Introduction

The primary goal of this session was to summarize the existing literature on the performance characteristics of radiographic methods for evaluating progression of tibiofemoral patelloarthropy in the OA knee.

The goal of serial radiography in knee OA is accurate and reproducible measurement of progression of the radiographic features of the disease. The tibiofemoral joint space width (JSW), or the distance between the radiographic projection of the cortices of the articulating femoral and tibial bone surfaces, is a surrogate measure of articular cartilage thickness. Measurement of loss of tibiofemoral JSW, or joint space narrowing (JSN), from weight-bearing radiographs is the most widely used radiographic parameter for assessing knee OA progression. Variability in the radioanatomic positioning of the knee across repeated examinations is an important source of error in the measurement of JSN. Changes between exams in the degree of knee flexion can have a critical influence on JSW measurements, as only a small region of the convex femoral surface articulates across the load bearing axis with the tibial plateau in any one position and cartilage loss occurs differentially across the femoral surface. Varus—valgus laxity increases with worsening of knee OA; in a lax joint, different regions of opposing articular surfaces may be in contact at different times. Change between exams in the position of the knee with respect to the x-ray beam and the x-ray film can alter the sectional plane of the inter-bone space that appears in the radiograph image. JSW is affected by radiographic compression from weight-bearing and may change depending upon how an individual distributes weight between the limbs; avoidance of weight-bearing may artfactually increase JSW on that side.

Performance metrics

Dr Lassere began the session with presentation of a conceptual framework that will be applied in evaluating the existing literature on the performance of radiographic methods for assessment of structural progression of knee OA. This assessment was still in progress at the time of the meeting.

Evaluation of radiography protocols for assessing the tibiofemoral joint space (JS) typically focuses on two performance characteristics. The first is the test—retest precision of the measurement of JSW from repeat films obtained over very short time intervals (minutes, hours, days, and a few weeks) in which true changes in cartilage thickness are probably very small. Over such short intervals and in the absence of true change, differences in JSW between serial radiographs of the same knee represent measurement error due to variable positioning, radiography technique or the measurement process. In a test—retest experiment, the common standard deviation of repeated measurements of JSW, sometimes called the standard error of the measurement—SEm — and estimated by the root mean square error — RMS error — from an analysis of variance, is an indicator of the measurement’s precision. Precision can also be expressed as the coefficient of variation — CV% — which is the common standard deviation of repeated measurements (or RMS error) divided by the average of the repeated measurements, times 100. A second key performance characteristic is sensitivity to JSN measured from serial films obtained over longer time intervals in which real loss of cartilage thickness is likely to occur in knees with OA. Sensitivity is typically expressed in terms of the CV% of the measured changes in JSW (standard deviation of change in JSW/mean change in JSW times 100) or its inverse, the standardized response mean — SRM (mean change/standard deviation of change). Measures of sensitivity reflect the magnitude of true change in JSW, true variability in this change in the sample and measurement error. Smaller variability of JSN relative to the mean JSN is associated with increased sensitivity for detection of real change. Stated another way, the smaller this ratio the greater the statistical power for detecting a significant change (or difference in change between groups) for a given sample size and underlying rate of JSN.

The short-term precision and long-term sensitivity to change of methods for assessing JSN are theoretically related, with more precise techniques generally more sensitive in the detection of change. But a large unknown in this equation for radiography in knees with OA is to what extent the degree of measurement error due to variability in knee positioning and radiography technique over short intervals (a few hours or days) is constant as the time between radiographs increases. For a variety of reasons, short-term reproducibility of radioanatomic positioning and short-term precision of JSW measurement may not be accurate guides to long-term performance. Changes in factors that can influence positioning and technique are more likely
to occur when the time between exams is months or years. These include changes in radiographer performance due to personnel turnover, deterioration of morale or drift in procedures. In addition, for the knee with OA changes in anatomy (deterioration of ligamentous support, increasing valgus laxity, and flexion contracture), changes in leg musculature and the waxing and waning of knee pain may all impede reproducible positioning. Some radiography protocols may be more robust than others to the effect of these factors. Consequently, long-term performance and sensitivity to change must be assessed directly from repeat films obtained over time intervals in which real loss of JS and other changes are likely to occur. It is also preferable that such evaluations take place in settings comparable to those in which the technique will be applied.

Measurement error attributable to variability in radioanatomic positioning can be inferred from short-term test–retest studies with repositioning. However, in long-term studies of knees with OA it may not be possible to disentangle the relative contributions to overall variability in JSN that arise from variable radioanatomic positioning vs variability arising from true differences among knees in the rate of cartilage loss. Consequently, the most informative and valid data for comparing the performance of different radiography acquisition techniques in detecting change in JSW are provided by head-to-head comparisons of these protocols applied in the same knees over the same time interval in longitudinal studies. This approach controls for study and cohort differences that may influence true variability in JSN over time or introduce other sources of variability not inherent to the radiography technique, per se. Such factors include differences in the disease severity and disease characteristics of subjects (e.g., presence of lateral compartment disease and flexion contractures, inclusion and exclusion criteria based on the amount of remaining JSW); different time intervals between examinations; differences in study setting (e.g., single lab vs multicenter field setting); manual vs automated JSW measurements; the care and skill exercised by the investigators; recruitment of subjects from the community vs clinic populations; and inclusion only of knees with OA or of both diseased and nondiseased knees.

Techniques for measuring JSW from knee films, which were discussed at the Bethesda Workshop by Dr Jeff Durfee, are another potential source of measurement error. While manual and automated measurements of JSW differ in precision, with the advantage going to automated measurements, the effect of this factor appears to be relatively small compared to that due to variability in radiography technique. There is very little, if any, data comparing the performance of various automated techniques for JSW measurement. In addition, studies are needed that compare the performance of alternative quantifications of JSW, such as the minimum JSW and the average JSW, particularly with respect to their robustness to radiography and positioning variability. For example, one recent study found that the SRMs for change in minimum JSW were substantially better in pairs of knee films that met radioanatomic positioning criteria compared to knees that did not. In contrast, the SRMs for changes in mean JSW and JS area were not affected by poor positioning.

Comparative performance of knee radiography protocols
There are two basic approaches in use to minimize variability in radioanatomic positioning of the knee across exams (The technical details of these protocols are reviewed thoroughly elsewhere in this volume.) In the Semi-flexed AP/PA protocol, fluoroscopy is used to visually align the central ray with the anterior and posterior tibial plateau rims and the floor of the tibial plateau by altering the degree of flexion for each knee. Alternatively, the nonfluoroscopic metatarsalphalangeal (MTP) and Fixed-Flexion protocols have been developed to fix the position of the knee relative to the x-ray source, the x-ray beam and the film in a manner that is reproducible between exams. In addition, a hybrid approach (the so-called “Lyon-Schuss”) has been developed that draws on both the Fixed-Flexion positioning technique and fluoroscopic visualization to align the x-ray beam with the tibial plateau rims by modifying the x-ray beam angle for each knee.

Importantly, all of these protocols position the knee with some degree of flexion in order to image a more posterior sectional plane of the medial femoral JS that corresponds to the location of peak load on the femoral cartilage during walking and stair climbing and where early cartilage loss often occurs. Knee flexion also avoids artifactual increases in apparent JSW that occur when the knee is fully extended. The protocols differ, however, in the factors that determine the degree of knee flexion and in the distribution of flexion values typically achieved. In the fluoro-guided semi-flexed view, natural knee-to-knee variability in the angulation of the tibial plateau determines the degree of tibial angulation and knee flexion that will provide alignment of the tibial rims. In the MTP and Fixed-Flexion (with and without fluoroscopy) protocols, tibial angulation is determined by the length of each subject’s foot and tibia. In all views individual patient comfort will influence to some degree the degree of femoral angulation achieved during the examination, while in the Fixed-Flexion protocols femoral angulation is also affected by the degree of obesity since the front of the legs are pressed up against the bucky tray (or a positioning frame, when used). As reported in a recent review, the fluoro-guided Semi-flexed and MTP views provide a smaller amount of knee flexion, on average about 7–10 degrees, compared to an average of 20–30 degrees for Fixed-Flexion with or without fluoroscopic guidance. These differences in knee flexion will influence the protocol’s sensitivity to femoral cartilage loss in various locations in the posteroanterior dimension. However, the optimal degree of flexion for assessing medial JS loss by radiography is uncertain and further study is needed.

Dr Ken Brandt summarized the published findings of the recent Versailles-NEGMA Workshop report, which systematically reviewed the existing data on short- and long-term performances of knee radiography protocols. Studies of the precision of JSW measurements from repeat films over short intervals show that fluoroscopically guided and nonfluoroscopically fixed positioning protocols (all with knees in flexion) perform comparably, with SEMs ranging from about 0.1 to 0.3 mm. All of these approaches tend to have better precision for JSW than the conventional weight-bearing, fully extended AP view, for which SEMs range from about 0.2 to 0.6 mm. For the conventional extended AP view, guidelines to further standardize positioning and the use of fluoroscopic visualization have each been shown to marginally improve precision.

The Versailles-NEGMA Workshop report concluded that insufficient data were available on performance, practicality and cost of alternative radiographic protocols to determine which protocols are the most suitable for disease modifying osteoarthritis drug (DMOAD) trials. A key gap in data at the time of the Versailles Workshop was data on long-term
performance and particularly head-to-head comparisons of protocols. Most of the existing long-term longitudinal data on performance are from studies using a single radiography protocol in a unique cohort of knees. Direct comparison of performance between methods using these data is limited, as suggested above, by study-specific factors that affect the actual rate of JSN and its variability. Consequently it is difficult to draw inferences from these studies about the relative sensitivity of various techniques by comparing performance metrics, such as the SRM, which are based on ratios of the mean of JSN and its variability. Even for the same method applied with the identical measurement error in two samples, these ratios will be greatly influenced by the sample-specific mean and variability in true rates of JSN.

Nevertheless, the Versailles Workshop report concluded that the conventional standing, fully extended AP protocol without fluoroscopic guidance was not suitable for use in DMOAD trials. This was based on data suggesting inferior short-term precision of JSW, including results from one head-to-head comparison to a flexed knee fixed positioning protocol, and a relatively large variance in JSN in relation to the observed mean seen in most of the published longitudinal data using this technique. Also cited in the report were data on alignment of the x-ray beam with the medial tibial plateau margins, an indicator of radioanatomic positioning, that suggested poor reproducibility between repeat exams, and an association of this positioning variability with greater variance in JSN.

An oft-mentioned concern with the conventional extended AP view is that the degree of knee extension adopted by the patient may vary with the waxing and waning of knee pain and that this may systematically affect measured JSW. Small changes in flexion with this protocol translate into disproportionally large changes in JSW due to a greater thickness of articular cartilage and meniscus in the anterior joint surfaces as well the effect of the femoral condyles rising up onto the anterior edge of the tibial rim. Thus, it has been suggested that a treatment which reduces knee pain might incorrectly appear to have a beneficial effect on JSN when assessed using the extended AP protocol as knees exhibiting pain improvement are more fully extended during follow-up radiography.

Dr Lucio Rovati thoroughly explored this possibility in his presentation of a reanalysis focusing on subsets of pain improvers from two published randomized controlled trials of glucosamine sulfate. Both trials used an extended AP protocol and both showed a reduction in knee pain and a decrease in JSN in the glucosamin sulfate treated groups compared to placebo. The reanalysis found that reductions in JSN in the glucosamine treated patients were independent of the greater pain relief observed in these subjects during the trial. This evidence strongly suggests that the JSN results of the two trials were not artifacts of greater knee pain improvement in the treated patients. However, data on knee flexion or radioanatomic positioning indicators in the two treatment groups were not available to directly confirm this conclusion. Interestingly, while both trials applied fluoroscopic guidance to the extended AP view, it is unclear how fluoroscopy was used in these studies to control radioanatomic positioning variability.

Two abstracts were presented at the Bethesda OMERACT workshop (both since published) from head-to-head comparisons of knee radiography protocols, adding new data on the comparative sensitivity of alternative protocols. One study compared the fluoro-guided AP semi-flexed protocol with one of the nonfluoroscopic fixed positioning alternatives, the semi-flexed MTP view, in 52 OA knees radiographed 14 months apart with both protocols. The point estimates for JSN at 14 months, and the variability in these estimates, differed between the fluoro-guided and nonfluoroscopic MTP methods, with the fluoro-assisted protocol showing a greater mean loss of JS and less variability in this estimate. Although neither method detected a statistically significant change, the results suggest that in a longer or larger study of the same patient population the fluoro-guided protocol would be more sensitive to JSN. A limitation of this study is that a manual technique was used to measure JSW in the nonfluoro view while an automated technique was applied to the fluoro-guided view; most studies show that automated techniques are more precise.

The other abstract reported results of a head-to-head comparison of a fluoro-assisted PA Fixed-Flexion protocol (so-called “Lyon-Schuss”) with a fluoro-assisted fully extended standing AP view. Fifty-eight OA knees were radiographed 24 months apart using both protocols. In both protocols, the technologist used fluoroscopy to vary the x-ray beam angle in an attempt to align the anterior and posterior medial tibial plateau rims. In the fluoroscopic Fixed-Flexion view the knee was radiographed in 20°–30 degrees of flexion. The point estimate for loss of JS at 24 months was greater, and the variability in the estimate less, for the Fixed-Flexion compared to the extended view. Consistent with this, the fluoro-guided Fixed-Flexion view showed a statistically significant loss of JS, whereas the extended view did not. This study demonstrates that a knee radiography protocol with the knee at 20°–30 degrees of flexion and fluoroscopy used to align the x-ray beam with the tibial plateau rims was able to detect a statistically significant loss of JS in a small sample of OA knees over 24 months. In addition, knee flexion of 20° or greater increased the responsiveness of the measure of JSN independent of the use of fluoroscopy to direct the x-ray beam.

With the addition of these two head-to-head, longitudinal comparative studies the evidence documenting sensitivity to JSN in OA knees is strongest for two fluoroscopically guided protocols. In one study the fluoro-guided Fixed-Flexion protocol outperformed a fluoro-guided extended AP view and detected a significant decrease in JSN at 24 months in a relatively small sample of OA knees. In the other study the evidence suggested that the fluoro-guided semi-flexed AP view performed better than the nonfluoro fixed position MTP view, although the former did not detect significant JSN. Both of these comparative studies include only a small number of knees. Additional single protocol and head-to-head comparative data in a variety of patient samples and research settings are needed to confirm the longitudinal performance characteristics of the different protocols.

Challenges of fluoro-assisted knee radiography

The apparent performance advantages of the fluoro-guided protocols are accompanied by a number of added practical, logistical, budgetary and technical challenges. The fluoro-guided methods are generally more costly to acquire than the nonfluoroscopic alternatives, which cost about the same as each other. This is in part because the fluoro-guided protocols place greater demands on the technologist, take more time and require specialized radiography equipment. Fluoroscopy also carries greater radiation exposure to the subject, with the additional dose depending on the duration of the fluoro exposure, generally 10–20 s. Repeat exposures are often needed in order to meet strict radioanatomic positioning criteria, and this will vary with the training and skill of the technician. Despite this, radiation
exposure remains at an acceptable level with proper shielding and coning.

While demonstrably feasible for single site studies, fluorographically-guided protocols are challenging to perform in large multicenter studies. Not all radiography units have suitable fluoroscopic x-ray equipment. Because of differences across sites in the type of equipment that is available, protocols and training may need to be customized for individual sites. In addition, the fluorographic equipment is often subject to greater constraints on patient scheduling and on ability to operate with a small number of trained technicians dedicated to the study, a requirement for fluorographic protocols.

Under controlled conditions that include rigorous training and quality control, it is possible for a high proportion of both initial and follow-up fluorographic films to meet radioanatomic positioning standards. However, longitudinal positioning success rates have been substantially better in single center studies than in the field setting of multisite studies. It is likely that substantial additional investment in training and QA infrastructure is needed to achieve success rates for radioanatomic positioning that approach those seen in single center settings. The current standard for radiographer training in the fluoro-guided AP semi-flexed protocol in a multisite study involves a weeklong central training for two or more technologists from each facility, and central QA center certification of each trainee based on qualitative and quantitative assessments of technologist performance. The introduction of digital radiography may further increase the frequency of re-calibration, would require the equipment to be recalibrated so as to ensure that a metal ball measured by the system at the start is the same at the end of the study. This is not an insignificant task.\(^6\)

In the AP semi-flexed view knee flexion is varied in order to fluoroscopically align the medial tibial plateau rims. If the beam is not properly centered on the JS, the degree of flexion needed to achieve tibial alignment will be affected by beam parallax, and changes in beam centering between exams would result in variability in knee flexion. A similar issue arises with the fluorographic Fixed-Flexion protocol, since the beam angle selected may vary between exams and this may in turn have small effects on the measured JSW. In knees with substantial flexion contractures (i.e., the knee is permanently flexed at 15 or 20 degrees or more), which are fairly common with severe knee OA, the knee may be flexed beyond the optimal amount required to meet radioanatomic positioning standards.

There are also issues related to the use of medial tibial rim alignment to guide positioning during fluoroscopic examination. This key radioanatomic criterion is optimized for the measurement of medial compartment JSW, which may yield a less than optimal view of the lateral compartment. While reduction in radiographic JSW is more common in the medial than the lateral compartment in OA, predominant lateral disease is present in 10–30% of OA knees.\(^22,^2^6\) In the setting of mild radiographic OA, i.e., prior to any visible JSN, it is often not possible to tell which compartment will be predominantly involved. One study found that short-term precision is worse for lateral compartment than medial compartment JSW in the AP semi-flexed protocol.\(^1^8\) The long-term performance of lateral compartment measurements in protocols that emphasize medial compartment visualization has not been established.

The threshold of acceptability for tibial inter-rim distance, 1 mm of loss, is arbitrary and it is uncertain whether these strict thresholds might not work equally well or even whether the threshold should be more strict. A 1 mm inter-rim distance at two time points is consistent with both perfect repositioning and at the same time with a 2 mm difference in relative rim positions between exams, which would correspond to a difference in knee flexion. It is also uncertain what proportion of radiograph pairs is required to meet this standard for adequate precision in estimates of JSN. In the study using the fluoro-guided Fixed-Flexion view, tibial plateau alignment was described as occurring in 60% of exams, and yet the SRM (ratio of JSN to its standard deviation) was relatively high and significant JSN was detected in 24 months in sample of 58 knees.

The tibial inter-rim distance is sometimes evaluated at the location of the minimum JSW in the medial compartment. In knees with mild or no JSN, this location may be difficult to pinpoint and can vary over time. Because the lines formed by the image of the two tibial plateau rims are complex intersecting curves, variability in the location used by the radiography technician to align the rims can result in changes in the degree of knee flexion across exams. The short period of time available to the technician to view the joint fluoroscopically may increase the variability in this aspect of the procedure. This limitation can be overcome by using a standard location, such as the midpoint of the medial compartment, for visual confirmation of alignment.

**Applicability to goals of the Osteoarthritis Initiative**

The Osteoarthritis Initiative (OAI) is an observational study designed to develop biomarkers for use in knee OA\(^b\)

\(^6\)This was discussed at the December 2002 Omeract Knee Imaging Workshop in Bethesda, MD, and in a personal communication from Dr Buckland-Wright. “One factor that needs to be taken into account is that radiographic exposure is different between centers and between patients; this affects the degree of radiation penetration at the margin of the ball and provides a different value for the size of the metal ball. Although this can be largely overcome by using a software program that provides gamma correction to enhance the image of the ball, there is inevitably variation in the extent to which the digital system detects the ball’s margin. Further, in a longitudinal study it will be necessary to ensure that there is no drift in the performance of the digital system throughout the study period at any of the x-ray hubs. Any changes to equipment, such as servicing, would require the equipment to be recalibrated so as to ensure that the digital values remained constant for a given test object across the digital array. In essence it will be necessary to ensure that a metal ball measured by the system at the start is the same at the end of the study. This is not an insignificant task.”

\(^b\)Also, L. Sharma, personal communication of unpublished data from the MA-K Study.
treatment evaluation and DMOAD trials. For the OAI, balancing the potential advantages of fluoro-assisted radiography protocols against their added costs and complexity in a multicenter study of 5000 subjects requires consideration of the several aims of the study. In the OAI, as many as 80% of participants will be at risk for developing symptomatic knee OA, and will be followed for this endpoint, but will not have it at the beginning of the study. Fluoro-assisted protocols were developed for measurement of JSN as a means of assessing medial compartment progression in knees with established OA. Radiographic JSN is not an early event in knee OA and may take years to first appear on x-ray. In epidemiological studies, the widely accepted and used definition of incident radiographic knee OA relies upon osteophyte development, a much earlier event in the course of OA disease as assessed by x-ray. Fluoro-assisted protocols were not developed for use in populations without disease and for the added cost they would appear to offer no advantage (even theoretical) over noninvasive approaches in the detection of incident radiographic OA. In such a population, it may also be difficult to justify the greater radiation exposure necessary in the fluoro-assisted protocols, since for most of these participants there would not be a clinical indication for a knee x-ray.

A stronger rationale exists for use of fluoro-assisted radiography in that segment of the OAI cohort that most resembles participants in a DMOAD trial, those who have asymptomatic knee OA at baseline and who will be followed for disease progression. As long as radiographic JSN remains the measure of choice for structure modification in treatment registration studies, it will be critical to delineate the relationships between biochemical and radiographic bone remodeling (MRI) markers of knee OA to this parameter. Based on the data available at the present time, when feasible and affordable either of the fluoro-assisted protocols appear to offer a proven technique for assessing JSN in patients with OA. An advantage of the fluoro-assisted PA Fixed-Flexion protocol for OAI is that it could be coupled with use of an otherwise identical nonfluoroscopic PA Fixed-Flexion protocol in the study participants without established knee OA at baseline.

In a more general context observational studies and clinical trials often have different requirements for radiographic methods because of different objectives and tradeoffs between performance, practicality and cost. Goals of observational studies typically encompass a broad range of primary outcomes while DMOAD trials may specifically focus on structure modification. The greater costs and risks to continued compliance of DMOAD trials necessitate that they be completed more quickly. It may be practical to recruit larger samples and follow them longer in observational studies, allowing more time for biologic changes in JS to emerge and be detected by radiography. This could alter the balance of benefits and costs between fluoro- and nonfluoro-guided protocols.

**Beyond radiographic JSN**

The literature does not provide a clear indication of the added value of quantitative measures of JSN, over and above JS progression assessed qualitatively. In recent reports in which both qualitative and quantitative JS outcomes were considered, it is not clear that analyses of JSN as a continuous variable are more helpful than a qualitative approach. In a recent marker study, Gamero et al. found 23 in analyses of qualitative JS outcome, a 1.7-fold increase (95% CI 1.15, 2.49) in the relative risk of medial progression (defined as a ≥0.5 mm loss of JS) for every one unit increase in the uncoupling index (Z score urine C-terminal crosslinking telopeptide of type II collagen — Z score serum N-propeptide of type IIA procollagen), and in analysis of JSN as a continuous variable, an R value of –0.46 for the relationship between the uncoupling index and JSN. In a recent study focusing on alignment and progression24, analyses of a qualitative JS outcome (i.e., progression defined as a ≥1 grade worsening of JSW) revealed that varus alignment increased the odds of medial OA progression 4-fold (95% CI 2.20, 7.62) vs non-varus, and 3.54-fold (1.85, 6.77) vs neutral. For every additional degree of varus, there was a significant 1.3-fold increase in the odds of medial progression (95% CI 1.21, 1.41). In analysis of JSN as a continuous variable, an R value of 0.52 for the correlation between severity of varus and JSN was found.

These reports suggest that the information for JSN as a qualitative and quantitative outcome may be complementary. Additionally, qualitative outcome offers advantages of easy interpretability and organ of OA, and that knee compartments while quantitative measurement is may only be valid in the medial compartment, at least with x-ray protocols currently in use. As noted in detail throughout the Bethesda Workshop, the quality of JSN assessment is vulnerable to small deviations in the acquisition protocol and positioning. Qualitative assessment of global and individual radiographic features may be less vulnerable to small protocol deviations25. However, the sensitivity of qualitative measures to change for DMOAD trials remains to be determined.

The emphasis in the methodologic literature on quantitative radiographic JSN as the primary structural outcome in studies of knee OA is based primarily on two concepts: (1) that cartilage loss is the primary target of OA, and that OA loses the essence of this disease; (2) that JSW and narrowing represent, respectively, the state of cartilage damage and ongoing loss. While JSW assessed by radiograph has been validated (e.g., against arthrography), how well a two-dimensional assessment of the narrowest inter-bone distance reflects a disease that diffusely involves cartilage over three-dimensional articulating surfaces remains a concern. Also, it is unclear whether any assessment of cartilage loss can serve as a surrogate for all of the other joint-organ tissue changes of OA.

Efforts to optimize quantitative JSW measurement also rest on the assumption that the change in JSW over a given time is a valid outcome. Despite the availability of x-ray protocols that optimize conditions to directly measure medial JSW, reports describing the relationship between a risk factor and quantitative JSN are rare. Another concern regarding the application of JSN as an outcome for DMOAD trials is the lack of information regarding the meaning of small differences in JSN rate between two drugs or between a placebo and a drug. Are such differences clinically or prognostically meaningful? There is a paucity of information about the relevance of JSN rate to patient-relevant outcomes. Hopefully, the OAI and other ongoing longitudinal studies will soon begin to fill this gap in our knowledge.

**References**


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Glossary of abbreviations

JSW: joint space width.
JSN: joint space narrowing.
RMS error: root mean square error.
SRM: standardized response mean.
MTP: metatarsalphalangeal.
DMOAD: disease modifying osteoarthritis drug.