibrillated or eroded, it does not mount a robust repair. Preserving cartilage is therefore paramount. Some chondral damage can be partially repaired with microfracture, cartilage grafting or chondrocyte implantation, and imaging is central to assessing the result.

Traditionally, cartilage integrity has been inferred from joint space narrowing on radiographs. Cartilage itself is not calcified and is invisible on radiographs. Radiography shows late changes, such as joint space narrowing, sclerosis and osteophytes, but is inadequate for the early changes, such as surface fibrillation and altered ultrastructure, that are crucial to recognize for timely intervention.

## High-Field Magnetic Resonance Imaging

MRI magnets are rated by field strength. For many years most clinical systems operated at 1.5 Tesla; 3.0 Tesla (high-field) systems, now widely available, represented a major advance in cartilage imaging. In general, a stronger field allows higher image quality and spatial resolution.

Cartilage is thin, ranging from less than 1 mm in the small joints of the fingers and wrist to 4 to 5 mm in the knee. Higher resolution, applied appropriately, lets the radiologist see cartilage better. Three-dimensional acquisition and post-processing allow quantification of cartilage thickness and volume. Surface fibrillation, fissuring, delamination and chondral defects are better seen and therefore better diagnosed. Semi-quantitative whole-joint scoring systems, such as MOAKS for the knee, use these images to grade cartilage, bone marrow lesions, menisci and synovitis consistently across readers.

## Compositional Imaging and T2 Mapping

The goal of cartilage imaging is to detect early degeneration before frank cartilage loss, when surgical or pharmacologic intervention can still preserve the joint. Hyaline cartilage has a zonal structure: a thin superficial zone of densely packed collagen fibrils parallel to the surface, a transitional zone of oblique fibrils, and a deep radial zone of fibrils perpendicular to the subchondral bone. Differences in fibril orientation and packing produce differences in water content, slightly higher superficially than in the radial zone, which water-sensitive MRI sequences can measure.

Early degeneration alters collagen packing and density before morphology changes, which changes water content. T2 mapping quantifies these alterations and so reflects cartilage quality. The knee is the joint most often mapped, in the medial and lateral compartments and the patella, typically in the axial, sagittal or coronal planes at about 3 to 5 minutes per plane. The resulting map is displayed as a color overlay in which healthy, low-water cartilage appears red to orange and degraded, high-water cartilage appears green to blue. Combined with high-resolution morphologic images, it gives a comprehensive picture of cartilage throughout the joint. Related techniques, including T1rho and delayed gadolinium-enhanced MRI of cartilage, probe proteoglycan content.

## The Regulatory Context

In its 2018 draft guidance on structural endpoints in osteoarthritis, FDA noted that no structural endpoint had yet been used for traditional or accelerated approval, and that it remains unclear what magnitude of structural change reliably predicts less pain, better function or longer time to joint replacement.[2] Imaging endpoints in osteoarthritis trials must therefore be precise and reproducible, and should be analyzed alongside measures of how patients feel and function.

## Guidance for Sponsors

**Imaging cartilage in an arthritis trial**

- **Standardize the scanner and protocol.** Use the same field strength, coil and sequences at every visit; quantitative T2 values vary between systems.
- **Combine morphology and composition.** Pair high-resolution 3D morphologic imaging with T2 or T1rho mapping.
- **Use validated scoring.** Apply semi-quantitative scores such as MOAKS and quantitative thickness or volume measures consistently.
- **Link structure to symptoms.** Plan analyses that relate imaging change to pain, function and progression to joint replacement.[2]
- **Control positioning and timing.** Standardize knee position, unloading time before scanning and time of day.
- **Read centrally.** Blinded musculoskeletal radiologists with calibration reduce reader variability.

## Summary

Cartilage preservation is the key goal of therapies for arthritis, including drugs for inflammatory and degenerative arthritides and devices and surgical techniques that preserve joint stability. High-field 3.0 Tesla MRI, with T2 mapping and other compositional techniques, can detect cartilage change at its earliest stages, before frank loss and the need for joint replacement. As new interventions are developed, these techniques will play a central role in showing whether they preserve hyaline cartilage.

## 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.

## References

1. Fallon EA, Boring MA, Foster AL, et al. Prevalence of diagnosed arthritis — United States, 2019–2021. *MMWR Morb Mortal Wkly Rep.* 2023;72(41):1101–1107. cdc.gov/mmwr

2. U.S. FDA. Osteoarthritis: structural endpoints for the development of drugs, devices, and biological products for treatment. Draft guidance, August 2018. fda.gov

## About Intrinsic Imaging, LLC

Intrinsic Imaging is an ISO certified medical imaging CRO and imaging core lab providing comprehensive services in support of Phase I-IV clinical trials and Class I, II, III medical device trials. Intrinsic Imaging is also a world leader in conducting Artificial Intelligence studies. With its team of more than 650 board-certified and fellowship-trained physicians, Intrinsic Imaging's team has sub-specialization in all therapeutic areas, including Cardiovascular, Central Nervous System,Gastroenterology, Musculoskeletal, Oncology and Ophthalmology. Certified by the British Standards Institution (BSI), Intrinsic Imaging is the only company in the world to hold five ISO certifications specifically for providing imaging core lab services on clinical trials. For more information, please visit www.IntrinsicImaging.com.

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