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Natural history of cartilage damage and osteoarthritis progression on magnetic resonance imaging in a population-based cohort with knee pain

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SUMMARY

Objectives: To determine the natural history of cartilage damage and of osteoarthritis (OA) progression using magnetic resonance imaging (MRI); to evaluate whether OA progression varies by stage of disease.
Methods: A population-based cohort with knee pain was assessed clinically, with X-ray (Kellgren–Lawrence [KL] grading) and MRI. Cartilage was graded 0–3 on six joint surfaces. Frequency of cartilage damage change was determined for each joint site. Progression of OA was defined as a worsening of MRI cartilage damage by ≥1 grade in at least two joint sites or ≥2 grades in at least one joint site. The association of KL grade with OA progression was evaluated using parametric lifetime regression analysis.
Results: 163 subjects were assessed at baseline and follow-up (mean 3.2 years). KL grade ≥2 was present in 39.4% at baseline. An increase in cartilage damage by ≥1 grade was seen in 8.0–14.1% of subjects at different joint sites. OA progression on MRI was present in 15.5%. Baseline KL grade was a significant predictor of OA progression with hazard ratio (HR) of 6.5 (95% confidence interval [CI] 1.4–30.7), 6.1 (95% CI 1.3–28.9), and 9.2 (95% CI 1.9–44.9) for KL grades 1, 2 and ≥3, respectively.
Conclusion: A low OA progression rate was seen over 3 years in this population-based symptomatic cohort. Radiographic severity, including KL grade 1, was a significant predictor of OA progression. Future interventions aimed at reducing progression will need to target not only radiographic OA, but also those with early abnormalities suggestive of pre-radiographic OA.

Osteoarthritis (OA) is the most common joint disease worldwide with symptomatic radiographic knee OA occurring in 6% of the population older than 30 years[1]. The progression of knee OA has been investigated extensively over several decades using radiography. More recently, magnetic resonance imaging (MRI) has been applied to the evaluation of structural knee abnormalities. Although cartilage degeneration is a key feature of OA, our understanding of the natural history of cartilage damage, particularly at earlier stages of disease, is incomplete. Progression rates previously reported have been variable[2–6], likely related to the fact that stage of disease, the definition of progression and the population studied contribute to such differences. Recent research suggests that OA progression is greater at more advanced/radiographic stages of disease[7–10]. The notion that early OA might be more amenable to disease-modification has been entertained, but little information is available in population-based studies on the risk of progression in clinically evident OA where radiographs are normal or questionably abnormal, i.e., pre-radiographic disease.

In this cohort we have previously reported that the majority of subjects have pre-radiographic knee OA[11,12]. As such, we had the opportunity to elucidate the question of whether risk of progression is related to stage of disease.

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The objective of this study was to report the natural history of cartilage damage over 3 years in a symptomatic population-based cohort with the full range of knee OA severity. Furthermore, we were interested in evaluating the OA progression rate based on MRI definition of cartilage damage changes and whether stage of disease is a predictor of OA progression in this symptomatic cohort.

Subjects and methods

Study population

The population for this cohort study was recruited between 2002 and 2005 and has been described previously[11,12]. Briefly, subjects, 40–79 years old, with knee pain were recruited as a random population sample in the Greater Vancouver area in Canada. Recruitment was conducted using stratified sampling to achieve equal representation within age decades and gender. Subjects were excluded at baseline if they had inflammatory arthritis or fibromyalgia, previous knee arthroplasty, knee injury or surgery within the previous 6 months, knee pain referred from hips or back, or were unable to undergo MRI. We have previously reported that this cohort of 255 subjects seen at baseline consists of the full spectrum of OA disease severity with 13% having no OA (normal MRI and X-ray), 49% having pre-radiographic OA (abnormal MRI, normal X-ray) and 38% having radiographic OA (abnormal MRI and X-ray)[12].

All subjects were invited for follow-up. Exclusion criteria at follow-up were: (1) total knee arthroplasty; (2) inflammatory arthritis; (3) inability to undergo MRI; (4) comorbidity; (5) inability to attend the study centre. Of 255 subjects seen at baseline, 1 (0.4%) was deceased, 25 (9.8%) were lost to follow-up with unknown status and 35 (13.7%) were not interested in participating (Fig. 1). The remaining 194 subjects (76.1%) were screened for eligibility. Of these, 28 (14.4%) were not eligible and three subjects did not complete their MRI (Fig. 1). A total of 163 subjects completed all study assessments and were included in this analysis. All subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Board, University of British Columbia.

Clinical evaluation

Subjects were evaluated comprehensively at baseline and follow-up with questionnaires to assess demographics, knee symptoms, OA risk factors and general health, as well as a painful joint count based on self-report of pain in other joints over the previous 12 months[11,12]. A standardized knee examination, previously shown to be reliable, was performed[13]. Subjects completed the Western Ontario and McMaster Universities (WOMAC) OA Index VA3.1[14]. Pain, stiffness and function scores were normalized to a 0–100 scale.

Radiographic evaluation

Baseline and follow-up knee X-rays were obtained using a fixed-flexion technique with the SynaFlexer positioning frame[15] and a skyline view in the supine position. The SynaFlexer positioning frame fixes the knee flexion angle for an individual subject such that the knee positioning is identical at baseline and follow-up examinations in longitudinal studies. Radiographs were obtained within a month of the clinical assessment[11]. X-rays were scored blinded to clinical and MRI information by two independent readers using the Kellgren–Lawrence (KL) 0–4 grading[16]. The interrater reliability was good, with an intraclass correlation coefficient of 0.79[11]. Differences in readings were adjudicated by consensus readings of the two readers. Isolated patellofemoral OA on radiographs, defined as the presence of patellofemoral osteophytes in conjunction with patellofemoral joint space narrowing, was present in two of 163 subjects (1.2%).

MRI evaluation

Baseline and follow-up MRI were obtained for all subjects on a GE 1.5T magnet using a transmit-receive extremity knee coil. The imaging protocol included four MRI sequences, previously described[11,12]: (1) Fat saturated T1-weighted three-dimensional (3D) spoiled gradient echo (SPGR) sequence with images obtained in the sagittal plane with reformatted images in the axial and coronal planes; (2) Fat saturated T2-weighted fast spin echo (FSE)

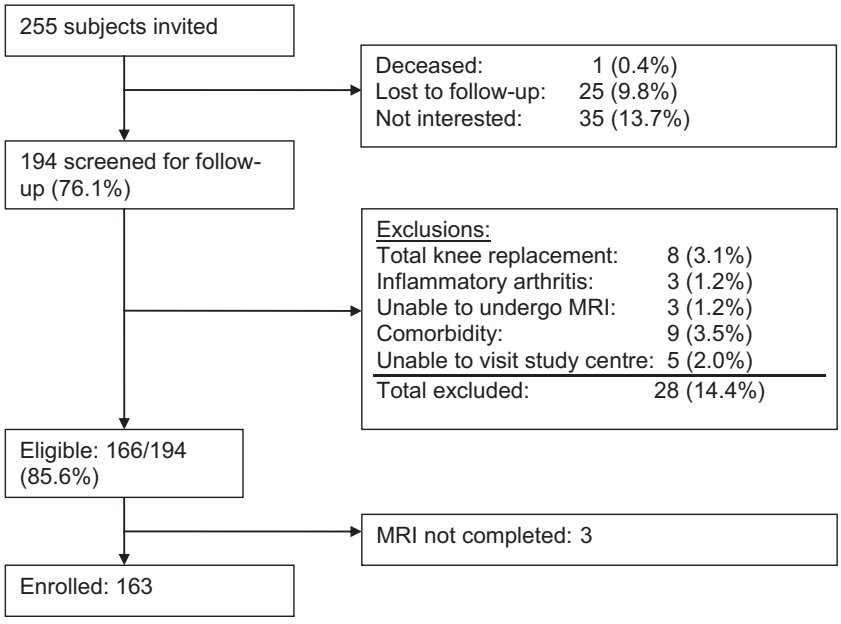

Fig. 1. Flow diagram of study enrollment for 3-year follow-up.

sequence with images obtained in the coronal plane; (3) T1-weighted FSE sequence with images obtained in the oblique sagittal plane (angulated according to the course of the anterior cruciate ligament); and (4) T2-weighted FSE sequence with images obtained in the oblique sagittal plane (angulated according to the course of the anterior cruciate ligament).

Cartilage damage assessment

Six joint areas were assessed, including medial and lateral tibial plateaus, medial and lateral weight bearing femoral condyles, patella and trochlear groove. The trochlear groove was delineated from the weight bearing surfaces of the femur by oblique lines, tangent to the anterior tips of the anterior horns of the medial and lateral menisci. Articular surfaces anterior to these two lines form the trochlear groove. Cartilage was graded on a 0–4 semi-quantitative scale based on the following definitions, previously described by Disler *et al*[17]: 0 = normal; 1 = abnormal signal without cartilage contour defect; 2 = contour defect of < 50% cartilage thickness; 3 = contour defect of 50–99% cartilage thickness; 4 = 100% cartilage contour defect with subjacent bone signal abnormality. In this study, we adapted this cartilage grading to include not only assessment of focal defects, but also more wide-spread damage. If multiple defects were present within a given joint site, the most severe score was assigned. On this scale, grade 1 does not represent a structural cartilage abnormality and this score was assigned infrequently. We therefore collapsed the original scale to a 0–3 scale, where the original scores of 0 and 1 were collapsed to zero, and the original scores of 2, 3 and 4 were relabeled 1, 2 and 3, respectively. Baseline and follow-up MR images were read side-by-side, blinded to time sequence, by a single reader (AG) who was also blinded to X-ray and clinical information. Intra-rater reliability of cartilage readings have previously been reported to range from 0.84 to 1.0 for different cartilage surfaces[11]. Cartilage damage worsening was defined as an increase in the damage score and cartilage damage improvement was defined as a decrease in the damage score. This definition of cartilage worsening included incident damage in areas of previously normal cartilage at baseline. It should also be noted that this definition of cartilage worsening only took into account change in lesion depth, not lesion area extent. As a result, within-grade cartilage change was not included in our definition of cartilage worsening. Since worsening can only occur in those with grade 0–2 damage, subjects with cartilage grade 3 damage at a given joint site were excluded from analysis for that site. As such, the analysis for lateral femur, lateral tibia, medial femur, medial tibia, patella and trochlear groove was based on exclusion of 10, 11, 13, 15, 11 and nine subjects, respectively. We also evaluated the change in cartilage damage score using the maximum knee cartilage score, defined as the worst cartilage score at any of the six joint sites.

Definition of OA progression

Because cartilage damage change on MRI is not equivalent to OA progression, and because no definition of OA progression based on MRI exists, we developed a novel definition of OA progression, based on consensus of study investigators. Progression of OA was defined as cartilage loss of ≥2 grades in at least one joint site or cartilage loss of ≥1 grade in at least two joint sites. This definition was chosen to serve as a conservative definition of OA progression based on worsening of cartilage damage at multiple sites or worsening by a substantial amount at a single site. In addition, such a definition allows for progression of subjects who have grade 3 damage at select joint sites.

Statistical analysis

Data were summarized using frequencies, means [+standard deviation (SD)] or medians (+interquartile range) as appropriate to their distributions. In this study, exact event times were not observed; observations were either left-censored (progression by follow-up visit) or right-censored (no progression by follow-up visit). To account for this type of censoring, we used exponential regression models, which take into account differential follow-up time, adjusted for age, gender and baseline body mass index (BMI), to determine the hazard ratios (HR) and 95% confidence intervals (CI) for the association of radiographic stage of disease with MRI progression rate of OA. The exponential regression likelihood function is a product of densities f(t) at observed event times, survival functions S(t) at right-censored times, and 1−S(t) at left-censored times. Regression parameters (and therefore HRs) can be estimated *via* maximum likelihood from any combination of such data[18].

To obtain population-based estimates, analyses were performed using age decade-gender stratum sampling weights. These weights were derived as the marginal (population) probability of each age decade-gender cell (obtained from the distribution observed during establishment of the baseline cohort[11,12]) divided by sample (actual) probability of the cell observed in this study.

All analyses were performed using SAS v9.2.

Results

One hundred and sixty-three subjects were assessed at a median follow-up time of 3.2 years (range 2.5–5.1). Of the original cohort of 255 subjects, participants seen in follow-up ($n = 163$), compared to non-participants ($n = 92$), were older (60 vs 57 years), were more frequently male (53% vs 43%) and Caucasian (80% vs 68%), with slightly lower BMI (26.1 vs 27.2). Baseline radiographic OA was present with similar frequency in participants and non-participants (42% vs 39%).

Characteristics of the study population ($n = 163$) are shown in Table I. Mean age at baseline was 57.6 years, 54.0% were female, mean BMI of 26.1, mean duration of pain of 11.8 years and mean normalized WOMAC pain, stiffness and function scores of 19.6, 23.7 and 17.4, respectively. KL X-ray grade 0 was seen in 39.9%, grade 1 in 20.7%, grade 2 in 21.2%, grade 3 in 10.0% and grade 4 in 8.2% of subjects at baseline. KL grade ≥2 was present in 39.4%.

The change in cartilage damage scores for each joint site and for the maximum knee cartilage score from baseline to 3-year follow-up are shown in Table II. In the lateral tibiofemoral (TF) compartment, only 8.1% and 6.4% of subjects had an increase in cartilage damage score in the femoral and tibial cartilage, respectively. In the

Table I
Characteristics of study population at baseline

	$n = 163$
Age (years)	57.6 (10.1)
Gender (% female)	54.0%
BMI (kg/m^2)	26.1 (4.2)
Pain duration (years)	11.8 (12.8)
WOMAC Pain (0–100)	19.6 (16.8)
WOMAC Stiffness (0–100)	23.7 (22.0)
WOMAC Function (0–100)	17.4 (17.0)
KL grade 0	39.9%
KL grade 1	20.7%
KL grade 2	21.2%
KL grade 3	10.0%
KL grade 4	8.2%
KL grade ≥2	39.4%

Data are shown as means SD, except for categorical variables where frequencies are shown.

Table II
Change in MRI cartilage damage score by ≥1 grade (0–3 scale) from baseline to follow-up

	Increased (%)	Unchanged (%)	Decreased (%)
Lateral femoral cartilage score	8.1	89.8	2.1
Lateral tibial cartilage score	6.4	93.6	0
Medial femoral cartilage score	14.1	84.2	1.7
Medial tibial cartilage score	8.9	90.6	0.5
Patellar cartilage score	8.0	92.0	0
Trochlear groove cartilage score	8.6	90.6	0.8
Maximum knee cartilage score*	22.7	76.6	0.7

* Maximum knee cartilage score was defined as the worst cartilage grade at any of the six joint sites (see methodology)

medial TF compartment, a cartilage damage score increase was seen in 14.1% and 8.9% for the femoral and tibial cartilage, respectively. In the patellar and trochlear groove cartilage, increased scores were seen in 8.0 and 8.6%, respectively. Using the maximum cartilage score at any joint site of the knee, an increase in cartilage damage was seen in 22.7% of subjects. A decrease in cartilage damage score was seen infrequently, ranging from 0% to 2.1% at different joint sites.

Overall, OA progression on MRI was seen in 15.5% of subjects (Fig. 2). For KL grades 0, 1, 2, 3 and 4, OA progression rates were 3.2%, 20.7%, 21.2%, 36.2% and 22.4%, respectively (Fig. 2). For subjects with KL grade ≥2, OA progression was 25.2% compared to a progression rate of 9.2% in those with KL grade <2. KL grade was a significant predictor of OA MRI progression with a HR (compared to KL grade 0) of 6.5 (95% CI 1.4–30.6) for KL grade 1, HR of 6.1 (95% CI 1.3-28.9) for KL grade 2, and HR of 9.2 (95% CI 1.9–44.8) for KL grade ≥3, after adjustment for age, gender and BMI (Table III).

Discussion

In this study, we report that worsening of cartilage, including incident damage in previously normal cartilage, occurred in 22.7% of subjects in this symptomatic population-based cohort with predominantly pre-radiographic stage of knee OA. Furthermore, we developed a definition of OA progression based on MRI and report an OA progression rate of 15.5%. Radiographic stage of disease, including KL grade 1, was significantly associated with an increased risk of OA progression.

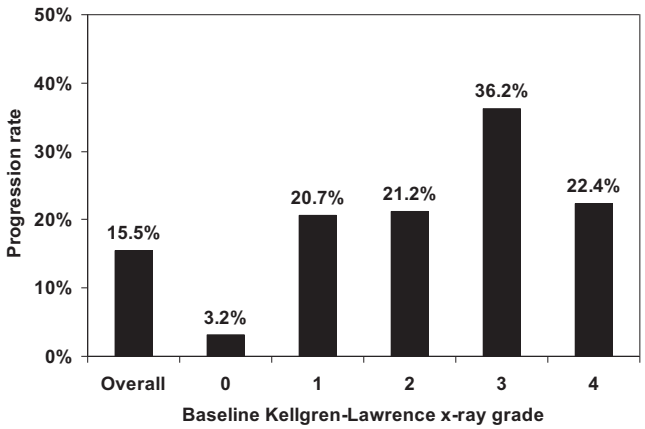

Fig. 2. Knee OA progression rate from baseline to 3-year follow-up – overall and by KL grade severity. OA progression on MRI was defined as cartilage loss of ≥2 grades in at least one joint site or cartilage loss of ≥1 grade in at least two joint sites (see methodology).

Table III
Association of radiographic stage of disease with OA progression on MRI*

	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
KL grade 0	Referent	Referent
KL grade 1	**7.0 (1.5–32.8)**	**6.5 (1.4–30.6)**
KL grade 2	**6.9 (1.5–31.9)**	**6.1 (1.3–28.9)**
KL grade ≥3	**11.6 (2.6–52.2)**	**9.2 (1.9–44.8)**

* OA progression on MRI was defined as cartilage loss of ≥2 grades in at least one joint site or cartilage loss of ≥1 grade in at least two joint sites (see methodology)
† Analyses adjusted for age, gender and BMI. Statistically significant results are in bold print.

In longitudinal MRI studies, progression rates of cartilage defects/damage based on semi-quantitative scoring have been reported to range from 17% to 68% over 1.8 to 2.5 years[2–6]. Higher rates of cartilage progression were seen in studies that included predominantly or exclusively subjects with radiographic OA[2–4]. Amin *et al*[2] reported progression of cartilage damage by ≥1 score (0–4 scale, based on modified Whole Organ MRI Score[19]) in 46% and 22% of knees in the medial and lateral compartments, respectively, over 2.5 years in symptomatic subjects, of whom 72% had a KL grade ≥2. Davies-Tuck *et al*[3] reported worsening of cartilage defects of 32–68% at different joint sites in a convenience sample of subjects with radiographic OA over 2 years. In a retrospective study by Biswal *et al*[4], in subjects with predominantly sports or motor vehicle accident injuries, development of new lesions and progression of lesions occurred frequently over 1.8 years. In that study, cartilage damage was assessed by grading lesion depth as well as size, which might account for the high rate of progression over a short period of time[4].

In contrast, studies that have included earlier disease cohorts have reported lower cartilage progression rates[5,6]. Boegard *et al*[5] included subjects aged 41–57 with chronic knee pain, only 32% of which had evidence of radiographic knee OA. An increase in cartilage defects was seen in 34% of lesions over 2 years[5]. In a study by Ding *et al*[6], where evidence of radiographic OA was present in 17% of subjects, worsening of MRI cartilage defects in any compartment by ≥1 score (0–4 scale) was reported in 33% of subjects at 2.3 years. Similar to the latter two studies, our cohort consisted predominantly of pre-radiographic OA and, in keeping with these studies, we have demonstrated a relatively low cartilage damage progression rate of 22.7% over 3 years.

Regression of cartilage damage occurred infrequently in our study. Other studies, with one exception[5] have reported higher frequencies of regression of cartilage damage[3,6,20]. It is not clear whether such differences in regression rates relate to stage of disease, methodology of MRI evaluations, such as MRI readings that are blinded to time sequence vs unblinded, or whether there is true regression.

In addition to reporting worsening of cartilage damage, we were interested in evaluating OA progression rates, using a definition based on MRI cartilage change. Although MRI has been used extensively to assess cartilage loss, it is unclear which of the many cartilage outcome measures are most responsive or most valid[21] and, to date, no standard MRI definition of OA progression exists. Our definition of OA progression has the advantage of using cartilage information from the knee as a whole and therefore reports a single progression rate, rather than progression of individual joint sites or compartments. More importantly, it serves as a conservative estimate of cartilage worsening, since a 1-grade change has to occur in at least two joint sites or a 2-grade change in at least one joint site, thereby minimizing the assignment of progression in cases where cartilage change is due to reader error. With this definition, we found an OA progression rate of 15.5% in this

symptomatic cohort. Amin *et al*[2] reported medial TF cartilage progression of ≥2 grades in at least one region in 14% of subjects and any cartilage loss at ≥2 regions in 21% of subjects, with lower frequencies seen in the lateral TF compartment. These rates are in keeping with our results. We are not aware of any other MRI studies reporting a similar outcome measure.

In this study, we report an increased risk of OA progression in subjects with radiographic abnormalities at baseline compared to those with normal X-rays. Interestingly, we also found that the risk of OA progression was similar in those with KL grade 1 [odds ratio (OR) 6.5] and KL grade 2 (OR 6.1), suggesting that KL grade 1 is a true disease entity, supporting the notion of 'pre-radiographic' disease. Our results are in keeping with previous studies where radiographic structural abnormalities, including KL grade 1, were reported to predict OA radiographic progression[22–24]. Similarly, in recent MRI studies, advanced stage of disease, assessed by radiographic joint space narrowing[7,8] or by cartilage defect severity[9,10], was associated with cartilage volume loss, both in healthy adults and in radiographic OA. Only one study reported that the presence of cartilage defects was not associated with cartilage volume loss over 2 years in the medial and lateral TF compartments, although an association was found for the patellofemoral compartment[25].

Our study is limited by the fact that we did not include an asymptomatic control group. As such, our findings are only generalizable to symptomatic populations. The development of a definition of OA progression based on MRI provides useful information, although this definition requires further validation in relation to symptomatic and structural outcomes. Our definition of cartilage worsening only took into account change in lesion depth, not lesion area extent. As a result, our study may have underestimated the rate of cartilage worsening. The choice of MRI sequence may also influence findings for progression or regression. In this study, assessment of cartilage damage was performed using the three sequences available, i.e., 3D sagittal SPGR with coronal and axial reformatted images, sagittal oblique dual-echo FSE T2-weighted and coronal fat-suppressed T2-weighted MRI. It is known that 3D gradient echo-type sequences are not ideal for focal defects[26,27]. Hence misclassification, specifically underscoring of focal cartilage defects, might occur with this type of sequence. While 3D gradient echo-type sequences may be suggestive of remaining cartilage, dual-echo and T2-weighted spin echo sequences may show full thickness loss. For this reason overscoring of cartilage damage on gradient echo sequences is also possible. When doubt persisted regarding cartilage grading, the lower cartilage grade was assigned. Cartilage assessment may also be influenced by MRI artifacts, leading to false-positive and false-negative findings. These include motion artifacts with the use of any MRI sequence, susceptibility artifacts that are especially relevant in 3D gradient echo-type sequences and partial volume effects which are seen in two-dimensional (2D) sequences with relatively thick slices.

The strengths of this study include the evaluation of a population-based cohort which allows for generalizability of results to the symptomatic population at large. This cohort includes the full spectrum of knee OA severity, which enhances our understanding of cartilage loss and OA progression at early pre-radiographic stage of disease.

In conclusion, in this population-based cohort with knee pain, OA progression over 3 years, defined by MRI, occurred in 15.5% of subjects. Radiographic stage of disease, including KL grade 1, was predictive of OA progression. Future interventions aimed at reducing progression of OA will therefore need to target not only symptomatic subjects with radiographic stages of disease, but also those with early abnormalities suggestive of pre-radiographic OA.

Contributions

Conception and design of the study: Cibere, Kopec, Esdaile, Thorne, Singer, Wong.

Acquisition of data: Cibere, Guermazi, Nicolaou, Esdaile.

Analysis and interpretation of data: Cibere, Sayre, Guermazi, Kopec, Esdaile, Thorne, Singer, Wong.

Drafting of article or revising it critically for important intellectual content: Cibere, Sayre, Guermazi, Nicolaou, Kopec, Esdaile, Thorne, Singer, Wong.

Final approval of the version of the article to be published: Cibere, Sayre, Guermazi, Nicolaou, Kopec, Esdaile, Thorne, Singer, Wong.

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Conflict of interest

Cibere: J. Cibere has received research grants from Centocor Research & Development Inc and from Amgen Inc.

Sayre: None.

Guermazi: A. Guermazi is President of the Boston Imaging Core Lab, LLC, and a consultant for Genzyme, Novartis, MerckSerono and Stryker.

Nicolaou: None.

Kopec: None.

Esdaile: None.

Thorne: None.

Singer: None.

Wong: H. Wong is a co-investigator on research grants received from Centocor Research & Development Inc and from Amgen Inc.

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