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Introduction
Workshop for Consensus on Osteoarthritis Imaging: MRI of the knee

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One of the critical challenges in developing structure-modifying/preserving therapies for arthritis, especially for knee osteoarthritis (OA), is measuring changes in progression of joint destruction. Radiographic measurement of joint-space narrowing, which is currently recommended in the Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) guidance documents as the imaging endpoint for clinical trials of disease-modifying OA drugs (DMOADs), is recognized to be an insensitive measure of disease onset, activity, and progression.

Accordingly, new and more sensitive biomarkers are needed. Magnetic resonance imaging (MRI) offers considerable promise in this regard. Not only can MRI enable quantification of articular cartilage volume and morphology with high precision and accuracy, it can also examine other important articular tissues simultaneously. It thus offers a unique opportunity to evaluate the knee and other joints as whole organs. This capability is important because OA is a joint disease that involves not only articular cartilage and bone but also synovium, menisci, ligaments, tendons and muscles. Until the relative roles and interdependencies of these structures in producing the pain and dysfunction experienced in OA are fully understood, focusing on only one or two of these features, as is the current practice, provides an excessively narrow perspective. A more holistic view is called for.

"Whole-organ" assessment could facilitate DMOAD clinical trials and studies exploring the pathophysiology and epidemiology of OA in a number of ways. For example, discriminating different patterns of involvement of articular tissues in knee OA could point to different potential causes of the disease and thereby suggest different therapeutic strategies for specific patient subgroups. Whole-organ assessment may also potentially uncover preclinical stages of OA or structural risk factors for developing clinical OA, as well as increase the sensitivity to change for disease progression and treatment response. This approach would aid in subject selection, treatment monitoring and safety assessment.

However, there are numerous practical and theoretical challenges associated with whole-organ assessment. These range from balancing conflicting objectives in imaging protocol design to maintaining construct validity when combining measurements from different structures or from different regions of the same structure.

In an effort to provide state-of-the-art reviews and recommendations on these and other important considerations which would offer meaningful guidance to scientists and pharmaceutical companies designing multi-center clinical studies of OA, OMERACT (Outcome Measures in Rheumatology Clinical Trials) and OARSI (Osteoarthritis Research Society International), with support from various pharmaceutical companies listed at the beginning of this supplement, held a workshop for Consensus on Osteoarthritis Imaging in Bethesda, MD, on December 5 and 6, 2002. The workshop included approximately 150 participants from the academic, pharmaceutical and regulatory communities from US, Europe and Australia. Prior to the workshop, a multidisciplinary, international panel of expert scientists and physicians met in New Orleans, LA, on October 29, 2002 to define a preliminary set of MRI features to include in whole-organ assessment of the knee and to review the relative strengths and weaknesses of various imaging protocols for multi-feature, multi-site MRI. To create focus and utilize available and developing data, only knee imaging was evaluated.

This panel was co-chaired by Charles Peterfy, M.D., Ph.D. (Synarc, Inc, San Francisco, CA, USA) and Roy Altman, M.D. (University of Miami, Miami, FL, USA) and also included Deborah Burstein, Ph.D. (Harvard-MIT, Cambridge, MA, USA), Flavia Cicuttini (Epidemiology, Monash University, Prahran, Australia), Gary Cline, Ph.D. (Biometrics and Statistical Sciences, Proctor & Gamble Pharmaceuticals, Madison, OH, USA), Philip Conaghan, M.B.B.S., F.R.A.C.P. (Rheumatology, Leeds University, Leeds, UK), Bernard Dardzinski, Ph.D. (MRI Physics, University of Cincinnati, Cincinnati, USA), Felix Eckstein, M.D. (MR image analysis, Ludwig-Maximilians-Universität, München, Germany[b]), David Felson, M.D., M.P.H. (Rheumatology, Boston University, Boston, MA, USA), Garry Gold, M.D., Ph.D. (Radiology, Stanford University, Stanford, CA, USA), Benjamin Hsu, Ph.D. (GlaxoSmithKline, Research Triangle Park, NC, USA[c]), Marissa Lassere, M.B.B.S., Ph.D., F.R.A.C.P. (Epidemiology, St George Hospital, Kogarah, Australia), Stefan Lohmander, M.D., Ph.D. (Orthopaedics, University of Lund, Lund, Sweden), Jean-Pierre Raynauld, M.D. (Rheumatology, University of Montreal and Arthrovision,

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Table I
Most important MRI features for evaluating disease severity and progression in OA of the knee

MRI feature	Ranked #1	Ranked #2
Articular cartilage loss	58	1
Osteophytes	36	11
Bone marrow abnormality	35	11
Synovitis	26	17
Meniscal abnormality	17	17
Synovial effusion	16	20

Results are based on a ballot survey of 64 workshop participants.

Montreal, PQ, Canada), Randall Stevens, M.D. (Hoffman-LaRoche Inc, Nutley, NJ, USA), Saara Totterman, M.D., Ph.D. (Virtual Scopics, Pittsford, NY, USA), James Witter, M.D. (FDA, Washington, DC, USA), and Thasia Woodworth, M.D. (Pfizer, Groton, CT, USA). The findings of this panel were presented to the participants of the workshop in Bethesda, MD, for open discussion. These presentations and discussions, along with any notable advances that have occurred since, are summarized in the four reports that follow in this Supplement.

The first of these reports, ''Magnetic Resonance Imaging (MRI) of Articular Cartilage in Knee Osteoarthritis: Morphological Assessment'' by Eckstein *et al.*, provides a comprehensive review of the current knowledge on semi-quantitative and quantitative assessment of this important tissue. The report asserts that cartilage morphology (volume and thickness) can be quantified accurately and precisely using widely available MRI techniques and that the annual rate of cartilage loss observed in most longitudinal studies (4–6%) exceeds precision error by a factor of approximately 50%.

In ''MRI of Articular Cartilage in Osteoarthritis: Novel Pulse Sequences and Compositional/Functional Markers'', Gold *et al.* review some recent innovations in MRI pulse sequences which promise to improve the contrast and speed of high-resolution 3D imaging of articular cartilage morphology. The report also explores novel techniques for probing the compositional integrity of this key articular tissue.

As discussed above, although articular cartilage loss is a cardinal feature of OA, loss of functional integrity of other articular tissues also plays an important role. Accordingly, many have proposed modeling OA as a disease of organ failure, in which dysfunction of one structure is associated with damage to other structures and collectively these lead to the pain and functional disability experienced in OA. In ''MRI of Non-Cartilagenous Structures in the Knee in Osteoarthritis'', Conaghan *et al.* review MRI evaluation of these other features of OA, particularly abnormalities of bone, synovium, ligaments and menisci.

In ''MRI Protocols for Whole-Organ Assessment of the Knee in Osteoarthritis'', Peterfy *et al.* discuss the technical challenges associated with multi-feature imaging of OA in multi-site, longitudinal studies. The report outlines the key considerations important for selecting and qualifying imaging sites, designing imaging protocols that will consistently provide high-quality images across all subjects and sites throughout the duration of the study, and for controlling image quality and managing the image data.

In addition to these discussions, data sets from previous clinical trials and epidemiological studies of OA were analyzed with respect to the metrological properties of the measurement methods employed. One of these analyses examined the internal construct validity of WORMS[1], a whole-organ MRI scoring method for assessing multiple structural abnormalities in the knee, using data from a clinical trial of OA. The results of this analysis were presented to the participants of the workshop for discussion. Subsequent to the workshop, a second clinical epidemiology data set using WORMS but with a more extensive range of pathology was also analyzed in order to strengthen the validity of the findings from the first analysis. ''Examining a Whole-Organ Magnetic Resonance Imaging Scoring System for Osteoarthritis of the Knee using Rasch Analysis'' by Conaghan *et al.* summarizes these two analyses and discusses the challenges associated with combining measurements from different structures or even from different regions of the same structure.

In ''Responsiveness, Effect Size, and Smallest Detectable Difference of Magnetic Resonance Imaging in Knee Osteoarthritis'', Hunter *et al.* examine the performance of five MRI measures for OA of the knee: quantitative cartilage volume and semi-quantitative cartilage, bone marrow abnormality, osteophyte and synovitis/effusion scores based on reanalysis of data from a prior clinical trial of OA.

Additionally, the workshop also included a poster session and a ballot survey of the participants' opinions of which MRI features were most important for evaluating OA of the knee. Based on this survey, which included 64 responding participants (39 rheumatologists, 10 MRI experts, 7 radiologists, 8 other participants), consensus was reached on a core set of structures to be included in whole-organ assessment of the knee (Table I). These were, in order of importance, articular cartilage, osteophytes, subarticular bone marrow abnormality (sometimes referred to as bone marrow edema), the synovium, the menisci, and synovial effusion.

Since this workshop, further advances have been made in some of the areas that were discussed. However, the pace of this progress has been slow; limited primarily by the rate at which the ideas and hypotheses put forth at the time of the workshop could be validated, since doing so often requires large, longitudinal studies, which take considerable time and resources. It is hoped that by publishing these reports, this research will be accelerated and the field will evolve more rapidly toward a deeper understanding of this enigmatic disease and how best to evaluate its severity, progression and response to therapy.

Reference

1. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al.* Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12(3):177–90.