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ORIGINAL ARTICLE

Individuals with incident accelerated knee osteoarthritis have greater pain than those with common knee osteoarthritis progression: data from the Osteoarthritis Initiative

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Abstract We evaluated whether accelerated knee osteoarthritis (AKOA) was associated with greater pain and other outcomes and if outcomes varied over time differently among those with incident AKOA or common knee osteoarthritis (KOA), which we defined as a gradual onset of disease. We conducted longitudinal analyses among participants in the Osteoarthritis Initiative who had no radiographic KOA at baseline (Kellgren-Lawrence [KL] <2). Participants were considered AKOA if ≥1 knees progressed to KL grade ≥3 and common KOA if ≥1 knees increased in radiographic scoring within 48 months. We defined the index visit as the study visit when they met the AKOA or common KOA criteria. Our observation period included up to 3 years before and after the index visit. Our primary outcome was WOMAC pain converted to an ordinal scale: none (pain score=0/1 out of 20), mild (pain score=2/3), and moderate–severe pain (pain score >3). We explored 11 other secondary outcome measures. We performed an ordinal logistic regression or linear models with generalized estimating equations. The predictors were group (AKOA or common KOA), time (seven visits), and a group-by-time interaction. Overall, individuals with AKOA (n=54) had greater pain, functional disability, and global rating scale as well as slower chair-stand and walking pace compared with those with common KOA (n=187). There was no significant interaction between group and time for knee pain; however, there was for chair-stand pace and global rating scale. In conclusion, AKOA may be a painful and disabling phenotype that warrants more attention by clinicians and researchers.

Keywords Disability · Knee · Musculoskeletal pain · Osteoarthritis

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Introduction

It has recently been appreciated that 3 to 17 % of people experience accelerated knee osteoarthritis (AKOA), a rapid progression of structural damage that leads to end-stage disease in less than 4 years [1–3]. Individuals who develop AKOA are more likely to be older, overweight, and more likely to experience a recent knee injury than individuals with a slower onset of osteoarthritis or no progression at all [1, 3]. Despite evidence that individuals with AKOA may be unique at baseline, it is unclear if knee pain, other patient-reported outcomes, and physical performance measures differ between individuals who develop AKOA versus those with a gradual

onset that is typically associated with common knee osteoarthritis. If individuals with AKOA experience more symptoms and impaired function than those with common knee osteoarthritis, it would emphasize the clinical relevance of this subset of knee osteoarthritis and the necessity to recognize individuals at risk for AKOA. Based on one study, individuals with incident AKOA, using a broad definition, are more likely to report greater worsening of knee pain and disability than individuals who do not develop osteoarthritis [4]. Unfortunately, it is unclear if their symptoms were worse than other individuals with slower disease onset and when the changes in knee symptoms occurred relative to the incidence of AKOA.

It would be important to understand when the symptoms worsen and if they continue to worsen for an extended period. Therefore, we aimed to evaluate whether AKOA was associated with greater pain and other outcomes and if outcomes varied over time differently among those with AKOA or common knee osteoarthritis, which we defined as a gradual onset of disease. We hypothesized that individuals with incident AKOA or common knee osteoarthritis would initially report similar symptoms. However, after the incidence of AKOA these individuals would report greater symptoms than those with common knee osteoarthritis. The goal was to gain a better understanding of the clinical implications of a phenotype of osteoarthritis that is characterized by accelerated joint damage.

Materials and methods

We identified individuals with incident AKOA or common knee osteoarthritis, which had a more gradual onset, and assessed symptoms and function over time using data from the Osteoarthritis Initiative (OAI). The OAI is a multicenter cohort study of individuals with or at risk for knee osteoarthritis that collected longitudinal clinical and image data [5] from 4796 participants. Four clinical sites (Memorial Hospital of Rhode Island, The Ohio State University, University of Maryland and John Hopkins University, and the University of Pittsburgh) recruited participants between February 2004 and May 2006. We identified two groups of participants—those with AKOA and those with a more common and gradual osteoarthritis onset. We then defined an index visit as the OAI study visit when they met the AKOA or common knee osteoarthritis criteria. Our observation period included up to 3 years before and after the index visit, if possible. Our primary outcome was WOMAC pain score, and we explored 11 other secondary outcome measures: knee-specific disability (WOMAC function), global impact of arthritis, walking pace, chair-stand pace, maximum isometric knee extension force, maximum isometric knee flexion force, Physical Activity Score for the Elderly, Short-Form 12 Physical Component Score, Short-Form 12 Mental Component Score, depression (Center for Epidemiologic Studies-Depression Scale), and number of prescription medicines. OAI data are available for public access [6]. Institutional review boards at each OAI clinical site and the OAI coordinating center (University of California, San Francisco) approved the OAI study and all participants provided informed consent prior to participating in the OAI.

Participant selection

Among participants with no baseline radiographic knee osteoarthritis (Kellgren-Lawrence [KL] grade <2) in either knee (n=1930), we identified two groups that we defined based on radiographic definitions: (1) incident AKOA: at least one knee progressed to end-stage knee osteoarthritis (KL grade 3 or 4) within 48 months and (2) common knee osteoarthritis: at least one knee increased in radiographic scoring within 48 months (excluding those defined as AKOA). Based on the definitions, an individual with incident AKOA had to develop a definite osteophyte *and* definite joint space narrowing, which suggests that multiple tissues progressed. Furthermore, an individual classified as common knee osteoarthritis showed a slower onset of disease defined by progression from either no radiographic osteoarthritis to a possible or definite osteophyte or from a possible osteophyte to a definite osteophyte. A prior study has suggested that a change of one KL grade may represent slow progression because this subtle change is not associated with worsening knee symptoms [4]. We omitted 364 (19 %) participants because missing radiographic scores precluded our ability to determine group assignment. We previously described the selection criteria and group characteristics in more detail [3].

Index visit and observation period

After identifying the two groups of interest, we determined the index visit. For individuals with AKOA, the index visit was when they first had a KL grade ≥3. For individuals with common knee osteoarthritis, the index visit was when they first had an increase in KL grade. Ten (5 %) individuals with common knee osteoarthritis and 3 (6 %) individuals with AKOA had missing radiographic readings between visits when the increase in KL grade occurred. Hence, we selected the visit with missing data as the index visit. The index visit could have occurred at the 12-, 24-, 36-, or 48-month follow-up visit. Our observation period included up to 3 years before and after the index visit, if possible. We included clinical data from baseline to the 84-month OAI follow-up. Participants typically went to the OAI clinical sites for each visit except for the 60- and 84-month OAI visits, which were phone interviews. We censored data after an individual had a total knee replacement.

All individuals with common knee osteoarthritis progressed during a 1-year period (e.g., the year between the

24-month and 36-month visit). Hence, we conducted a secondary analysis among 34 individuals with AKOA that progressed from no knee osteoarthritis to end-stage osteoarthritis during a 1-year period.

Knee radiographs

Bilateral, weight-bearing, fixed-flexion, posterior-anterior knee radiographs were obtained at baseline and the first four annual OAI visits. Central readers, who were blinded to sequence of follow-up radiographs, scored paired images for KL grades (0 to 4). The read-reread agreement for these readings was good (weighted kappa=0.70 to 0.78). KL grades are publicly available (Files: kXR_SQ_BU0#_SAS; version 0.6, 1.6, 3.5, 5.5, and 6.3) [6].

Clinical data

The study outcomes, which we selected a priori, were acquired based on a standard protocol (data and protocol are publicly available [6]). Our primary outcome was WOMAC pain subscale score because knee pain is likely to contribute to diminished function and quality of life. We explored 11 other secondary outcome measures (see list above). All of the outcome measures were available at each clinical visit. For the two phone-interview visits (i.e., 60- and 84-month visits), a limited set of outcome measures were available: WOMAC subscales, Center for Epidemiologic Studies-Depression Scale (CES-D), and a global rating scale (0–10). The global rating scale was based on the question "Considering all ways knee pain and arthritis affect you, how are you doing today?". The data are publicly available (Files: allclinical0#; version 0.2.2, 1.2.1, 3.2.1, 5.2.1, 6.2.1, 7.2.1, and 8.2.1) [6].

Statistical analyses

We initially explored the distribution of each outcome measure across visits. Since over 40 % of person-visits had a WOMAC pain score=0 (possible range=0 to 20), we converted it to an ordinal scale: no pain (pain score=0 or 1, 60.8 % of person-visits), mild pain (pain score=2 or 3, 12.7 % of person-visits), and moderate–severe pain (pain score >3, 26.6 % of person-visits). Similarly, over 40 % of person-visits had a WOMAC function score=0 (possible range=0 to 68); hence, we converted it to an ordinal scale: no disability (functional score=0, 45.3 % of person-visits), mild disability (functional score=1 to 6, 19.9 % of person-visits), and moderate–severe disability (functional score >6, 34.8 % of person-visits). Finally, over 50 % of person-visits had a global rating scale score=0; therefore, we converted it to an ordinal scale: no impact (global rating scale=0 or 1, 67.9 % of person-visits), mild impact (global rating scale=2 or 3, 22.8 % of person-visits), and moderate–severe impact (global rating scale >3, 9.3 % of person-visits). The selected cut-points were based on the distribution of the scores and ensuring that the categories met the proportional odds assumption of the analyses described below.

For knee pain and other ordinal outcome measures, we performed an ordinal logistic regression with generalized estimating equations (GEE) to account for within-participant correlations over time (independent correlation structure). For the ordinal logistic regression models, we verified that we met the proportional odds assumption based on the results of the Score Test ($p>0.05$). Similarly, for continuous outcomes, we developed a linear model using GEE (autoregressive [1] correlation structure). The predictors in all models were group (AKOA or common knee osteoarthritis) and time (seven visits, categorical variable). We also ran a final set of models with a group-by-time interaction.

All knees with common osteoarthritis progressed during a 1-year period while individuals with AKOA could take longer to progress. Therefore, we conducted a secondary analysis among 34 individuals with AKOA that progressed from no knee osteoarthritis to end-stage osteoarthritis during a 1-year period.

Due to the small sample size, we did not adjust for potential confounders in our primary analyses. However, as a secondary analysis, we ran two extra sets of models with knee pain: one with age (continuous) and another model with body mass index (continuous) as covariates. We selected age and body mass index because we have previously found in this study sample that both participant characteristics are associated with AKOA and common knee osteoarthritis. Furthermore, individuals with AKOA tend to be older than those with common knee osteoarthritis [3]. All analyses were performed in SAS 9.3 (Cary, NC, USA).

Results

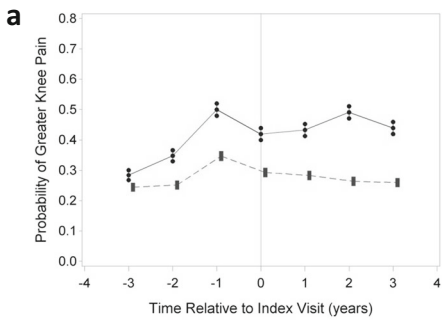
We previously described the baseline characteristics of OAI participants with common knee osteoarthritis (n=187, 65 % female, mean age of 58.0 [8.3] years, mean body mass index of 27.8 [4.5] kg/m^2) and AKOA (n=54, 63 % female, mean age of 61.8 [8.6] years, mean body mass index of 28.9 [4.7] kg/m^2) [3]. Among those with common knee osteoarthritis 82 (44 %) progressed from KL 1 to 2, 76 (41 %) progressed from KL 0 to 1, and 29 (16 %) progressed from KL 0 to 2. Among those with AKOA, most individuals progressed from no radiographic knee osteoarthritis to end-stage knee osteoarthritis in less than 12 months (63 %), 17 % progressed over 2 years, 13 % progressed over 3 years, 2 % progressed over 4 years, and 6 % had a missing interim X-ray that precluded us from determining the precise visit of progression. Most individuals with AKOA (n=34, 63 %) progressed from KL 1 to 3. Furthermore, 17 (31 %) individuals with AKOA progressed

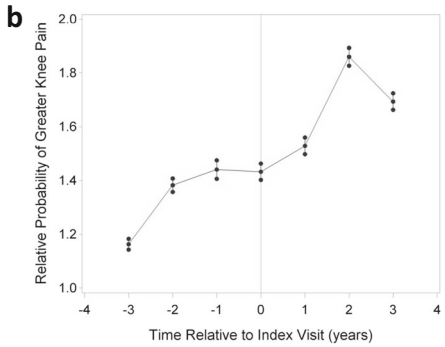
from KL 0 to 3, and 3 (6 %) individuals progressed from KL 0 or 1 to 4. Figures 1, 2, 3, and 4 indicate the number of participants at each visit for the primary outcome and secondary outcomes that had a significant interaction between group and time.

We found statistically significant main effects for group, when adjusting for time, that indicated that individuals with AKOA had greater knee pain (WOMAC pain: odds ratio [OR]=2.00, 95 % confidence interval [95 % CI=1.33 to 3.00), greater knee-specific disability (WOMAC function: OR=1.68, 95 % CI=1.10 to 2.55), greater global impact of arthritis (OR=1.89, 95 % CI=1.18 to 3.03), slower walking pace (estimate [standard error]=−0.07 [0.03]), and slower chair-stand pace (estimate=−0.05 [0.02]) compared with those with common knee osteoarthritis (Figs. 1, 2, and 3). We found no significant group differences, while adjusting for time, for maximum isometric knee extension force (estimate=−13 [17]), maximum isometric knee flexion force (estimate=−13 [8]), Physical Activity Score for the Elderly (estimate=−12 [11]), Short-Form 12 Physical Component Score (estimate=−1.3 [1.1]), Short-Form 12 Mental Component Score (estimate=0.6 [1.0]), depression (Center for Epidemiologic Studies-Depression Scale; estimate=0.1 [0.9]), and number of prescription medicines (estimate=−0.59 [0.38]).

There was no significant interaction between group and time for knee pain (see Fig. 1a); however, there was for chair-stand pace (p=0.008) and global impact of arthritis rating scale (p=0.04; see Figs. 2 and 3). Both groups started with similar chair-stand pace, but individuals with common knee osteoarthritis subtly and gradually improved over time while individuals with AKOA gradually slowed until their index visit and then fluctuated over time (see Fig. 2). Individuals with common knee osteoarthritis were gradually less likely to report greater global impact of arthritis at each visit while individuals with AKOA were more likely to report greater global impact of arthritis at each visit before the index visit (see Fig. 3).

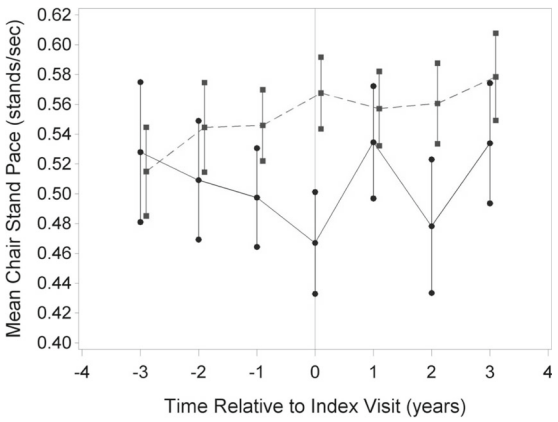
Our secondary analyses among individuals with AKOA that progressed from no knee osteoarthritis to end-stage osteoarthritis during a 1-year period had similar results as the primary analyses but with attenuated estimates (see Fig. 4). The only significant differences between groups were greater knee pain (OR=1.82, 95 % CI=1.09 to 3.02) and slower walking pace (beta estimate=−0.7 [0.03]) among those with AKOA. There was also a significant interaction between group and time for the global rating scale (p=0.03).





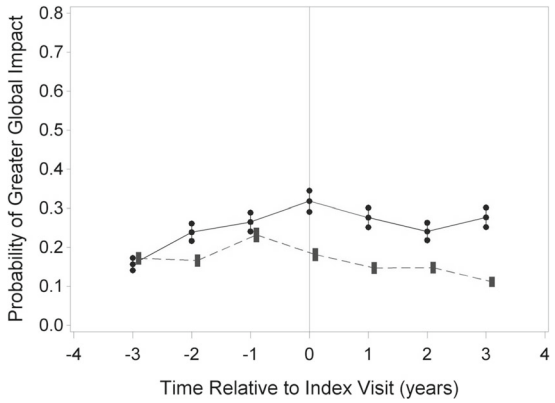
Time	-3	-2	-1	0	1	2	3
AKOA ●●●	n=30	n=40	n=54	n=52	n=47	n=50	n=50
Common KOA ■■■	n=53	n=93	n=187	n=185	n=183	n=183	n=181

Fig. 1 Probability of greater knee pain over time among accelerated knee osteoarthritis (AKOA) and common knee osteoarthritis (KOA). **a** Mean (95 % confidence interval) probability of having a higher category of knee pain over time among those with AKOA or KOA. **b** Relative probability (mean probability of AKOA reporting greater pain divided by mean probability of KOA reporting greater pain) of individuals having greater knee pain. WOMAC pain ordinal scale: no pain=WOMAC pain=0 or 1 (61 % of person-visits), little pain=WOMAC pain=2 or 3 (13 % of person-visits), moderate–severe pain=WOMAC pain score >3 (27 % of person-visits). *Error bars*=95 % confidence interval. The probabilities were derived from the ordinal logistic regression with estimating equations



Time	-3	-2	-1	0	1	2	3
AKOA ●●●	n=30	n=35	n=48	n=44	n=35	n=23	n=28
Common KOA ■■■	n=51	n=90	n=176	n=166	n=154	n=137	n=113

Fig. 2 Mean chair-stand pace over time among accelerated knee osteoarthritis (AKOA) and common knee osteoarthritis (KOA). There was a significant group*time interaction for chair stand (p=0.008). *Error bars*=95 % confidence interval



Time	-3	-2	-1	0	1	2	3
AKOA ●●●	n=30	n=40	n=54	n=52	n=47	n=50	n=50
Common KOA ■■■	n=53	n=93	n=187	n=185	n=183	n=183	n=181

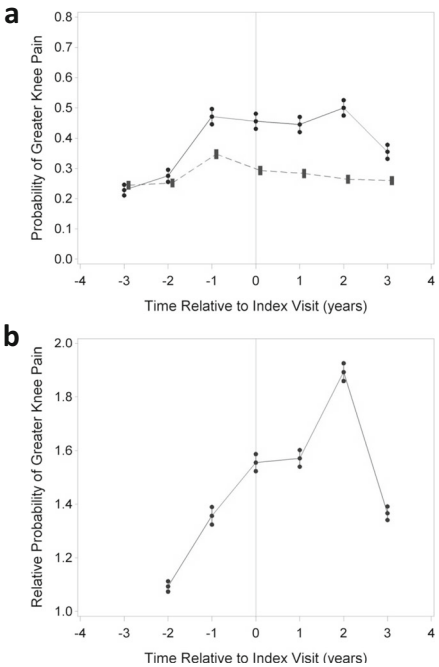
Fig. 3 Probability of a being in a higher category of global impact over time among accelerated knee osteoarthritis (AKOA) and common knee osteoarthritis (KOA). Global rating ordinal scale: no impact by arthritis=global rating scale=0 or 1, mild impact by arthritis=global rating scale=2 or 3, moderate–severe impact by arthritis=global rating scale >3. There was a significant group*time interaction for global impact (p=0.04). *Error bars*=95 % confidence interval. The probabilities were derived from the ordinal logistic regression with estimating equations

Finally, adding age or body mass index to the models did not change the results of the current analyses for knee pain (age-adjusted model: OR for group effect=2.13, 95 % CI=1.39 to 3.27, group*time interaction p=0.62; body mass index adjusted model: OR for group effect=1.92, 95 % CI=1.28 to 2.87, group*time interaction p=0.53).

Discussion

Individuals with AKOA are more likely to report greater pain and functional limitations compared with individuals with common knee osteoarthritis, regardless of time (before or after the index visit). Individuals with AKOA tend to report being more affected by their knee pain (global rating scale) and have diminished performance on the chair-stand test years before developing end-stage knee osteoarthritis—a similar trend although not significant was also detected for knee pain. Overall, AKOA when compared with common knee osteoarthritis is a painful and disabling phenotype and it warrants more attention from clinicians and researchers. Clinicians should be concerned about adults without radiographic osteoarthritis who report knee pain because it may be an early sign of AKOA.

Our knee pain and disability findings complement a prior study that used data from the OAI and Cohort Hip and Cohort Knee study [4]. Our study used a more conservative definition of AKOA (not including knees that progress from KL 0 to KL 2 [definite osteophyte]) and found that people may complain of greater pain and functional limitations before the onset of AKOA.



Time	-3	-2	-1	0	1	2	3
AKOA ●●●	n=16	n=20	n=34	n=34	n=29	n=30	n=31
Common KOA ■■■	n=53	n=93	n=187	n=185	n=183	n=183	n=181

Fig. 4 Probability of having greater knee pain over time among common knee osteoarthritis (KOA) and accelerated KOA (AKOA) when limited to the 34 knees that developed AKOA in 1 year. Probability of greater knee pain over time among accelerated knee osteoarthritis (AKOA) and common knee osteoarthritis (KOA). **a** Mean (95 % confidence interval) probability of having a higher category of knee pain over time among those with AKOA or KOA. **b** Relative probability (mean probability of AKOA having greater pain divided by mean probability of KOA having greater pain) of AKOA having greater knee pain. WOMAC pain ordinal scale: no pain=WOMAC pain=0 or 1 (61 % of person-visits), little pain=WOMAC pain=2 or 3 (13 % of person-visits), moderate–severe pain=WOMAC pain score >3 (27 % of person-visits). *Error bars*=95 % confidence interval. The probabilities were derived from the ordinal logistic regression with estimating equations

Individuals with AKOA may initially be characterized by subtle changes related to knee pain that precede radiographic progression [7, 8]. In preliminary analyses, we found that individuals with incident AKOA (n=18) often have cartilage damage and meniscal pathology before any radiographic evidence of AKOA [8]. Within the OAI, magnetic resonance imaging revealed that individuals with no radiographic osteoarthritis (KL=0) had a high prevalence of cartilage damage (76 %), bone marrow lesions (61 %), and meniscal pathology (>20 %). In that study sample, these lesions were associated with prevalent knee symptoms and incident symptoms [7]. Magnetic resonance images acquired prior to radiographic progression may help us understand the etiology of AKOA and why these individuals experience pain during early stages of AKOA development. Ultimately, magnetic resonance

imaging may enable clinicians to identify high-risk adults who report knee pain without radiographic osteoarthritis.

The findings of this study help clarify a conceptual model for the etiology of AKOA. Based on our prior work, being older and overweight are key risk factors for AKOA [3]. Furthermore, aging [7, 9, 10] and being overweight [7, 11, 12] are associated with bone marrow lesions, cartilage damage, and meniscal pathology, which are related to knee symptoms among individuals without osteoarthritis [7]. Knee pain is a risk factor for a new knee injury [13], which is likely a catalyst for AKOA [3]. Once an individual with AKOA develops end-stage knee osteoarthritis, it appears that at least for the next 3 years they are likely to report greater pain and functional limitations than other individuals. To prevent this sequela, it may be vital to recognize patients without osteoarthritis who report knee pain because their pain may be early evidence of AKOA, which is a painful and disabling phenotype. Furthermore, it will be advantageous for future research to identify which lesions among knees without radiographic osteoarthritis are risk factors for AKOA because this could help us identify at risk patients.

While this study offers novel insights into the clinical implications of AKOA, there are some important limitations to this study. First, we had a small sample size of individuals with AKOA. This may limit the generalizability of our findings and our ability to detect significant interactions. For example, in Fig. 1a, the two groups have a similar probability of reporting greater pain 3 years before the index visit, but as can be seen in Fig. 1b, individuals with AKOA increase their probability of reporting greater pain over time relative to the probability among those with common knee osteoarthritis. Despite our sample size, we found a significant group effect for knee pain, our primary outcome, and several secondary outcomes supported our primary findings. We also acknowledge that analyzing 11 secondary outcomes raises issues with multiple comparisons but we believed it was important to include these outcomes to support the primary findings, regarding knee pain, and to help characterize individuals with AKOA. The small sample size also limited our ability to control for multiple potential confounders, but when we adjusted for age and body mass index, the results agreed with our primary findings. These analyses provided us initial insights into the implications of AKOA. Future studies may explore novel statistical techniques to assess trajectories of joint symptoms over time among those with and without AKOA.

In conclusion, AKOA is a painful and disabling phenotype in which symptoms and functional limitations may precede the development of end-stage knee osteoarthritis. Furthermore, the effect of AKOA may linger for at least 3 years after the development of end-stage knee osteoarthritis. Clinicians should be concerned about adults without radiographic osteoarthritis who report knee pain because it may be an early sign of AKOA.

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Compliance with ethical standards

Ethical standards Institutional review boards at each OAI clinical site and the OAI coordinating center (University of California, San Francisco) approved the OAI study and all participants provided informed consent prior to participating in the OAI.

Disclosures None

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