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Clinical Development Programs for Human Drugs, Biological Products, and Medical Devices for the Treatment and Prevention of Osteoarthritis

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In the fall of 2007, the Osteoarthritis Research Society International (OARSI) submitted a formal answer to the above noted request for proposals promoted by the Commissioner's Office of the Food and Drug Administration (FDA). Beginning in June 2008, OARSI coordinated and conducted a critical appraisal to answer the August 14, 2007, Federal Register notice issued by the FDA seeking additional information on issues related to clinical development programs for human drugs, biological products, and medical devices for the treatment and prevention of osteoarthritis (OA). OARSI established an infrastructure to support the work of the critical appraisal ("Initiative"). A steering committee was identified and eight working groups were established with representation from academia, clinical practice, nonprofit professional societies, and industry. These working groups were constructed to develop responses to the specific questions posed by the FDA within the federal register notice. With the assistance of a vendor, OARSI conducted two public meetings as well as interim workshops to discuss relevant questions related to OA assessment and trial design. These public meetings provided input on the following key concepts:

1. Should the scope of the guidance apply to OA alone? Are there particular clinical subgroups of OA that need to be explicitly considered and addressed?

2. For a claim of symptomatic relief in OA, what are the optimal outcome measures and trial designs? Currently, withdrawal and flare designs are commonly used. These designs, while believed to be predictive of efficacy, may lack generalizability. It is also difficult to understand the actual size of the treatment effect based on a flare design. If withdrawal and flare designs are not optimal, what alternative designs could be used to support a symptomatic relief claim? What should the size and duration of exposure of the safety database be for symptomatic relief?

3. Is a claim of decreased rate of progression useful and, if so, what would be the appropriate outcome measure(s) to establish the claim? What is the desirable duration of a trial for this claim? What comparator arms might be used?

4. For a claim of prevention or risk reduction for the development of OA, what are potential outcome measures? If biomarkers are used what is their state of qualification? What is the desirable duration of a trial for such a claim? What is an appropriate safety database for a prevention of OA claim?

5. Are there additional claims that should be considered? If so, what outcome measures and trial designs should be used?

6. In any long-term studies, what are the best statistical comparisons for inference testing (is, for instance, a comparison of mean changes from baseline suitable, or should responses be graded according to points on established scales)? Because longer trials inevitably have substantial dropouts, what imputation methods for dropouts are most appropriate or should the trial results be based on a survival analysis or a time-to-event (for treatment failure) analysis?

Initiative Leadership

I. Steering Committee

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Definition of Disease State

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Claim of Symptomatic Relief

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Robert Dworkin, PhD

Assessment of Structural Change

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Safety Considerations

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Prevention or Risk Reduction

Joanne Jordan, MD, MPH

Biomarkers

Virginia Kraus, MD, PhD

Devices

Victor Goldberg, MD

Statistical Considerations

Daniel Bloch, MD

The full membership of each working group is listed in **Appendix 1.**

OARSI invited numerous stakeholders to participate in the Initiative. Involvement of representatives from the listed stakeholder organizations does not necessarily indicate that the listed organizations have endorsed the final recommendations.

OARSI invited numerous ***stakeholders*** to participate in the Initiative, including the following:

- American College of Rheumatology
- American Academy of Orthopedic Surgeons
- Orthopedic Research Society
- Arthritis Foundation

- American Pain Society*
- European League Against Rheumatism
- Bone & Joint Decade*
- Executive Committee of OMERACT (Outcome Measures in Rheumatology)

* With the exception of the American Pain Society and the Bone & Joint Decade, the stakeholder organizations nominated individuals to participate on specific Working Groups and/or to interface with the Initiative's steering committee.

Additionally OARSI invited the following ***governmental organizations***:

- Division of Analgesic, Anesthetics and Rheumatology, HFD170, CDER/FDA, members of SEALD, within the immediate Office of the Director of Office of New Drugs CDER/FDA
- Members of the Commissioner's Office FDA
- Members of the appropriate division within CDRH
- Members of the Office of Review Policy, CDER/FDA
- Members of the Office of Surveillance and Epidemiology, CDER/FDA
- Members of the Statistical Evaluation Group CDER/FDA
- National Institutes of Health (NIH)
- Leadership of the NIH Osteoarthritis Initiative (OAI)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- Centers for Disease Control
- Agency for Healthcare Research and Quality

**Representatives from the governmental agencies were invited to all public meetings and were available to serve as consultants to the work undertaken by the Initiative.

Recognizing the importance of input from the ***industrial community***, OARSI created a Business Advisory Committee. The membership of this committee was comprised of one individual from each corporate entity participating in the Initiative. Members of the Business Advisory Committee participated in meetings of the Working Groups, and were allowed to elect a representative to the Steering Committee. **Appendix 2** provides a list of organizations/companies that provided financial support to the Initiative as well as a list of all individuals from industry who participated in the Working Groups or as members of the Business Advisory Committee.

Disclosure of Conflicts of Interest

All individuals participating in the Initiative were required to complete a disclosure statement (**Appendix 3**). The Initiative Executive Committee as well as the OARSI Ethics Committee reviewed the disclosures and resolved conflicts of interest as per the established OARSI Ethics Committee policies. Disclosures were updated annually or as changes occurred. Individuals having a significant interest in a for-profit business were prohibited from voting on issues at the Working Group or Steering Committee level or during the public meetings.

Process

The Executive Committee established the goals of the Initiative, action items, timelines, and deliverables. These action items and deliverables included the following:

- Confirmation of Meetings with Steering Committee and Working Groups
- Scheduling of conference calls for Working Groups
- Review of previous guidelines
- Development of evidence and critical messages to be discussed during the first Public Meeting
- Literature review and compilation of references
- Initiation of concept papers by each Working Group
- Confirmation of first Public Meeting; discussion of key evidence and critical messages as presented within the draft Working Group concept papers
- Updating of concept papers with input received during Public Meeting discussions
- Posting of draft recommendations as outlined within Working Group concept papers to the OARSI Web site for public comment
- Confirmation of second Public Meeting; review and discussion of concept papers and proposed recommendations based on current knowledge
- Development of a research agenda by individual Working Groups
- Submission of recommendations to the FDA with rationale for various approaches to key issues; submission of ongoing research agenda
- Development and submission of manuscripts (concept papers) to peer reviewed journal(s)

To facilitate the communication within the Working Groups and the committees a Web site was established allowing for interactive dialogue and posting of references as well as posting of documents requiring group comment and editing. Conference calls were regularly scheduled by each Working Group to discuss the series of questions posed to each Working Group. The Claim of Symptomatic Relief, Assessment of Structural Change, and Prevention/Risk Reduction Working Groups were tasked with performing systematic reviews of the literature to develop data supportive of the answers to the questions posed by the FDA in the original federal register notice. The questions posed to each Working Group included the following:

For the Working Group assigned to consider ***Definition of Disease State***:

1. What is OA? How do we define OA for purposes of treatment or prevention?
2. Are oligoarticular, monoarticular, and polyarticular OA the same disease? Similarly, one joint vs polyarticular disease?
3. Is hand OA different from hip OA? Knee OA? Are outcome measures different for different joint groups? Should this be further broken down by compartment (eg, tibiofemoral vs patellofemoral OA for the knee, CMC vs DIP OA for the hand)?
4. Where does degenerative disc disease fit in? Should this be included in the deliberations?
5. How many sites need to be studied for approval of an oral therapy? For a topical therapy?
6. Should there be uniform definitions of inclusion and exclusion criteria?
7. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Claim of Symptomatic Relief***:

1. What are the key domains that are critical to measure improvement in OA—pain, function, disability, quality of life, other?
2. Of these key domains, which are absolutely required for a drug approval? Which are of interest but are not essential for approval?
3. Are there domains that should be considered primary outcomes and, if there are several, how would the investigator propose to account for multiplicity of measures; the *P*-value sacrifice? Should there be a required *P*-value less than 0.05 for each? Should

there be a requirement for a *P*-value less than 0.05 for pain and a "trend" for the others? Should "step down" approaches be used?

4. Is pain an acceptable independent domain? Is pain relief enough for an indication for symptomatic relief of OA?
5. Are there important domains that have not been considered in the past, such as fatigue and sleep disturbance?
6. What research/validation agenda would be necessary?
7. What functional assessments would be useful, if any? What is the value of observed functional performance vs self-report of functional limitation?
8. Is a Western Ontario McMaster University Osteoarthritis Index (WOMAC) scale equivalent to a visual analog scale (VAS) scale for pain? What is the role of the Lequesne Algofunctional Index? What of other measures of pain (eg, Brief Pain Index [BPI], McGill Pain Questionnaire [MPQ], Computerized Adaptive Test [CAT])?
9. Should there be an effort to design a per patient responder index vs means, area under the curve, etc?
10. Flare design trials—what is their utility/necessity?
11. New trial designs (eg, withdrawal trials, etc)?
12. Inclusion/exclusion criteria?
13. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Safety Considerations***:

1. What concerns should be considered for approval of chronic therapies that may be palliative or analgesic only?
2. How should one balance risk vs benefit?
3. How should a safety trial for chronic use therapies without cure be designed?
4. How long should a safety database be required to last to define risk for a chronic therapy? If intermittently used, should a therapy be expected to be studied for safety as rigorously as if the therapy were used very day for years?
5. How large should a safety database be?
6. How should one deal with issues regarding multiple risks?
7. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Assessment of Structural Change*:**

1. For the current tools for assessing structure modification (eg, x-ray, MRI, biomarkers): What are the performance metrics for each individual feature that they detect? How can they be used optimally in clinical trials? What are the relative strengths and weaknesses of these assessment tools?
2. What do these putative tools measure? How to determine change over time?
3. How can rapid structural progression patients be identified? Is that necessary?
4. What is the relationship between symptoms and structural progression? What is the relationship between disability and measured structural change?
5. Could the need for a joint replacement be a clinical outcome, which might supplant imaging as a measurement?
6. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Prevention or Risk Reduction:***

1. What are potential outcome measures?
2. If biomarkers are used as outcomes, what is their state of qualification?
3. What is the desirable duration of a trial for prevention?
4. What is the desirable population of a trial for duration?
5. What is an appropriate safety database for prevention? Is there any risk acceptable in a therapy designed to be given to someone with no signs or symptoms of disease?
6. What does prevention or risk reduction mean in terms of a clinical study and therapeutic intervention?
7. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Biomarkers***:

1. What biomarkers now exist?
2. What is their utility?
3. What evidence is available to support surrogacy for clinical outcomes?
4. What is the face validity?
5. What is the practicality?
6. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Devices***:

1. How to measure efficacy with a device; is it the same as for a pharmacologic treatment, or should there be different measures?
2. How to determine relative risk to relative benefit; what is an acceptable control arm for such studies?
3. What are the optimal outcomes parameters for evaluation?
4. Are the parameters substantially different with respect to different joints under study?
5. Short-term vs long term benefit?
6. Complications and their prevention?
7. Clinical indications?
8. Cost factors vs conservative therapy?
9. What is the research agenda required to inform each of the above questions?

For the Working Group assigned to consider ***Statistical Considerations***:

1. This Working Group will consider all of the questions posed by the other Working Groups.
2. Imputation analysis needs to be considered, last observation carried forward (LOCF), baseline observation carried forward (BOCF).
3. Need for landmark log rank analysis vs result expressed as a Kaplan Meier time-to-event.
4. Does a landmark analysis convey more important data than an area under the curve or time weighted average?
5. Is there utility in developing a responder analysis?
6. How to determine an effect size for a safety trial evaluating multiple different safety signals in same trial with different incidence of event?

The first phase of the OARSI Initiative focused on providing responses to the FDA federal register notice and culminated after approximately 18 months with an open Public Meeting held in Washington, DC, in December of 2009. The answers provided by each Working Group to the specific FDA-posed questions and issues are provided herewith. Each Working Group approached their charge in different ways and reported their consensus in differing formats. The Steering

Committee has elected to maintain the formats of each individual Working Group to reflect the individuality of each Working Group's approach. As some of the Working Groups have provided reference listings, this information has remained within the individual Working Group response sections and not as a separate appendix merging references from all of the Working Groups. A number of appendices are cited within the responses of the Working Groups. These appendices appear at the end of this document.

Finally, the recommendations contained herein have been approved by the Osteoarthritis Research Society International's (OARSI's) Board of Directors. The stakeholder organizations previously listed were invited to participate and provide input throughout the process to better inform OARSI's recommendations but were not requested to review the final scientific content of the recommendations prior to this final submission.

Working Group Responses

The responses from each Working Group represent the consensus of the Working Group members. As previously discussed in the section entitled ***Disclosure of Conflict of Interest***, only those individuals without identified conflict were allowed to vote on the final recommendations put forward by their respective working groups.

Definition of Disease State Working Group Recommendations

Should the scope of the guidance apply to OA alone? Are there particular clinical subgroups of OA that need to be explicitly considered and addressed? To address these general questions, the Working Group decided to first address the issue of what OA is and then explore other issues raised during this initial discussion.

What is OA? How do we define OA for purposes of treatment or prevention?

Recommendation: OA is a progressive disease representing the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intra-articular stress. Supra-physiologic loads or aberrant loading, even when normal in magnitude (impulsive loading), may be detrimental. Synovial inflammation in OA may be secondary to the breakdown of cartilage and bone. All of the tissues of the joint are involved, including the articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, and peripheral nerves, and OA may be initiated by an abnormality in any of these tissues.

How do we define OA for purposes of treatment or prevention?

Recommendation: For the purpose of treatment or prevention, it is helpful to consider OA in the context of a *disease* (structural damage) as well as an *illness* (how a patient experiences OA). Although late-stage OA usually combines evident structural damage with patient-reported symptoms of pain and dysfunction, there is not universal concordance between symptoms and pathophysiology, particularly in earlier disease.

How do we improve the definition of OA?

Recommendations:

1. Perform studies of large longitudinal populations of subjects (eg, OAI, Multicenter Osteoarthritis Study [MOST]) who develop symptomatic and/or structural OA during the observation period. Analyze the association between specific measurements and subsequent onset of OA to determine which measurements, individually or in combination, are the most sensitive and specific risk factors for development of OA, indicators of the onset of OA, or predictors of the rate of progression of OA.

2. Study more homogenous longitudinal populations of high-risk patients (ie, patients with recent acute ACL injury) to discover associations between specific measurements and onset of OA with fewer confounding factors related to aging or other disease.

The illness of OA, or how a patient perceives and experiences OA, should be defined separately from the disease of OA.

Recommendation:

1. Develop more objective, validated and reliable tools (eg, the use of Von Frey filaments to define the neuropathic component of the pain of OA as opposed to the nociceptive component) to evaluate the presence and severity of the above features of the illness routinely in OA therapeutic trials, with the aim of determining which aspect(s) of the illness the intervention is likely to improve and which it is unlikely to benefit, especially muscle strength, function, and physical function. This may ultimately permit treatment to be matched to symptoms that are important to the patient.

2. Develop tools/measures to identify subjects with different types of OA pain (eg, predominantly nociceptive, predominantly neuropathic, or mixed nociceptive/neuropathic). Perform targeted interventions appropriate to the type of pain. OA patients should be stratified in interventional trials based upon the type of pain to determine whether responses differ according to type, with the goal of better

targeting pain therapies to individual patients. Similarly, tools/measures should be developed to identify subjects with different types of dysfunction, with corresponding trials to determine response and targeting for specific dysfunction (eg, stiffness, mobility).

Are oligoarticular, monoarticular and polyarticular OA the same disease? Similarly, one joint vs polyarticular disease? Is hand OA different from hip OA? Knee OA? Are outcome measures different for different joint groups? Should this be further broken down by compartment (eg, tibiofemoral vs patellofemoral OA for the knee, CMC vs DIP OA for the hand)?

Recommendation: In examining the efficacy of therapeutic interventions, do not consider that all OA is the same. For example, the impact of OA at the 1st CMC joint on function, participation, pain, and fatigue is likely to be different than that of nodal, hip or knee OA. Trials should distinguish between OA at different joint sites. Which OA joints and/or patterns of OA joint involvement are associated with greater illness than others is not well understood. Whether existing datasets can answer this question should be ascertained.

Where does degenerative disc disease (DDD) fit in? Should this be included in our deliberations?

Recommendation: Because of the complex and inconsistent relationship between degenerative disc disease, spinal OA, back pain, and extremity pain, DDD should be considered separately from these deliberations. Relief of pain specifically from DDD, as well as therapies directed towards disc restoration, should be addressed in separate clinical trials. Regarding back pain in general, it is reasonable to document the effects of OA therapies, but only as secondary or tertiary endpoints.

How many sites need to be studied for approval of an oral therapy? For a topical therapy?

Recommendation: Because of the variability in causes and characteristics of OA between joints, approval of topical therapies should be based on joint-specific efficacy (eg, treatment of the pain of OA in the knee). It may be possible that with systemic treatment more than one joint could be evaluated.

Should there be uniform definition of inclusion and exclusion criteria?

Recommendation: Inclusion and exclusion criteria should be site specific. However, we recognize that there may be variation in the inclusion and exclusion criteria, depending on the mechanism of action [MOA] of the medication or device being studied, and we recommend the criteria be similar

for therapeutic interventions with the same MOA. Also, as is appropriate, the systemic toxicity for all interventions should be as similar as is possible to allow for comparison across interventions

What is the research agenda required to inform each of the above questions?

Recommendations: To standardize the evaluation of OA, research is needed to achieve the following:

- Define the phenotypes of OA between joints and for joint groups. Individual joints vs generalized OA need to be standardized.
- The OA phenotypes defined need to be based on study outcomes to improve the correlation between the treatment and outcome. For example, an individual with severe pain as the phenotype should be evaluated with an analgesic or pain modifying medication, not necessarily a structural modifying medication.
- Information on genotypes associated with OA onset and progression will help to refine the OA phenotypes and improve study subject selection.
- Epidemiologic databases with OA structural and symptomatic progression data need to be compiled to standardize definitions and outcomes.

Claim of Symptomatic Relief Working Group Recommendations

For a claim of symptomatic relief in OA, what are the optimal outcome measures and trial designs? Currently, withdrawal and flare designs are commonly used. These designs, while believed to be predictive, may lack generalizability. It is also difficult to understand the actual size of the treatment effect based on a flare design. If withdrawal and flare designs are not optimal, what alternative designs could be used to support a symptomatic relief claim? What should the size and duration of exposure of the safety database be for symptomatic relief?

Are there additional claims that should be considered? If so, what outcome measures and trial designs should be used?

In any long-term studies, what are the best statistical comparisons for inference testing (is, for instance, a comparison of mean changes from baseline suitable or should responses be graded according to points on established scales)? Because longer trials inevitably have substantial

dropouts, what imputation methods for dropouts are most appropriate or should the trial results be based on a survival analysis or a time-to-event (for treatment failure) analysis?

Recommendations:

The Working Group attempted to deal with the issues raised in the aforementioned series of questions, however, consensus was not reached on the issues of area under the curve versus the change from baseline. The group believed that this would best be dealt with as part of a research agenda since the data do not yet exist. As mentioned in the individual sections below, consensus of the group was that mean change from baseline in terms of pain relief, function, and patient global assessment are meaningful and serve to discriminate better from placebo than other methods, such as grading responses according to absolute measured points on established scales (eg, comparing the results of one arm vs another in terms of absolute values of pain). Farrar, et al have allowed for patient input to inform us about the clinical relevance of changes in pain from baseline, and thus consensus of the group was that change from baseline should be what is required. [Farrar JT, Young Jr JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. 2001; *Pain.* 94:149-158]

Furthermore, it is expected in longer-term trials that patient dropouts might be significant, and thus a rigorous methodology needs to be applied to allow for sensitivity analyses to interpret efficacy results under these conditions. The use of LOCF although popular is not robust enough for a true understanding of efficacy, thus consensus was for longer term trials, either a mixed model, or for more rigor, a worst case carried forward result (WOCF or BOCF: baseline carried forward) (no response) be imputed. The Working Group also believed that a time-to-event analysis might be of interest, but it should also be added to a research agenda since not enough experience has to date been documented to allow for such an analysis to be considered primary for regulatory approval.

What are the key domains that are critical to measure improvement in OA – pain, function, disability, quality of life, other?

Recommendations:

Although there were varied opinions about the primary nature of the domains, there was general consensus that key domains to be measured should include the following:

1. A change in pain, either by a simple VAS or numerical rating scale (NRS) measure (100 mm or 10 cm, anchored with worst pain imaginable or comparable phrase on right and no pain on left) should be used to answer a simple question (eg, "How much [joint] pain do you have at this time or in the last 24 hours [and if related to a specific joint, regarding the effect of local therapy either topical or by injection]?") or the Brief Pain Inventory (BPI) or other such validated pain measure. A convenient method to measure pain in knee or hip OA might be the WOMAC pain scale, which is designed for knee and hip OA pain. This represents the first five questions of the WOMAC. For systemic therapies, this might be adequate for a pain measure. However, for local therapies for weight bearing joints such as knee or hip, the WOMAC A1 ("How much pain do you have while walking?") may be more relevant.

   In the attached appendix regarding this section of the document is a systematic review assessing the utility of various outcomes to demonstrate benefit. As can be seen, the pain outcomes alone consistently discriminate more effectively from placebo than WOMAC pain or the WOMAC A1 question. This is of interest in that the effect size in the successful trials that have been published of a simple pain question is consistently more informative than other forms of measuring pain as studied.

   While there have been newer methods devised to measure pain, such as the OARSI Intermittent and Constant Osteoarthritis Pain (IOACP), these have not had much time to be considered; thus, at this time the group suggested such outcomes to be considered secondary. The Australian/Canadian Osteoarthritis Hand Index (AUSCAN), a measure similar to the WOMAC for hand pain, has been used in the past but has not been as widely used as the WOMAC. If validated consistently in hand OA, its use should be encouraged as a primary outcome for hand pain. Other specific joints have not been graced with the development of unique outcome measures. At this time, applying the WOMAC or the AUSCAN to these joints is not warranted. Furthermore, it is unclear if the OARSI IOACP has been validated in these other joints as well. The use of the total WOMAC as the primary outcome is not recommended. The use of the pain components of the WOMAC are recommended as well as the consideration of the WOMAC A1, when appropriate (eg, when local intra-articular or topical therapies are studied for effect in one joint which is weight-bearing).

2. A functional score would be necessary, and in OA (particularly of the knee and hip), the functional score has typically been the WOMAC function questions representing 17 validated questions, although the Luquesne Index or the Knee Injury and Osteoarthritis Outcome Score (KOOS) have also been used in the past and any one of these should be considered in future studies. In addition to the AUSCAN for the hand, more work needs to be done in other joints such as shoulder, elbow, and ankle. However, it is clear that a functional index should be included as an outcome. General consensus was that for the indication of pain of OA, which might be applicable to topical or local therapies, a pain measure, specifically a change from baseline, without inherent recall other than up to 24 hours, should be the primary outcome with secondary outcomes of function and, as discussed later, a patient global assessment. Although function and a patient global assessment are secondary outcomes, they should not worsen. Consensus was also reached that a similar approach would be appropriate regarding the requirements for a "true" analgesic that would be delivered as systemic therapy rather than local. Thus, success for such a therapy and an acceptable study approach would be a primary outcome for pain with secondary outcomes, which do not worsen, including function and global. Alternatively, for an indication of the improvement in the signs and symptoms of OA, the consensus was success on a change from baseline in terms of pain benefit, a functional outcome, and a patient global. The primary outcome could be all three, which would ideally be assessed in hierarchical fashion, first with success on pain, next on function, and then the patient global. Alternatively, a sponsor could use a validated responder index such as the OARSI OMERACT responder index. Finally, a sponsor could develop a statistical plan that evaluates each outcome, thus there would be three co-primary outcomes, which would necessitate the appropriate *P*-value corrections for multiplicity of measures.

   The systematic reviews appended demonstrated that the Luquesne Index discriminated from placebo better than the WOMAC although both functioned well. Unfortunately, in these trials that were studied, there were few that utilized the KOOS so that remains a future research question.

3. A patient global question (eg, "In all ways, how is your pain in your joints (or joint such as a target joint) at this time?" or "In all ways, how is your OA?") may be useful. A change score can be determined for any time point compared to baseline. This question has previously

been demonstrated to be very discriminative from placebo. It also provides not only some reflection of efficacy but also of how well the patient has tolerated the putative therapy.

4. Other dimensions of outcome that might be informative (ie, secondary, but not compulsory) might include the following:
    a. Fatigue
    b. Sleep
    c. Physician global assessment of improvement
    d. Health thermometer
    e. Short Form Health Survey (SF-36)
    f. Pain O Meter (Self-administered pain assessment tool)
    g. Stiffness, which is reflected in the WOMAC by two questions, has not been an important outcome to date for approval. If studied by a sponsor, there should be concurrence with the FDA that it could be included in the clinical trials (studies) section of the label where data describing the results of trials is listed. In general, there was consensus that this could apply to any secondary outcome. The expectation would be that if the primary outcome(s) in such a trial was (were) positive, the secondary outcomes could be considered. If replicate evidence and the secondary outcomes were proven clinically relevant and could be argued successfully, a description of the outcomes should be included within the clinical trial results portion of the label.
    h. Minimally clinically important differences regarding patient reported outcomes: since it is expected that any measure which attains statistical significance will also demonstrate clinical relevance, it is useful to consider any measured changes in the above in the context of what makes clinical sense. These should be calculated based both on the current literature as well as developed within the specific clinical program development. [Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146: 238-244; Dworkin RH, Turk DC, Wyrwich KH, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *J Pain.* 2008;9:105-121.]

i. Applying a minimal acceptable threshold for success to the OARSI-OMERACT responder index that takes into consideration pain, function, and patient global assessment of improvement allows the evidence to be stated as a percent of the number of patients who achieve the a priori stated thresholds and thus provides a proportion of responders rather than just a mean of change. This allows for less impact of the statistical problem of multiple measures when all of the first three measures are considered important enough to be listed as co-primary outcomes.

Of those key domains, which are absolutely required to achieve for a drug approval? Which are nice to have but are not essential for approval?

Recommendation: Clearly, if a drug is to be approved for signs and symptoms, the outcome that reflects those issues should be a primary outcome. Thus, an improvement in pain might be considered such a primary outcome. However, some also consider that if pain is improved, the patient should be able to function measurably better. Some would argue it is important enough to be part of a primary outcome. Certainly the OARSI-OMERCT responder index follows that schema.

There was clear consensus that, if a sponsor wants an indication for improvement in signs and symptoms of OA, a measure of change in pain, a measure of function, and a patient global assessment would be required in some format as the primary outcome. However, there was also consensus that if the therapy was intra-articular, local, or topical and might affect only one joint, the change in pain of OA of the knee, for example, would be an acceptable primary outcome with function and patient global as important secondary outcomes. Additionally, these outcomes would not be expected to worsen. Further, there was significant support that the WOMAC A1 might be the appropriate question used as a pain measure for the primary outcome of change in pain, if it were measured in a weight bearing joint. The achievement of an improvement in pain with no worsening of the secondary outcomes of function and a patient global would be acceptable for a primary outcome of the improvement in pain of OA for those therapies, which would only be expected to be analgesics.

Are there domains that should be considered primary outcomes and, if there are several, how would you propose to account for multiplicity of measures, thus the* P*-value sacrifice? Should

there be a required* P-*value less than 0.05 for each? Should there be a requirement for pain and "trend" for the others?

Recommendations: As noted in the comments above, the consensus was that three successful co-primary outcomes should be required. Typical success is measured with a *P*-value less than 0.05. However, suggestions have been made using either a hierarchical process (ie, pain, then function then a patient global, each succeeding with a $P < 0.05$) or a validated responder index to allow for the problem of multiplicity of measures. Furthermore, the use of three co-primary outcomes is also modified by the choice of indication. If for pain alone of a single joint as observed with local therapy, including systemic analgesic therapies, intra-articular therapy, or topical agents, a change in pain measure alone should be sufficient as the primary outcome. If of a weight bearing joint, then the WOMAC A1 might be sufficient as the primary question, although secondary outcomes would include the remainder of the WOMAC pain questions expressed as a mean change, function, and patient global outcomes. None of these secondary outcomes should worsen. Furthermore, if these secondary outcomes were shown to be successful and were replicated, it would be informative to the healthcare provider and the patients if this information were available in the descriptive sections, which reflect the measured responses from the replicated clinical trials.

Is pain an acceptable independent domain? Is pain relief enough for an indication for OA?

Recommendation: Yes, if applied to individual joints, but not if a sponsor expects that studying the knee, in replicate, that improvement in the knee would reflect improvement of OA throughout the body. Thus, if a sponsor seeks an indication for improvement in the signs and symptoms of OA, pain is not an acceptable single primary outcome.

Are there important domains that have not been considered in the past, such as fatigue?

Recommendation: As noted above, fatigue, sleep, and stiffness are all considered important; however, consensus was that there are few data validating these outcomes in OA nor significant understanding at this time of the clinical relevance of change in measurements of these domains. Thus consensus was that, if measured, they should be secondary outcomes, and they should be measures studied in the future, thus added to the research agenda.

What research/validation agenda would be necessary?

Recommendation: For any newly considered outcome measures, the following would need to be considered:

a. Question fatigue: too many questions asked of a patient at each assessment period.
b. How has it been validated as a Patient Reported Outcome (PRO) (FDA guidance of 2009)?
c. How well does any measured outcome discriminate from placebo?

What functional assessments would be useful, if any? What is the value of observed functional performance vs self-report?

Recommendation: There are many physical therapeutic modalities that have been used and developed by functional assessments to ascertain problems and improvements both in the postoperative state as well as in patients suffering from acquired disabilities, including disease states such as OA. These are typically observed functional performance measures. If quantitated and validated, these should be considered as valid observed outcomes but should not substitute for patient reported outcomes. By measuring both domains, it is possible that there may be increased information regarding both the inability to perform activities at baseline as well as responsiveness after intervention. With increased understanding of their function, their discrimination from placebo, their clinical applicability, and their clinical relevance, these types of measures may become more important in determining outcomes in OA after therapy.

Is a WOMAC pain equivalent to a VAS scale for pain? What is the role of the Luquesne Index? What of other measures of pain—BPI, MPQ, CAT?

Recommendation: The Working Group cannot provide answers to these questions; however, a systematic review is underway and will be able to inform our response once completed.

Should there be an effort to design a per patient responder index vs means, area under the curve, etc?

Recommendation: One index has already been designed. The OARSI-OMERACT responder index has been used for secondary outcomes in many trials, and needs to be explored further in terms of

AUC and landmark analyses. This issue has been captured within the Working Group's research agenda.

Flare design trials – what is their utility/necessity?

Recommendation: Flare design trials became popular with the onset of trials studying the effects of the nonsteroidal anti-inflammatory drugs (NSAIDs). It became apparent that if the drug was studied without first determining a patient group who was responsive by flaring them with withdrawal of their clinically used NSAID, the trials would recruit patients who were not responsive in the first place, thus diluting the clinical results. This tended to provide results that seemed to overemphasize the observed or potential benefits of drugs. Some of these drugs have been shown over time to be quite overused and, with their associated safety signals, the risk/benefit question was not fully explored within the standard flare design development program.

It is possible that a form of a randomized withdrawal design would be an improvement over the flare design. This design would recruit all patients with an acceptable amount of pain at baseline, and then all would be treated with the specific study drug for a specified period of time. There would be efficacy measures and safety would be noted. After a period of time, the patient responders defined a priori by some acceptable response criteria would be randomized in blinded fashion to either continue the drug or withdraw. This would lead to two or more blinded groups (eg, different doses of drug) being treated for 12 weeks. This provides efficacy and safety data with a control group, although the control group is biased by including patients who originally tolerated the experimental therapy, thus this data, although useful, cannot substitute for another safety data base but does give relevant information about safety in those patients who had and maintained a response.

There are several down sides to a withdrawal design, including the fact that there would be a safety study requirement to study all patients, not just those patients who were responders, thus increasing the size of the development program. The initial "run in " period would provide some of these data, but the time of exposure during this period would likely not be long enough, and there would be no comparator arm. However, these safety observations are also a failing of the flare design, and at least in the "run in" period for a withdrawal design, patients who are at first nonresponders would be exposed, but not for very long. In addition, the use of rescue has to be

appropriately considered. This is not inconsequential, and rescue therapy cannot be seen to be only background therapy. In fact, rescue therapy may mask measurable benefit and complicate a full understanding of safety.

Another concern for trials is the requirement that over-the-counter products are provided for pain relief for up to only 10 days. Safety data sets may be for up to one month, but none of these trials extend for the time period required for prescriptive products. Thus these trials need to demonstrate benefit in situations in which they would be used.

Inclusion/exclusion criteria

Recommendation: This is always an area of important debate. The patients to be studied have to be indicative of who is to be treated. However, trials designed for regulatory approval are not the same as effectiveness trials. Thus, there need to be limits on how sick patients entering the study can be since determining causality of safety signals is difficult enough without significant polypharmacy and comorbidities confounding the observational safety data set. However, the efficacy and safety data cannot be only in young healthy individuals and must be collected from exposed experimental subjects who reasonably reflect the patients who will be at risk once the drug is available and prescribed. This tension is significant but must be on a case-by-case basis. It is possible that phase 1 and 2 data sets should be more limited in exposure, but the phase 3 program should be planned to include a significant portion of those patients who will require such therapy. This should be considered either through stratification of the patient populations or balanced randomization criteria applied early in the design of the protocol. (See **Appendix 9**)

Safety Considerations Working Group Recommendations

Summary of Recommendations

The symptomatic treatment of OA with oral agents remains to be improved, as many patients, especially later in the disease, do not respond well to NSAIDs and other analgesics, eventually opting, when possible, for total joint replacement, which although effective is associated with substantial short-term morbidity and mortality. All treatments have risks, and there is an important need to estimate the ongoing risk (known and unknown) of any novel therapeutic over short- and long-term use. Given the unmet need for innovative oral symptomatic treatments for OA, it is

important that requirements for identifying the safety and tolerability of a new agent not create barriers that would limit such development. Therefore, the optimal timing for identifying and estimating certain risks and the need to narrow the confidence limits around such risks requires careful consideration of whom and what to study, both before and after approval of a new therapeutic.

For therapeutics that promise to alter structural progression of the disease, the risk-to-benefit ratio of how many patients will actually not structurally progress, as opposed to the number of patients to whom significant harm might be done, will define what are tolerable risks for a product to be used, let alone approved. The data do not yet exist since we have no successful data sets, even though there have been large populations studied to date with structural progression as the primary outcome. For products that will prevent the onset of OA, there is a paragraph in that section from the Working Group on safety. The majority of this material will discuss the issues surrounding tolerable safety signals for therapeutics that are palliative, treating the signs and symptoms of OA. This is the only group of drugs for which there are actually data to inform the Working Group in developing its consensus.

Introduction

Newer agents for symptomatic treatment of OA, which were developed in the last decade with improved gastrointestinal (GI) tolerability, permitted accumulation of larger and longer safety databases, thereby leading to identification of rare but associated cardiovascular risks. Other risks, less common or predictable (eg, idiosyncratic skin rashes, including Stevens Johnson Syndrome and/or Toxic Epidermal Necrolysis), those reflective of associated comorbidities, including hypertension and diabetes and associated with the polypharmacy frequently present in subjects with OA, should be considered. A question posed by the FDA in 2007 regarding the Draft 1999 Guidance Document for development of novel agents for the treatment of OA was: "What should the size and duration of exposure of the safety database be for symptomatic relief?" Herein are outlined recommended data regarding the safety of novel symptomatic oral agents for treatment of OA.

Other agents, including intravenous or subcutaneously administered agents, topical or intra-articular agents without significant systemic exposure, will not be addressed in this section. Analgesics without antiinflammatory effects are not addressed. However, we are agreed that simple analgesics such as over-the-counter acetaminophen and oral opioid drugs are not without risks. However, these risks are well characterized and any new analgesic molecular entity to be

developed should certainly evidence no additional risk since these agents are palliative in nature and do not alter the natural history of the disease. Thus, it is important that newer therapies have definitive data sets describing drug-drug interactions in this patient population, often compromised by polypharmacy, as well as defining whether or not the chronic use of the new drug may induce instability in blood pressure, blood sugar, or renal function.

Since OA is a common and heterogeneous arthritis that occurs worldwide, predominantly in older individuals, the associated pain, impairment in physical function, and disability vary greatly from mild and intermittent to severe and continuous, prompting patients to seek a wide variety of treatments, from use of intermittent analgesics to total joint arthroplasties, with greatly varying associated risks.

As cyclooxygenase-2 selective (COX-2) agents with improved GI tolerability were developed to decrease the risk of GI bleeding, it became apparent that NSAIDs/COX-2s were also associated with increased risk of cardiovascular (CV) events. The data to date have concluded that such risk varies by individual patient risk, individual characteristics of the specific NSAID/COX-2, and by dose of drug. Furthermore, this absolute risk for an untoward CV event is small and varies by length of exposure and underlying individual risk factors, thus prompting the need to examine, not only large randomized-control trials (RCTs), but also large post-approval, randomized pragmatic trials or nonrandomized, longitudinal observational studies (LOSs). Thus RCTs and LOSs contribute information to the evolving safety profile of a novel therapeutic, once approved, and each offer different types of information. Conveying the risk of such uncommon adverse events (AEs) must rely upon such observational studies, which include voluntarily reported events that may underestimate and/or be confounded by other comorbidities and risk factors.

Herein, we will focus upon studies with a novel agent and acknowledge that its safety profile is likely to evolve further once it is approved and marketed with regards to recognized concerns related to its MOA, potential GI or CV risk, as with NSAIDs, and/or unidentified ones such as off-target effects and/or idiosyncratic reactions. Furthermore, the important benefits for this novel therapeutic will define what number of patients is required to understand its risks, but also what clinical benefit is achieved with intervention. If a disease modifying drug, more potential AEs will be tolerated than if the drug is only palliative in its effects.

Current Guidance

Safety databases vary according to size and populations studied, either pre- or post- approval, by recognized risks, and classes of therapeutic (Table A). Depending upon the a priori concern, based upon nonclinical information or early clinical studies, larger studies and safety databases are useful to better understand the safety profile of a drug.

The previous 1999 FDA OA Draft Guidance Document did not specifically address safety recommendations, and International Conference on Harmonisation (ICH) recommendations (1994) were generally applied for development of novel agents that would be used both intermittently and regularly on a chronic basis. ICH guidelines recommended 1500 as the minimum number of subjects to have received a new therapeutic at any dose and for any time frame, and at its proposed dose, 300 to 600 patients for 3 to 6 months and a minimum of 100 individual patients exposed to the proposed dose for 1 full year.

With identification of relatively rare AEs of variable incidence, the evaluation of risk based upon exposure (eg, number of events per 100 patient-years) has become important. For example, 3-month RCTs in OA for symptomatic relief typically resulted in databases with approximately 1000 patient-years of exposure. Following approval of the early biologic TNF- inhibitors in rheumatoid arthritis (RA) with limited safety databases, postmarketing surveillance identified uncommon AEs that often had not been observed in the relatively small RCTs. This prompted the requirement for 1500 to 5000 patient-years of exposure for approval of a new disease modifying antirheumatic drug (DMARD) in RA.

More recently, requirements for new agents to treat diabetes mellitus (DM) were set at 3000 patient-years of exposure (FDA Draft DM Guidance Document 2008 and FDA CV Risk Guidance Document 2009) based on baseline comorbidities of the study subjects and recognized increased CV risks in these populations to allow for identification of rare treatment-associated and underlying disease-associated AEs. These requirements are based upon point estimates of relative CV risk but also the confidence intervals estimated around that risk. These confidence intervals may be better defined, and thus narrowed, for example, by performance of large postmarketing safety RCTs with a goal to increase patient-years of exposure by ~5000+ or studies of higher-risk subjects than those enrolled in pre-approval trials. Based on potential "signals" identified during development or postapproval, such studies are requested on a more frequent basis.

Risk assessments for newly approved agents continue to change over the time a product or class of therapeutics has been available on the market, based on use in larger numbers of subjects exposed,

who are likely different than those included in RCTs, and are largely based on information from postmarketing RCTs, observational studies, and voluntarily reported AEs (ie, Adverse Event Reporting System [AERS] database).

The recent CV risk guidance document lends insight into similar documents and their implementation (FDA DM CV risk 2009).

Clear premarketing and postmarketing acceptable limits of exposure are proposed and may act as a guide for initial approval of novel agents for symptomatic treatment of OA. Postmarketing commitments for RCTs and/or observational studies should be focused upon patient populations likely at higher risk for uncommon AEs and, therefore, not frequently studied in sufficient numbers prior to approval to estimate such risk.

A commitment for safety information after approval to narrow the "window" of CI estimates around actual risks (known or unknown) to <1:10,000 - 1:30,000. To achieve this, RCTs and other means (eg, claims databases) should be used. An outcomes study prior to registration was not felt to be needed prior to approval, if the a priori concern is low (ie, no preclinical or clinical signal).

Oral, symptomatic treatment of OA: Setting

Oral agents for the treatment of OA are administered to large numbers of patients in a primary care setting as that is where most OA patients seek treatment. Such agents are systemically active and, therefore, may interact pharmacokinetically and/or pharmcodynamically with other drugs/drug classes and nonpharmaceutical agents (eg, herbals). Thus their safety profile must be carefully characterized in a broad setting of chronic intermittent or daily use, in contrast to topical or intra-articular symptomatic agents with less or no systemic exposure and/or administration in a more controlled and/or specialist setting.

Proposal:

Based upon various FDA presentations regarding the RCT database requirements in diabetes studies, the following is proposed:

A standard phase 2 and phase 3 program, in toto, which meets the FDA's current requirements and, assuming a 1% or 2% annual CV event rate at baseline for the study population, respectively, has approximately 50% to 75% power to exclude a hazard ratio of ≥1.8 in terms of CV events.

Assuming the observed CV event rate in a typical phase 3 program is approximately 1% annually, additional clinical work will be necessary. Options could include either increasing exposure and number of patients in pivotal trials or conducting a separate CV safety study (initiated prior to submission). At present, such a CV outcome trial would likely require >20,000 patients treated for at least 3 years. From this descriptive data set predicated on a diabetic population, it would be possible to extrapolate this requirement to patients with OA, who are typically older than a typical DM patient population, in a clinical trial but with similar comorbidities and underlying risk.

1. What concerns should be considered for approval of chronic therapies that may be palliative or analgesic only?
    - 1.1. Are there any nonclinical concerns regarding these effects ?
        - 1.1.1. For instance, does the MOA, clinical and/or biological, predispose for potential serious AEs (SAEs) in the first clinical phases?
    - 1.2. Dose-related
    - 1.3. Anaphylactic/hypersensitivity risk
    - 1.4. Regardless of MOA, demonstration of overall safety profile should be held to the same standard as that for COX-2 selective inhibitors (ie, large RCTs to detect AEs of low occurrence, such as the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET): deaths estimated overall as 1 in 10,000 for a serious GI event; 1 in 30,000 for a CV event)
    - 1.5. GI tolerance
    - 1.6. Metabolism – especially hepatic and overall risk for DILI
    - 1.7. Elimination; potential for accumulation with chronic therapy
    - 1.8. Drug interactions (eg ,low-dose aspirin and assessing CV risk)
    - 1.9. Effect of comorbidities (eg, diabetes, hypertension)

2. How should one balance risk vs benefit?
    - 2.1. Benefit should exceed risk
        - 2.1.1. What unmet medical need is being met
        - 2.1.2. Risk should be minimal
    - 2.2. What have safety markers shown in clinical trials?
    - 2.3. What are the risks if pain is untreated? (eg, hypertension, CV events, depression, OTC analgesics)

2.4. What alternatives exist to treat the patient?

3. What concerns should be considered for approval of chronic therapies that may be palliative or analgesic only?

3.1. vs positive control ≥6 months; placebo (negative control) ≥6 weeks and, for new molecular entities, greater than 12 weeks, and at least ICH minimums should be attained as stated above

ICH guidelines (E1, 1994) are considered "minimums" to characterize the safety of a new agent, but, don't reveal rare (<1/1000) or long-term AEs, nor AEs in at-risk, or special populations (for example, those with hypertension on low-dose aspirin or other concomitant medications),

Duration Time	Exposure (patients)	Incidence Rate Characterized
Short-term, ≤3 months	1500	~1%
Mid-term, 6 months	300–600	0.5–5%
Long-term, 1 year	100	3%
Not ICH characterized, ≥1 year	2500–3000	1%–0.1%

3.2. What is the appropriate control: placebo, acetaminophen, NSAID, other/standard of care?

3.2.1. Ideally, double-blinded, however, consideration should be given for large safety trials, which might include large simple trials or Prospective Randomized Open label with Blinded Evaluations (PROBE) trials for therapeutics that have been extensively studied in double blind RCT's previously

3.3. When should an outcomes study be required

3.3.1. Efficacy comparable to recent practice (NSAIDs) regardless of MOA

3.3.1.1 Objective to detect SAEs: CV, GI (POBs), hepatic

3.3.1.2 Comparable safety to current agents

3.3.1.3 TARGET/Multinational Etoricoxib and Diclofenac Arthritis Long-term Study Program (MEDAL) type RCTs depending on the information available before registration thus it could be either before registration or after

Some examples of risk for CV events as defined in different types of studies are listed in the following table:

Drug	**Type of study**	**CV rate or hazard rate**
Celecoxib	RCTs	1.10 (0.70-1.60)
		1.30 (0.60-2.60)
		2.30 (0.90-5.50)
	Cohort study	1.32 (0.69-2.16)
	Case control	1.01 (0.90-1.13)
Naproxen	RCTs	HR 1.57 (0.87-2.61)
	Cohort study	0.94 (0.85-1.04)
	Case control	0.96 (0.84-1.10)
Ibuprofen	RCT	1.18 (0.93-1.19)
	Cohort study	1.12 (0.90-1.38)
	Case control	1.06 (0.95-1.18)
Diclofenac	RCT	1.05 (0.93-1.19)
	Cohort study	1.36 (0.51-3.65)
	Case control	1.36 (1.21-1.54)

Legend: various event rates in various study approaches for selected NSAIDs for perspective regarding approach to safety recommendations.

Challenges

- Annual CV event rates I RCTs generally ≤1% but higher in CV outcomes trials; 2% in homogeneous high-risk populations as background
- Event rates may be lower in subjects with newly diagnosed or earlier disease (eg,, DM, RA, OA subjects with fewer comorbidities)
- New requirements are designed to provide an incremental increase in the knowledge of CV risk associated with new therapeutic agents; effective implementation of this guidance will be challenging
    - Potential to increase clinical development times by 1–3 years and costs by $150–300M
    - Potential time and cost implications limit incentives

3.3.2. Fewer therapies may be developed; fewer sponsors may be able to develop such therapies, thus limiting access to new treatments.

If a drug had 'greater efficacy' than NSAIDs, what does that mean for the risk/benefit ratio?

3.3.2.1. How is better efficacy in a head-to-head study defined/determined?

3.3.2.2. What about on a background of an NSAID/existing standard of care TARGET/MEDAL type RCTs before or after registration

4. What is the duration of exposure to be required in a safety database to define risk for a chronic therapy?

4.1. 2500–3000 patient-years exposure

4.2. What is feasible to accomplish?

4.2.1. Maybe a median of 18 months, but let subjects continue as long as tolerating and desiring therapy, although dropout rates are frequently high

4.2.2. Need to perform an interim analysis of safety for initial submission

4.3. Two circumstances would alter the bar on pre-approval safety

4.3.1. If a drug does not have demonstrated disease modifying osteoarthritis drug (DMOAD) effect and by MOA could have potential SAEs

4.3.2. If a drug had 'greater efficacy' than NSAIDs, what does that mean re: risk/benefit ratio? Does this alter the safety bar to any substantial degree, possibly regarding the confidence intervals regarding risk?

5. If intermittently used, should a therapy be expected to be studied for safety as rigorously as if the therapy were used every day for years?

5.1. Yes

5.2. The highest/most frequent “intermittent” use should be studied, even if daily.

6. How large should a safety database be?

6.1. 2500–3000 patient-years by the traditional Rules of 3 to approach 0.1% SAEs

6.2. What controls or comparators (including placebo) are recommended?

6.2.1. How to maintain patients on these other agents for sufficient periods of time?

6.2.2 The concept of rescue therapy defines duration of use of nominal new therapy

7. How should one deal with issues regarding multiple risks?

7.1. Known risks can be anticipated, and should be estimated pre-approval

7.2. Unknown risks cannot be a priori tested prior to approval and should be part of any postapproval plan

- Recent RCTs indicate as many as 40–50% have hypertension (HTN) with these patients twice as likely to develop myocardial infarction and 70% more likely to suffer a cerebrovascular accident (CVA)
- Increased risk of osteoporosis
- Increased risk of type II diabetes with its own associated CV Risks
- Chronic obstructive pulmonary disease and other respiratory diseases
- Peptic ulcer and other GI diseases
- Increased risk of obesity/metabolic syndrome
- Increased incidence of comorbid CV disease
- Increasing age
- Renal impairment contributes

8. What is the research agenda required to inform each of the above questions?
    8.1. How to define an acceptable level of "number needed to harm"?
    8.2. Need to include health related quality of life measures as measures to be achieved (improved) and compared against risk of an AE.
    8.3. Need a means to calculate "acceptable" risk/benefit ratio; AE scoring system; risk calculators vs measure of "clinically meaningful difference"
    8.4. Define at-risk populations for study pre- and postapproval.
        8.4.1. Obese
        8.4.2. Older
        8.4.3. Family history
        8.4.4. Biomarkers of risk
    8.5. Surveillance for "nontarget" and other unknown effects
    8.6. Look at hypertensive, CV, cholesterol, diabetes mellitus RCTs for models
    8.7. How may we be informed by administrative databases?
    8.8. Large, simple studies, pragmatic studies and their role, the use of patient reported outcomes as safety signals
    8.9. Understanding what level of risk for a new agent that the target OA population is willing to accept

8.10 Need to assess the utility of the proposal from above: A standard phase 2 and phase 3 program, in toto, which meets the FDA's current requirements and assuming a 1% or 2% annual CV event rate at baseline for the study population, respectively, has approximately 50% to 75% power to exclude a hazard ratio of ≥1.8 in terms of CV events. Assuming the observed CV event rate in a typical phase 3 program is approximately 1% annually, additional clinical work will be necessary. Options could include either increasing exposure and number of patients in pivotal trials or conducting a separate CV safety study (initiated prior to submission).

Table A: Size of some safety databases

	Patient-years exposure (approximate)
OA efficacy studies and ICH guidelines (estimated summation)	1000
Rheumatoid arthritis recent approvals (disease-modifying drugs, DMARDs)	2500
Diabetes mellitus CV risk guidance for approval (based upon RR 95% upper CI <1.8)	3000
Diabetes mellitus cardiovascular risk guidance safety study (based upon RR 95% upper CI <1.3)	5000
OA CV outcome study (TARGET, MEDAL, PRECISION studies)	10,000 – 30,000

Alternatives

It is possible to develop a statistical estimate of the number of SAEs of interest considered "tolerable" for a given number of patient-years, for an "acceptable" SAE rate per 1000 patient-years. As an example, for an SAE rate of 1/1000 patient-years, one can calculate that after 3000 years of patient follow-up, there should be no more than 6 SAEs, or the 95% confidence intervals will have been violated.

This "tolerable" SAE number can be calculated repeatedly as patient-years are accumulated throughout a trial or in a clinical development program. Hence, one could propose that after every incremental 500 patient-years are accrued, the number of observed SAEs of interest would be compared to the "tolerable" number to decide if the SAE rate is in danger of violating the 1/1000 patient-years "acceptable" rate. More specifically, we assume the number of SAEs observed for a given number of patient-years is distributed as a Poisson random variable, with the mean equal to

the theoretical SAE rate we establish (eg, 1/1000 patient-years) and variance equal to this mean multiplied by the total number of patient-years observed.

These assumptions permit us to establish confidence intervals for actual SAE rates, to decide if it violates the "tolerable rate" we have established. For example, 3000 patient-years should have mean of three SAEs but could have as many as six before exceeding the confidence intervals—and thereby statistically violating the "tolerable rate."

Statistically, this same metric can be applied to patient populations in postmarketing situations. Practically, this requires an agreement regarding an estimate of patient-years and confidence that all SAEs are reported and adjudicated. More realistically, this metric for RCTs can be applied to longitudinal follow-up studies to monitor SAEs after significantly larger patient-years of follow-up are accrued. This could be similar to current registries for RA and other health provider databases—but NOT postmarketing surveillance. A critical consideration is the definition of an "acceptable" SAE rate per 1000 patient-years.

What to Recommend

- Does what applies to systemically administered, symptomatic relief products apply to all?
- Do the comorbidities in OA require consideration as if a type II diabetes product?
- Can we consider an alternative, such as ongoing estimates of adjudicated CV events during the clinical development program?
- What do we apply to nonsystemically absorbed, topical and/or IA-administered products?
- What about potentially structure-modifying and/or "preventive" agents?
- How do we strike a "reasonable balance" between potential risk and promising benefit?

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Assessment of Structural Change Working Group Recommendations

For the current tools for assessing structure modification (x-ray, MRI, biomarkers), what are the performance metrics for each individual feature that they detect? How can they be used optimally in clinical trials? What are the relative strengths and weaknesses of these assessment tools?

Recommendation: For the purposes of replying to the questions posed, we have focused this response on the currently used, readily available tools for assessing OA structure modification, conventional radiography (CR) and magnetic resonance imaging (MRI). Where data are available, we have provided information on imaging of different peripheral joint OA for knee, hip, and hand. The vast majority of literature, though, pertains to knee studies. The fuller explanation for many of the questions is included in the appropriate Appendices.

The performance metrics of these tools are derived from systematic reviews performed for the initiative process and based on large numbers of clinical trials and hence refer to optimal use. However, it should be noted that there are issues with heterogeneity of studies included for the main systematic reviews in **Appendix 4**. For the CR review, there are limited numbers of studies using individual acquisition techniques. For the MRI review, studies have used different acquisition

methodologies with variations in magnet strength surface coils and in the sequences acquired; the latter is important because certain sequences may be inappropriate for useful detection of a given pathology. Issues on specific acquisition techniques are included below where relevant.

Performance metrics

1. Reliability:

   Conventional Radiography

   Knee: Overall, there was excellent inter-reader reliability for the knee, independent of the technique used. See **Appendix 5, Section 3.2.2.3, Figure 1.**

   Hip: Overall, there was excellent inter- and intra-reader reliability for hip scoring methods. See **Appendix 5, Section 3.3.2.3, Table 1.**

   Hand: Although the reliability of total hand scores has rarely been evaluated, it appears to be substantial and frequently excellent. The inter-reader reliability of the Kallman's system might be lower than that observed with some other scores but remains substantial. The reliability of different scoring methods of individual joints appears usually substantial to excellent. However, the inter-reader reliability of the most frequently evaluated method (ie, the KL method) is moderate or substantial according to the different studies. The reliability of the measurement of change during time has been evaluated in two studies. It was excellent for the four evaluated methods in the first study, and was substantial to excellent in the other study. See **Appendix 5, Tables 26-27** and **Appendix 5, Section 3.4.2.3 .**

   MRI

   Inter- and intra-reader coefficient of variation measures were confined to quantitative or compositional measures (**Appendix 6, Section 4.3.3, Tables 1-2**). The pooled coefficient of variation for quantitative cartilage was 0.03 for both inter- and intra-reader reliability. Test-retest coefficient of variation measures were confined to quantitative or compositional measures **(Appendix 6, Section 4.3.3, Table 3).** The pooled coefficient of variation for quantitative cartilage was 0.04 for both test-retest. The inter-reader and intra-reader intraclass correlations for quantitative, semi-quantitative, and compositional measures were all excellent (range 0.8-0.94)(**Appendix 6, Section 4.3.3, Table 3-5**).

2. Responsiveness

Conventional Radiography

Knee: The standardised response mean (SRM) for annual joint space loss was 0.341 with a pooled annual joint space loss of 0.132 mm and a pooled annual standard deviation of 0.437. The pooled annual joint space loss tended to be higher in studies using extended views without fluoroscopy while the pooled SRM tended to be higher in studies using semi-flexed or flexed views but with overlap in confidence intervals. See **Appendix 5, Section 3.2.2.4, Figures 1-3.**

In the pooled analysis different radiographic techniques were differentiated (ie, extended views with or without fluoroscopy and flexed or semi-flexed techniques with or without fluoroscopy). However, there are numerous different techniques, in particular for semi-flexed and flexed views, which were not possible to analyse separately. The pooled responsiveness was low, whatever the radiographic technique used, and without significant differences between techniques. However, the head-to-head comparisons suggest that responsiveness is higher with the semi-flexed views with fluoroscopy in comparison with other techniques. There are concordant data, which suggest that satisfactory serial medial tibial plateau alignment allows a better responsiveness to be obtained. Head-to-head comparisons suggest that there is no difference in responsiveness between assessments of change of minimal joint space, mean joint space, and joint area. Responsiveness of x-ray depends greatly on study timeline: longer studies offer better data on responsiveness. Therefore, joint space narrowing (JSN) should not be used to assess treatment efficacy over short periods of time. Computerized reading reduces the measurement error leading to somewhat better responsiveness compared to manual read responsiveness in short-term studies on flexion, although responsiveness is still poor. However, in studies longer than 2 years, advantages of computerized vs manual read are much less apparent. See **Appendix 5, Section 3.2.2.4, Table 1.**

Data suggest that semi-flexed or flexed views with fluoroscopy and satisfactory serial tibial plateau alignment enable better responsiveness to be obtained and predictors of joint space loss are more easily discriminated in patients with satisfactory serial tibial plateau alignment. Most studies did not use semi-flexed or flexed views with fluoroscopy and did not separately evaluate patients with satisfactory serial tibial plateau alignment, leading to difficulties in the interpretation of the literature. See **Appendix 5, Tables 13-14.**

Hip

See **Appendix 5, Section 3.3.2.4, Table 1**.

Hand

The responsiveness of global hand OA scores, as evaluated by SRM or ES, was found to be low in most studies. Data on the percentages of progressors have mostly been evaluated on cohorts with a longer follow-up than that usually used in RCTs). With the most frequently used definition (increase of the highest KL grade recorded), 50%–60% of progressors can be expected after 10 years. There is only one short-term study (mean 2.3 years) that used this definition. Only 18.2% of progressors for DIP + thumb IP, and 13.3% for PIP + 1st MCP were observed. Thus, it can be expected that an RCT of 2–3-years duration aiming at showing a reduction of the percentage of progressors would need to include a huge number of patients. See **Appendix 5, Tables 28-29** and **Appendix 5, Section 3.4.2.4**.

MRI

The pooled SRM for quantitative measures of cartilage for medial tibiofemoral joint was -0.58 (95%CI -0.75 to -0.41), for lateral tibiofemoral joint was -0.56 (95%CI -0.92 to -0.20), and for the patella was -0.60 (95%CI -2.23 to 0.97).

The pooled SRM for semi-quantitative measures of cartilage for medial tibiofemoral joint was 0.55 (95%CI 0.47 to 0.64), for lateral tibofemoral joint was 0.37 (95%CI 0.18 to 0.57), and for the patella was 0.29 (95%CI 0.03 to 0.56). The pooled SRM for semi-quantitative measures of synovium was 0.52 (95%CI 0.28 to 0.76), and for bone marrow lesions (BMLs) was 0.19 (95%CI 0.07 to 0.30). See **Appendix 6, Section 4.3.4, Tables 1-6** and **Appendix 6, Table 7**.

3. Strengths and weaknesses

Conventional Radiography

Conventional radiographs (CRs) have traditionally been the method of choice in clinical trials because of their relative feasibility. Radiography is at present the most economical, easily available, and accepted imaging technique to assess structural changes of OA. Reproducibility of radiography is dependent on control of a number of technical issues, including patient positioning (including use of fluoroscopy), radiographic procedure

(centering of x-ray focus spot, focus-film distance, etc), and the measurement process. Standardisation of radiographic methodology is critical in order to reliably assess sequential changes in joint anatomy.

CR presents an image of the joint space of a diarthrodial joint, the width of which represents the thickness of articular cartilage. However, in some joints, notably the knee, joint space width (JSW) also reflects the presence, location, and condition of other structures (eg, meniscus), and JSW is a composite measure of the combined thickness of those structures. Change in JSW may be influenced by the status of one compartment and malalignment (eg,, increase lateral TF JSW secondary to severe JSN in medial TF compartment). As demonstrated above, much is now known of the performance metrics of CR JSW in the knee and to a lesser extent in the hip. In the knee, the use of fluoroscopic positioning and semi-flexed views improve responsiveness, although it is acknowledged that access to fluoroscopic facilities is restricted. Studies will generally need to be of at least 12 and probably 24 months duration.

MRI

MRI allows unparalleled visualization of all the tissues involved in OA joint pathology, including cartilage, menisci, subchondral bone and other soft tissue. Synovitis and its extent can be confirmed with the addition of intravenous contrast agent followed by T1-w imaging. The ability to image in 3-D allows cross-sectional views of the anatomy to be obtained in any given plane, enabling the joint to be evaluated as a whole organ and eliminating problems of morphological distortion, magnification, and superimposition, thereby providing more detailed analysis of change than with other imaging techniques. The lack of ionizing radiation provides a distinct advantage in a clinical setting. Using MRI, it is possible to accurately and feasibly measure change in cartilage morphometry over 12 months for knee OA, and we recommend that this is included in future guidance.

However, MRI does have its limitations. There can be difficulties in safely putting patients with pacemakers or imbedded metal foreign objects inside the magnet. A small proportion of patients have problems with claustrophobic reactions. The size of the joint being imaged—for example, a large knee in an obese patient—may be too large for the cylindrical RF coil typically used, leading to potential inaccuracies in joint imaging. Just as in radiographs, there are artefacts, the commonest one being movement artefact or, at the

knee, 'ghosting' due to a pulsatile popliteal artery which can be reduced by variation in the sequence parameters with tradeoffs with chemical shift artefacts and in-plane resolution. Further work on MR semi-quantitative scores and compositional measures is required before they can be more widely advocated.

What do these putative tools measure? How to determine change over time?

4. Concurrent Validity

Conventional Radiography

Knee: Joint space metric measurement in the knee was moderately or strongly associated with arthroscopic findings. The 1-year change in joint space was moderately associated with the 1-year changes of some arthroscopic findings (but not with others). In the general population, the results were heterogeneous, but most suggested that there is an association between the presence of knee pain and of knee OA. In the knee OA population, the results were heterogeneous, but most suggested that there is no cross-sectional association between the knee pain and joint space metric measurement. In addition, in all studies, no association between the disability and joint space metric measurement was observed. It must be stated that most of the evaluated studies did not use a semi-flexed or flexed technique with fluoroscopy. In the knee OA population, baseline joint symptoms might be weakly correlated to further joint space loss, and changes in joint symptoms might be weakly correlated to changes in joint space loss, but results are heterogeneous. There were insufficient data to conclude on the predictive validity of joint space metric measurement on the evolution of symptoms in knee OA patients. See **Appendix 5, Tables 1-8** and **Appendix 5, Section 3.2.2.1.**

Hip: In the general population as well as in the general population with hip pain, there is an association between the presence of hip symptoms and of hip OA. In the hip OA population, baseline joint symptoms are moderately correlated to further joint space loss. A strong association was found between 1- and 2-year changes in minimal joint space and further pain and disability in hip OA patients. See **Appendix 5, Tables 20-21** and **Appendix 5, Section. 3.3.2.1.**

Hand

A weak relationship between the level of pain and total hand OA x-ray scores was observed. In the general or general geriatric population, there was a modest or no association

between the presence/absence of hand pain and the presence/absence of hand radiographic OA. In the general population, the prevalence of pain increased with radiological OA severity. In both the general population and in hand OA subjects, pain intensity was related to radiological OA severity. Baseline pain was higher in patients with subsequent 2-year JSN progression but not osteophytes. On the contrary, the 2-year change in pain was not associated with the 2-year radiographic progression. The relationship between total hand radiological scores and disability scores was unclear, with three studies demonstrating no association; three, a modest association; and two, with heterogeneous results. On the contrary, a moderate or modest association was demonstrated with grip strength in three out of four studies. Similar results were obtained on the relationship between disability and radiological hand OA presence/absence and severity. In one study, the 2-year change in function score was not associated with the 2-year radiographic progression. The results on physical examination are difficult to summarize since they are heterogeneous and since some studies do not discriminate the different findings. Globally, physical examination seems to correlate with underlying radiological OA, but the sensitivity might be low. The results on range of motion and nodes are heterogeneous. See **Appendix 5, Table 25** and **Appendix 5, Section 3.4.2.1**.

Joint pain is influenced by numerous factors, including patient-related factors. A recent study showed that the relationship between pain and joint space is increased when the patients are their own controls. This study was not included in the present analysis, since joint space was not evaluated using metric measurement. However, it might suggest that the results on correlations between pain and joint space obtained from longitudinal data are more valid than those obtained from cross-sectional studies. It is also important to consider that OA is a waning and waxing disease. Thus, again, the correlations between pain and joint space obtained from longitudinal data might be more valid than those obtained from cross-sectional studies. Finally, most studies did not adjust for analgesic and nonsteroidal anti-inflammatory drug consumption, which might alter the associations, at least with pain.

MRI

The relationships between radiographic OA and cartilage volume, cartilage thickness and compositional measures were found to be inconsistent. On the contrary, a higher frequency of meniscal tears, synovitis, increased bone area, increased bone attrition/curvature was found in persons with radiographic OA while a strong relationship was observed between

meniscal subluxation and increased subchondral bone area and reduced radiographic joint space. There was an inconsistent (but generally moderate) relationship between reduced cartilage volume/thickness and reduced radiographic joint space and radiographic change was found to be insensitive to early changes found on MRI. A strong correlation was found between cartilage volume and measurement of histologic findings while a moderate to strong relationship was found between arthroscopic findings to cartilage and meniscal findings on MRI. There was a strong relationship between CT arthrography and MRI cartilage volume. The presence of pain showed an inconsistent but generally strong relationship with large bone marrow lesions, an inconsistent but generally moderate relationship with synovitis, a weak relationship with cartilage volume/thickness and no relationship to meniscal tears. See **Appendix 6, Table 1** and **Appendix 6, Section 4.3.1.**

5. Predictive Validity

Conventional Radiography

Knee: There are not sufficient data to conclude on the predictive validity of joint space metric measurement on the evolution of symptoms in knee OA patients. Although data are sparse and heterogeneous, the symptomatic and structural efficacy of knee OA treatment might be decreased in patients with lower joint space metric measurement. The further arthroscopic changes might be more important in knee OA patients with lower baseline joint space. However, the data are too sparse and heterogeneous to conclude. The amount of joint space might be predictive of further knee surgery. However, the data are sparse and heterogeneous thus, again, no definite conclusion is possible. See **Appendix 5, Tables 9-12** and **Appendix 5, Section 3.2.2.2.**

In surveys, surgeons usually state that they are weakly or moderately influenced by x-rays when deciding whether joint replacement is indicated or not. However, it has been shown that, in reality, the amount of JSN is a major predictive factor of the decision, at least for hip replacement. Thus, the validity of prediction of joint replacement as an outcome to evaluate the predictive validity of JSN is questionable. On the other hand, the reasons why joint space influences the surgeons' decision remain unclear. If these reasons are differential diagnosis (ie, some surgeons might consider that pain and functional impairment are certainly due to OA in patients with severe JSN, but might be due, at least in part, to another disease in those with mild joint narrowing), optional treatments (ie, the surgeons might consider that an additional or complementary medical treatment is less likely to be efficient in patients with

severe joint narrowing), and/or disease's potential evolution (ie, OA is frequently a waxing and waning disease, and surgeons might consider that a spontaneous clinical improvement is less likely observed in patients with severe joint loss), joint replacement might be considered as a valid outcome.

Hip: In our unpublished data, there was a strong association between 1- and 2-year changes in minimal joint space and further pain and disability in hip OA patients. The amount of joint space narrowing might be predictive of further joint space loss, but data are heterogeneous. The amount of joint space narrowing and the rate of joint space loss are predictive of further hip replacement. See **Appendix 5, Tables 23-24** and **Appendix 5, Section 3.3.2.2**.

Hand: There were insufficient data to conclude on the predictive validity of joint space metric measurement on the evolution of symptoms in hand OA patients. See **Appendix 5, Section 3.4.2.2.**

MRI

Quantitative cartilage volume change and presence of cartilage defects or BMLs are potential predictors of total knee replacement. Existing data need to be corroborated. An inconsistent but generally weak relationship between cartilage loss and symptom change was observed and a moderate relationship between BML change and incident symptoms and pain change. There was a weak relationship between change in synovitis and change in pain and a weak relationship between change in cartilage thickness and change in joint space. The presence of meniscal damage, cartilage defects and BMLs predicts MRI progression. See **Appendix 6, Tables 2-3** and **Appendix 6, Section 4.3.2**.

How can rapid structural progression patients be identified? Is that necessary?

Given the high costs of clinical trials, the numbers of subjects required for CR and MRI studies, and the study duration required for evaluation, there will often be need for identifying inclusion criteria that will 'enrich' for rapid progressors.

Conventional Radiography

Knee: A higher baseline joint space narrowing, or a baseline KL 3 grade, might be predictive of more rapid joint space loss. However, the results are conflicting and, for baseline joint space metric measurement, the most relevant threshold needs to be established. Malalignment is strongly or moderately associated with joint loss. This relationship might be due to an increase in the knee adduction moment. However, since the adduction moment cannot be evaluated everywhere, malalignment might be a better criteria to select fast losers in trials. There is no evidence that demographic data allow prediction of change in metric measurement of joint space. Female sex and high BMI might be predictors, in particular in subjects with a satisfactory serial tibial plateau alignment, but data are sparse and most studies did not find any relationship. Two studies suggest that a joint uptake on bone scan is predictive of further joint loss. However, this relationship might be related to structural degradation. Data suggest that semi-flexed or flexed views with fluoroscopy, and satisfactory serial tibial plateau alignment, improve the responsiveness, whilst predictors of joint space loss are more easily discriminated in patients with satisfactory serial tibial plateau alignment. Most studies did not use semi-flexed or flexed views with fluoroscopy and did not separately evaluate patients with satisfactory serial tibial plateau alignment, leading to difficulties in the interpretation of the literature. See **Appendix 5, Table 17-19** and **Appendix 5, Section 3.2.2.4**.

Relevant thresholds of acceptable sensitivity and specificity are lacking. Moreover, it would be useful to define what constitutes an acceptable sensitivity and specificity (increasing specificity with decreasing sensitivity would lead to a more powerful selection of fast losers, but would increase difficulties of inclusion, decreasing specificity with increasing sensitivity would lead to the opposite). The inclusion of fast losers in trials may lead to increased responsiveness, but data are needed on the effect of rate of joint space loss on treatment effect.

Hip: This analysis was not performed, since a systematic review of the literature was published recently (Wright et al, 2009). In this analysis, progression was associated with age, joint space width at entry, femoral head migration, femoral osteophytes, bony sclerosis, KL grade 3, baseline hip pain, and Lequesne's index score ≥10. Evidence was weak or inconclusive regarding associations between other radiographic or clinical features, biomarkers, and use of NSAIDs.

Hand: Middle-aged and female subjects might progress faster but there are discrepancies in the data, which moreover are sparse, heterogeneous, and not adjusted for confounding variables. Surprisingly, there are very few data on baseline x-rays, which do not allow any conclusion. There are concordant data on the predictive value of bone scans. However, all studies evaluated joints rather than subjects. In addition, no adjustments for confounding variables were done. See **Appendix 5, Tables 28-29** and **Appendix 5, Section 3.4.2.4.**

MRI

The presence of severe meniscal extrusion, severe medial tear ($P = 0.005$), medial and/or lateral bone marrow lesions and pre-existing cartilage defects predicted fast MRI progression. See **Appendix 6, Tables 2-3** and **Appendix 6, Section 4.3.2.**

What is the relationship between symptoms and structural progression? What is the relationship between disability and measured structural change?

Conventional Radiography

Knee: Joint space metric measurement in the knee was moderately or strongly associated with arthroscopic findings. The 1-year change in joint space was moderately associated with the 1-year changes of some arthroscopic findings (but not with others). In the general population, the results were heterogeneous, but most suggested that there is an association between the presence of knee pain and of knee OA. In the knee OA population, the results were heterogeneous, but most suggested that there is no cross-sectional association between the knee pain and joint space metric measurement. In addition, in all studies, no association between the disability and joint space metric measurement was observed. It must be stated that most of the evaluated studies did not use a semi-flexed or flexed technique with fluoroscopy. In the knee OA population, baseline joint symptoms might be weakly correlated to further joint space loss and changes in joint symptoms might be weakly correlated to changes in joint space loss, but results are heterogeneous. There were insufficient data to conclude on the predictive validity of joint space metric measurement on the evolution of symptoms in knee OA patients. See **Appendix 5, Tables 1-12** and **Appendix 5, Section 3.2.2.1 and 3.2.2.2.**

Hip: In the general population as well as in the general population with hip pain, there is an association between the presence of hip symptoms and of hip OA. In the hip OA population, baseline joint symptoms are moderately correlated to further joint space loss. A strong association was found between 1- and 2-year changes in minimal joint space and further pain and disability in hip OA patients. The amount of joint space narrowing might be predictive of further joint space loss, but data are heterogeneous. The amount of joint space narrowing and the rate of joint space loss are predictive of further hip replacement. See **Appendix 5, Tables 20-24** and **Appendix 5, Section 3.3.2.1** and **3.3.2.2**.

Hand: A weak relationship between the level of pain and total hand OA x-ray scores was observed. In the general or general geriatric population, there was a modest or no association between the presence/absence of hand pain and the presence/absence of hand radiographic OA. In the general population, the prevalence of pain increased with radiological OA severity. In both the general population and in hand OA subjects, pain intensity was related to radiological OA severity. Baseline pain was higher in patients with subsequent 2-year JSN progression but not osteophytes. On the contrary, the 2-year change in pain was not associated with the 2-year radiographic progression. The relationship between total hand radiological scores and disability scores was unclear with three studies demonstrating no association, three a modest association, and two with heterogeneous results. On the contrary, a moderate or modest association was demonstrated with grip strength in three out of four studies. Similar results were obtained on the relationship between disability and radiological hand OA presence/absence and severity. In one study, the 2-year change in function score was not associated with the 2-year radiographic progression. The results on physical examination are difficult to summarize since they are heterogeneous and since some studies do not discriminate the different findings. Globally, physical examination seems to correlate with underlying radiological OA, but the sensitivity might be low. The results on range of motion and nodes are heterogeneous. See **Appendix 5, Table 25** and **Appendix 5, Section 3.4.2.1**.

Joint pain is influenced by numerous factors, including patient-related factors. A recent study showed that the relationship between pain and joint space is increased when the patients are their own controls. This study was not included in the present analysis, since joint space was not evaluated using metric measurement. However, it might suggest that the results on correlations between pain and joint space obtained from longitudinal data are

more valid than those obtained from cross-sectional studies. It is also important to consider that OA is a waning and waxing disease. Thus, again, the correlations between pain and joint space obtained from longitudinal data might be more valid than those obtained from cross-sectional studies. Finally, most studies did not adjust for analgesic and nonsteroidal anti-inflammatory drug consumption, which might alter the associations, at least with pain.

MRI

In the knee OA population, an inconsistent but generally strong relationship was found between large bone marrow lesions (BMLs) and the presence of pain, and a moderate relationship was observed between BML change and incident symptoms and change in pain. An inconsistent but generally moderate relationship was found between synovitis and effusion and presence of pain, with a weak relationship between change in synovitis and change in pain. The relationship between cartilage volume/thickness and presence of pain was weak as was the relationship between cartilage loss and symptom change. No relationship was found between meniscal tears and presence of pain. See **Appendix 6, Tables 1-3** and **Appendix 6, Sections 4.3.1 and 4.3.2.**

Could the need for a joint replacement be a clinical outcome, which might supplant imaging as a measurement?

The group did not attempt to answer this question as it was the focus of another OARSI-OMERACT Task Force with an ongoing program due to report in 2010. This work is addressing the development of an endpoint represented by the need for joint replacement. Thus, since the possibility of performing a joint replacement varies by region and demographics (country, health system, insurance, comorbidities evident in the patient, etc), the concept of a virtual joint replacement is being developed. Thus, what are those clinical characteristics that qualify a patient for consideration for a joint replacement and are these uniform around the world? It is believed that this would be a relevant outcome for prevention of its occurrence for defining a structure modifying therapy.

What is the research agenda required to inform each of the above questions?

Conventional Radiography

- Studies to further elucidate the relationship between JSN and symptoms

- Studies to improve our understanding of predictive (ie, does JSN predict subsequent joint replacement?)
- Studies to improve our understanding of construct validity (ie, correlation between JSN and mean pain or function)
- Studies in knee OA on the effect or rate of joint space loss on treatment effect
- Studies examining the performance metrics of nonknee acquisition techniques and scoring methods

MRI

- Studies to define more responsive measures of structural change
- Studies that measure change at an earlier stage of disease when it may be more suitable for DMOAD intervention
- Studies to improve predictive validity of current structural measures for important clinical outcomes (eg, total joint replacement (TJR), virtual TJR)
- Studies to improve assessment precision of structural measures more closely related to symptom change (eg, BMLs, synovitis)

All Modalities

- Studies to develop and improve semiquantitative and quantitative measurement of OA imaging pathology
- Studies of the performance metrics of novel and existing nonknee joint measurement tools

Summary and Recommendations of the ASC Working Group

In the last decade since the FDA produced its draft guidance for industry, much evidence has been accumulated on the assessment of structural change in OA. This report has attempted to examine a number of key issues about the performance metrics of the commonest imaging tools used assessing structural change in OA. The following summary and derived recommendations attempt to overview the large amount of literature reviewed in this document.

The underlying assumption of these recommendations is that the manifestations of joint pain and disability currently associated with OA are strongly related to the pathophysiology of OA seen in joint structures. This postulate is strongly supported by epidemiological evidence of the association

between radiographic OA, joint pain, and disability in the general population. Further, the systematic reviews suggest there is a direct relationship between structural severity of the disease and severity of symptoms (pain and disability), that between-patient variability in symptom severity can be explained by variations in structural severity of OA, and that worsening symptoms of OA can be accounted for by progressive changes of OA in structures of the joint.

Much of the published evidence in this area relates to OA of the knee, with much less evidence (especially for modern imaging modalities) relating to OA of the hip and very limited information available for hand OA. This report must therefore be seen as largely related to trials for OA of the knee and to a lesser extent, the hip.

Importantly most of the therapeutic studies on OA have included symptomatic and structural moderate-to-severe OA, but there is an absence of literature and definitions for "early" OA, especially studies entering people before the currently recognized clinical syndrome is apparent and when structural pathology is presumably minimal. So the literature on the performance of existing imaging modalities in this important area is sparse.

When mentioned, the term *therapies* refers to drugs, devices, and biological products entered into the treatment of OA. The summary and recommendations in this document should be read in conjunction with the subsequent section on Research Recommendations.

Summary and Recommendations

Conventional radiography (CR)

- Conventional radiographs have traditionally been the method of choice in clinical trials because of their relative feasibility.
- CR presents an image of the joint space of a diarthrodial joint, the width of which represents the thickness of articular cartilage. In some joints, notably the knee, JSW also reflects the presence, location, and condition of other structures (eg, meniscus), and JSW is a composite measure of the combined thickness of those structures.
- Much is now known of the performance metrics of CR JSW in the knee and to a lesser extent in the hip (see details in previous chapters). In the knee, the use of fluoroscopic positioning and semi-flexed views improve responsiveness, although it is acknowledged that access to

fluoroscopic facilities is restricted. Studies will generally need to be at least 12 and more likley 24 months duration.

- It is possible to 'enrich' a study population to increase the rate of joint space loss, for example, by including higher KL grade.
- Automated methods for assessing parameters of JSW offer promise of improved precision, and therefore, improved responsiveness.
- In terms of correlations with concurrent symptoms, there is a weak association between progression in JSN and progression of symptoms. There is little information on how progression in JSN during the course of a study reflects poststudy change in symptoms. JSN progression is associated with increased rate of subsequent total joint replacement, but these may not be truly independent events as JSN is one of the features used to select people for joint replacement surgery.
- The natural history of hip OA appears different to that of knee OA, and although the literature concerning the hip is much less extensive, there is some evidence for better performance metrics for JSW at the hip. Hip JSW as a construct does not include a meniscus. There is little evidence on enriching cohorts for purposes of increasing rate of JSN progression.

Recommendation

For assessing CR JSW, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness. At the knee, JSW represents a composite construct, and a semi-flexed acquisition is recommended for knee trials. We support continued use of CR JSW.

MRI

- There has been a growing awareness that symptomatic OA represents a process involving all the tissues in the OA joint. Structure modification should therefore be considered in a broader context than that of cartilage alone. MRI has evolved substantially over the last decade, and its strengths include its ability to visualize individual tissue pathologies, as well as the interrelationship between tissue pathologies.
- Using MRI, it is possible to accurately and feasibly measure change in cartilage morphology over 12 months for knee OA.

- It is possible to 'enrich' a knee OA study population to increase the rate of cartilage loss, for example, by including higher KL grade.
- In terms of correlations with concurrent symptoms, there is a weak association between progression of cartilage loss and increasing symptoms. There is little information on how change in cartilage parameters during the course of a study reflects poststudy change in symptoms. There is some predictive validity with progression of cartilage loss predicting subsequent total joint replacement.
- More information is required on the performance metrics of MRI semi-quantitative and compositional measures of cartilage morphology. There may be a role for semi-quantitative assessments for assessing focal cartilage defects.
- Since MRI alone has the capacity to image the other tissues, further work is needed on the quantification and predictive validity of noncartilage MRI pathologies. The performance metrics of noncartilage MRI features have not been extensively studied but there is a rapidly emerging literature in this field.

Recommendation

For assessing MRI cartilage morphometry in knee OA, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness. We recommend inclusion of MRI cartilage morphometry in the next guidance document.

Other imaging modalities

- Ultrasound is currently the other imaging modality with most information available, and at this stage it appears it is most promising as a tool for evaluating OA synovitis. Ultrasound-detected pathologies have been associated with current OA symptoms. Further work is required to better understand the performance methods of ultrasonographic quantification of pathology.

Recommendation

The potential for non-CR or MRI modalities to assess relevant noncartilage tissues should be considered.

Research Recommendations

Conventional Radiography

1. To further understand the relationship between JSN and symptoms:

- Cross-sectional studies in which the patients are their own controls, such as the one recently published by Neogi et al (*BMJ* 2009) to better evaluate the potential correlation.
- Longitudinal studies evaluating the relationship between changes in symptoms and changes in joint space.
- Predictive validity studies (ie, does joint space predict subsequent pain and disability and subsequent joint replacement?). For example, does JSN between month 0 and month 12 correlate with joint replacement between month 12 and month 60?
- Construct validity studies, (ie, correlation between JSN and mean pain or function). For example, is JSW between month 0 and month 12 correlated with mean pain and function evaluated every 3 months between month 0 and month 12, or between month 12 and month 24?

2. For Knee OA:

- Studies of the relationship between symptoms and radiographic joint space evaluated on semi-flexed x-rays with fluoroscopy.
- Studies on predictors of joint loss evaluated on semi-flexed x-rays with fluoroscopy and optimal serial tibial plateau alignment.
- Studies on the effect of rate of joint space loss on treatment effect.
- Studies to determine the acceptable thresholds of sensitivity and specificity.

3. For Hand OA:

- Studies comparing the metrological properties of hand OA scoring systems.

Magnetic Resonance Imaging

- Studies to define more responsive measures of structural change.
- Studies that measure change at an earlier stage of disease when it may be more suitable for DMOAD intervention.
- Studies to improve predictive validity of current structural measures for important clinical outcomes (eg TJR, virtual TJR).
- Studies to improve assessment precision of structural measures more closely related to symptom change (eg BMLs, synovitis).

Prevention or Risk Reduction Working Group Recommendations

For a claim of prevention or risk reduction for the development of OA, what are potential outcome measures? If biomarkers are used, what is their state of qualification? What is the desirable duration of a trial for such a claim? What is an appropriate safety database for a prevention of OA claim?

The Prevention or Risk Reduction Working Group dealt with the first question. The Biomarkers Working Group added its deliberations in a subsequent section and the Safety Working Group added a small comment within this section.

What are potential outcome measures?

Recommendation: For these purposes, *primary and secondary prevention* and *risk reduction* of structural and symptomatic indicators of OA would require outcomes relevant to these domains. As definitions of "at risk" populations change and measurements of the disease process and outcomes advance, it is expected that design features and relevant outcomes of prevention trials would necessarily evolve as well. Additionally, the working group focused on knee OA; outcomes, study design issues, populations at risk, duration of trials may vary depending upon the joint site under evaluation.

For example, if the prevention trial hypothesis is that an intervention among obese adults with no or doubtful evidence of radiographic knee OA (Kellgren Lawrence [KL] radiographic score = 0, 1) will be associated with a delayed onset of knee OA compared to the placebo group, this delay could be reflected in two co-primary outcomes: less symptom report and minimal structural change in relation to the untreated group. Candidate measures to detect these areas include changes in: (1) KL score and (2) questionnaire-based pain assessment (PRO's). Other potentially relevant outcome measures could include newer technologies once validated, such as MRI or T2 mapping to assess morphological changes in joint structures or articular cartilage degradation and/or bone marrow lesions. As imaging and molecular techniques advance to the stage where they could be surrogates of downstream clinical outcomes, it may be that an intervention might be able to show a primary effect on structure of the OA process, regardless of its immediate effect on symptoms. Examples in other conditions abound, that is, interventions directed toward lowering serum cholesterol or altering lipid profiles to prevent future cardiovascular events,[1,2] or altering bone mineral density to

prevent osteoporotic fractures.[3] It is unlikely, though, that requirements that a proposed intervention affects relevant clinical outcomes would be waived entirely.

Secondary outcomes could include some or all of the following largely predicated on the nature of the proposed intervention: (1) clinical measures of function, pain, and mobility; (2) mechanistic measures of the OA disease pathways such as knee alignment, knee external adductor moment, knee joint compressive, and shear forces; (3) biomarker measures of pro-inflammatory molecules (eg, IL-6, Tumor Necrosis Factor-α, C-RP) and joint metabolism (eg, CTX-II, COMP); (4) lower extremity strength and power; (5) limb proprioception; and (6) abdominal and thigh fat depots measured by CT.

In addition to OA outcome measures, investigators need to select or develop appropriate measures of intervention-related processes and adherence to the intervention.

What is the desirable duration of a trial for prevention?

Recommendation: A primary prevention trial is likely to require a 10-year follow-up with further follow-ups at 1- or 2-year intervals with the interval distance based on time required to detect meaningful differences in the measures of interest and motivate subjects to maintain optimal participation in the trial. Shorter duration trials could be envisioned with improvement in the sensitivity and responsiveness of outcome measures and the OA process.

What is the desirable population of a trial for duration?

Recommendation: In a prevention trial, the optimal study population should be at high risk for future OA but free of full evidence satisfying the disease definition. Therefore, the study population selection is dependent upon the definition of disease that is employed.

A prevention trial study population can be selected to represent the three major domains of disease definition related to OA: 1) structural compromise, 2) pain and other symptoms, and 3) impaired function. Additionally, physiological/immunological locally or systemically measured biomarkers, such as synovial fluid aggrecan, serum C-reactive protein (CRP) or cartilage oligomeric matrix protein (COMP), urinary type II collagen telopeptides (uCTX-II), or combinations of biomarkers, might be incorporated to either define an at-risk population or to exclude individuals from selection into a prevention trial.[4] Further, population selection can be predicated on addressing each of these domains singularly or in combination.[5]

If the eligible population for a prevention trial is to be **free of structurally-defined OA,** one option for defining a "disease-free" population includes enrollment of persons with K-L radiographic grades 0 or 1. Decision-making based on the selection of a population with a K-L score of K-L = 0 vs K-L = 1, which is designated as "doubtful OA," must acknowledge that there is an embedded probability that individuals with a K-L = 1 have early OA,[6] or the underlying conditions leading to OA, but which has not yet been identified definitively on the radiograph. This probability should be factored into estimating the sample size and in the development of data analytic strategies. Efforts are underway to define OA by media other than the standing knee radiograph. For instance, static MRI to define OA based on morphologic changes in cartilage, bone, or other soft tissues[7] or functional magnetic resonance imaging (fMRI) or other types of MRI (such as DGEMRIC, T2-mapping, T1rho, sodium imaging, etc) to define OA based on compositional changes in cartilage, bone or other soft tissues,[8,9] may become modalities of choice. Currently, there is no agreed upon definition of OA based on these technologies. However, the field is rapidly evolving, and these developments must be anticipated in developing a trial.

If the eligible population **lacks characteristics defining symptoms, especially pain or stiffness**, the limits of allowable symptoms must be carefully defined, including how pain is to be assessed, its severity and duration, and the allowable frequency for transient pain, and potentially whether or not pain in joints apart from the target joints are considered informative. The use of usual and rescue medications, such as analgesics or NSAIDs also needs to be factored into the methodologic strategy to assess symptoms of OA.[10]

If the eligible study population is to be **free of functional performance impediments**, investigators will need to determine whether inclusion criteria are based on self-report instruments or performance-based assessments. There are numerous questionnaire-based instruments to characterize functional status. For the selection of a study population, it is particularly important to choose an instrument or combination of instruments that have a known specificity (the known probability of truly being free of functional compromise), and that specificity should be relevant to the population from which the prevention trial population will be recruited. The use of performance-based assessment in prevention trial recruitment is limited by the relative absence of normative data in persons younger than age 65, thereby precluding the ability to estimate the probability of any specific assessment value's actually representing the disease-free state for a prevention trial. Further, there are many determinants of function, which may or may not be directly relevant to OA. Alternatively, these measures may be considered to be estimates of

an "at-risk" state and therefore eligible for study in a prevention trial; it is important that the predictive capacity of these performance measures over a period of time for increased compromise be known.

If the eligible study population will be selected based on **physiological or immunological biomarker measures**, there are at least two expectations. First, there must be adequate information to discern when a specific value of the biomarker(s) truly represents a "disease-free" state and, second, information about the rapidity of the biomarker change (if treated as a continuous variable) or conversion (if treated as a discrete variable) in relation to the development of disease, must be known and available. Additionally, the biomarker must have been previously validated against a clinically relevant endpoint for its use as a surrogate measure.[11] Even if the biomarker is used only as a criterion for inclusion or exclusion for participation in a prevention trial, it must have sufficient evidence of predictive relevance to warrant its application.

What is an appropriate safety database for prevention? Is any risk acceptable in a therapy designed to be given to someone with no signs or symptoms of disease?

Recommendation: Because a prevention trial for OA could involve an intervention with active agents administered to otherwise healthy individuals or to individuals with comorbid conditions for extended periods of time, the safety database must be extensive and involve information from multiple organ systems. The extent of this safety database may depend upon the intervention. For example, some interventions may have pleiotropic effects (ie, statins or bisphosphonates[12-15]), reinforcing the need to monitor multiple organ systems for toxicity. A more localized intervention, such as an unloading brace, might not require the same degree of vigilance for safety in remote organ systems. Observations must also be long in duration, particularly for agents that might impact the immune system and be associated with infections or subsequent development of cancer.

Safety Working Group Comments

As discussed above, for safety, the Safety Working Group determined that since "a prevention trial for OA could involve an intervention with active agents administered to otherwise healthy individuals or to individuals with co-morbid conditions for extended periods of time" and the subjects of the study would not yet suffer the disease of interest; for such a preventive therapy used BEFORE a disease state is established there is a different level of acceptance of the potential for AEs than that tolerated in an observed treatment for an established disease state. Thus, consensus was that such a therapeutic would need to be very safe. In this context it is important to keep in mind

the concept of benefit to risk and number needed to treat for benefit and number needed to harm. Thus, a preventative therapeutic would need to have a very low number of patients to be treated for clinical benefit with a very large number needed for exposure to lead to harm. At this time, there are no drugs for treating OA once it has been established that fulfill these criteria and certainly no therapeutic to prevent the disease has been developed.

What does prevention or risk reduction mean in terms of a clinical study and therapeutic intervention?

Recommendation: For these purposes, *prevention* refers to those agents or actions that curtail or delay the onset or new occurrence of clinically diagnosed OA at the joint site of interest in someone initially without evidence satisfying the clinical definition of the condition; components of this definition may include structural evidence (eg, on radiographs) and characteristic signs and symptoms (eg, bony enlargement, crepitus, pain).

Risk reduction refers to decreasing specific and modifiable risk factors associated with the development of OA in an attempt to decrease the likelihood of developing OA or to delay its onset. For example, since obesity and overweight are strong risk factors for knee OA, a weight loss intervention could be evaluated to determine its ability to reduce the risk of developing knee OA in the obese. Similarly, since joint trauma, with its frequently resultant altered biomechanics, is a strong risk factor for the development of OA, an intervention to alter abnormal biomechanics in those with joint injury could also be considered in a preventive context for OA. As our ability to identify high-risk groups earlier and earlier with more sophisticated imaging or molecular biomarkers, it might be possible to prevent the development of abnormal levels of such markers, which themselves are surrogates for the future development of OA.

Because OA is frequently generalized (ie, affects more than one joint in more than one joint group), an intervention could be applied in someone with OA in one joint site, in order to prevent the development of OA in another joint site unaffected at the start of the trial. For example, those with hand OA could be the subject of a prevention trial to prevent the development of OA in the knees or hips.[16] This situation blurs the distinction between incidence of new disease and progression of established disease and may need to be considered on a case-by-case basis, with statistical methodology applied to allow for the nonindependence of multiple joints within the same person. This also suggests that information about joints beyond the target joint should be collected at the

beginning and throughout the trial, both for the purpose of recognizing important secondary effects of the intervention and for identifying potential safety signals of the intervention.

What is the research agenda required to inform each of the above questions?

Recommendation: Observational studies with both short and long-term follow-up can be particularly helpful to define molecular, structural, and symptomatic correlates of disease and to identify risk factors predictive of the development of disease and its clinical impact. Attention to gender and minority inclusion, with the requisite consideration of distinct issues regarding their participation in prevention trials, should be part of this research agenda.

- Evaluation of existing datasets with particularly long follow-up times (10, 20, or more years) in order to identify risk factors that may be exposed long in advance of disease onset
- Evaluation of existing datasets with detailed genetic, biomarker, and imaging data to link to various OA phenotypes along the continuum from molecular to preradiographic OA to radiographic to symptomatic OA
- Addition of short follow-up times (ie, months) to existing cohorts to obtain sensitive, dynamic imaging and other biomarker data to aid prediction of the development of structural and clinical disease
- Evaluation of distinct ethnic/racial subpopulations to ascertain accurate assessment of the burden of disease in these groups, differences in risk factor profiles, and genetic, imaging, and biomarker subtypes in order to tailor trials to relevant groups, (ie, differences in BMI that might be used to screen Asians or African Americans into prevention trials for the overweight/obese)
- Methodological study of distinct threats to validity of prevention trials and their execution, related to cultural differences in attitudes toward trial participation and risk factor reduction; techniques to maximize adherence and retention; ways to measure and overcome biases such as preventive misconception and behavioral disinhibition. Studies in other diseases have shown that study participants may have misconceptions about the potential effectiveness of a preventive intervention and/or may have inflated estimates of the likelihood that they will be randomized to get the active agent, and may have exaggerated impressions of the likelihood that the intervention will be personally effective for them. Simon and colleagues have called this the “preventive misconception,” defined as

"the overestimate in probability or level of personal protection that is afforded by being enrolled in a trial of a preventive intervention."[17] This can be particularly problematic when accompanied by "behavioral disinhibition" or the adoption of behaviors that may pose a risk to the participant or others.[17]

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Biomarkers Working Group Recommendations

If biomarkers are used, what is their state of qualification? What is the desirable duration of a trial for such a claim? What is an appropriate safety database for a prevention of OA claim?

Biomarkers and Their Applicability

OA is a disease characterized by a prolonged asymptomatic molecular phase, a preradiographic phase, followed by a recalcitrant, later radiographic phase with evident structural joint changes, frequent pain, and loss of function. OA is a chronic and slowly progressive disease for which biomarkers may be able to provide a more rapid indication of therapeutic responses to therapy than is currently available; this could accelerate and facilitate OA drug discovery and development programs.

What biomarkers now exist?

Recommendation: Although many OA-related biomarkers are currently available (see **Tables 1 and 2** below), they exist in various states of qualification and validation. Qualification is a process applied to a particular biomarker to support its use as a surrogate endpoint in drug discovery, development, or postapproval and, where appropriate, in regulatory decision-making.[1] In contrast, validation of a biomarker is much broader and can relate to verification of analytical performance characteristics (such as precision, accuracy, dynamic range, etc) as well as clinical correlation of a biomarker with a biological process or clinical outcome. The success of biomarker qualification on a structural modifying endpoint depends critically on the performance and specificity of the endpoint. With regard to structural modifying endpoints, OA is currently analogous to osteoporosis 30 years ago,[2] namely a disease in search of a robust, gold-standard outcome measure to inform clinical trials. By 1984, the FDA Osteoporosis Guidelines upgraded dual-energy photon absorptiometry from investigational to a valid and reliable method for measuring trabecular bone mass of the spine. This was critical to the subsequent development and regulation of osteoporosis drugs.[2,3] Because the process of qualification is only as good as the clinical and structural outcomes used in a study (to date, pain and radiographic joint space narrowing in OA), the extent of improvement in endpoints will strongly influence the success of biomarker applications in clinical trials in the future.

What is their utility?

Recommendation: A system called BIPED, which stands for Burden of disease, Investigational, Prognostic, Efficacy of Intervention, and Diagnostic biomarkers, classifies the major types of biomarkers[4] into five categories corresponding to their utility. We have added a Safety category to the BIPED system, thereby updating the classification scheme to BIPEDS. The reason for adding a safety category was based on the fact that some of the new OA targets that are currently being exploited in drug discovery and development (eg, the proteolytic metalloprotease enzymes) are not unique to the affected tissues but are ubiquitous in their expression. The modulation of such targets by new pharmacological agents could produce unexpected AEs in addition to those usually encountered and monitored during drug development. The utility of known OA-related biomarkers is included in Tables 1 and 2 as defined by the BIPEDS scheme. **Table 3** (below] lists the hypothetical utility of each type or class of biomarker in the BIPEDS classification scheme. Based on the BIPEDS scheme, the biomarkers that are likely to have the earliest beneficial impact on clinical trials fall into two general categories. The first category is one that will allow us to target trials to

subjects that are likely to either respond and/or progress (prognostic value) within a reasonable and manageable time frame for a clinical study (for instance, within 1 to 2 years for an OA trial). The second category of biomarkers includes those that provide early feedback for preclinical decision-making and for trial organizers that a drug is having the desired effect on the primary target. Both types of biomarkers are particularly desirable in chronic diseases such as OA where conventional clinical outcomes may take years to present.[5] In some cases, the biomarker might be sufficiently qualified that the researchers have confidence in using it to justify advancement to phase 2 trials or to determine a dosing schedule. These two categories reduce the burden and risk of early stage trials by delivering essential early information, making OA a more manageable disease and, therefore, a more attractive target for drug developers.

What evidence is available to support their use as surrogates of clinical outcomes?

Recommendation: A second useful classification system referred to here divides biomarkers into four categories according to their current level of qualification [6]:

Exploration level biomarkers are research and development tools accompanied by *in vitro* and/or preclinical evidence for which there is no consistent information linking the biomarker to clinical outcomes in humans (these are used for hypothesis generation);

Demonstration level biomarkers are associated with clinical outcomes but have not been reproducibly demonstrated in clinical studies (this category corresponds to ''probable valid biomarkers'' in nomenclature suggested in draft guidance from the FDA [7] and are useful for decision-making by providing evidence to support the primary clinical evidence);

Characterization level biomarkers are reproducibly linked to clinical outcomes in more than one prospective clinical study in humans (this category corresponds to ''known valid biomarkers'' in nomenclature suggested in guidance by the FDA[7] and are useful for decision-making, dose finding, and secondary and tertiary claims); and

Surrogacy level biomarkers can substitute for a clinical endpoint (this category corresponds to ''surrogate endpoint'' and requires agreement with regulatory authorities as an FDA registrable endpoint).

Table 1 (p 65) represents a list of 12 commercially available OA-related biomarkers and an approximate categorization with regard to level of qualification. However, it must be noted that qualification is dependent on a specific context and what is represented here is the demonstration of general utility in one of the four qualification categories described. There are currently no qualified biomarkers that can be considered as surrogate clinical endpoints in OA. It is also important to note that advances in the field will lead to rapid expansion of this list and more specificity with regard to qualification gleaned from trials in the context of specific drug treatments.

What is the face validity?

Recommendation: Face validity refers to a biomarker "looking like" it is going to measure what it is supposed to measure. The face validity for all the biomarkers listed in Tables 1 and 2 is high given that all are either joint tissue components or a protease known to be involved in the development of OA pathology.

What is the practicality?

Recommendation: The practicality of all the biomarkers listed in Table 1 is high as all 12 can be measured by a commercially available assay. In addition, each of these biomarkers can be measured from easily available and collectable matrices such as serum or urine without the need for invasive procedures.

What is the research agenda required to inform each of the above questions?

Recommendation: There have been few published clinical trials reporting biomarker results. The lack of clinically effective therapies with established chondroprotective activity in OA has limited the availability of clinical samples in which to test for or qualify potential efficacy of intervention biomarkers.

In many cases, biomarker results are not reported in a systematic and standardized manner so it is difficult to utilize published data from current trials to power future trials or to draw conclusions by comparing across studies. Recommendations regarding standardization can be found in the white paper document.

Of those clinical trials reporting biomarker results, relatively few biomarkers have been tested, often using different assay methods and methodologies, and few trials have tested multiple

biomarkers in the same samples. Only recently have a variety of biomarkers started to be examined head to head in the same studies.[8]

The following points summarize a research agenda related to advancing biomarkers for use in the development of drugs for OA:

- To develop better structural endpoints for biomarker qualification;
- To develop biomarkers for various stages of disease;
- To develop biomarkers reporting on specific joint sites and to elucidate the specific joint site contributions to the systemic concentrations of existing biomarkers;
- To determine the effect of the clearance of the biomarkers from the joint, from the lymphatics, and from the blood as well as the renal processing and elimination via the urine on their measurement and correlation with disease progression. In addition, to assess if there is a circadian rhythm in the level of a biomarker in a particular matrix to better design the sample collection schedule and the interpretation of the results;
- To assess if there are covariates that affect the concentration of a biomarker in the selected matrix such as age, gender, BMI, concomitant diseases/medications, or joint site involvement;
- To run a fit-to-purpose analysis of the identified biomarker(s);
- To establish an ongoing critical assessment of the value of existing biomarkers in clinical trials to assess how the biomarker is modulated by the progression of the disease;
- To establish minimal clinically relevant differences in biomarkers once the minimal clinically important differences are defined for the qualifying endpoints for biomarkers, namely with respect to symptomatic and structural endpoints.

Table 1. Commercially available OA-related biomarkers qualified for various OA outcomes

Biomarker	Process (Preliminary)	BIPEDS Classifications	Surrogacy Based on Human Clinical Trials (Preliminary)	ELISA Assay Type
Urinary CTX-II	Type II collagen degradation	Knee: BPED Hip: BPD	Characterization: changed significantly in 3 pharmacologic trials that met primary clinical endpoints[9,10,11]	Competitive-inhibition
Serum COMP	Cartilage degeneration	Knee: BPD Hip: BPD	Exploration: not used to date in published pharmacologic trial	Competitive-inhibition & sandwich
Serum HA	Osteophyte burden, synovitis	Knee: BPED Hip: P	Demonstration: changed significantly in one pharmacologic trial that met primary clinical endpoints[11]	Sandwich protein binding assay
Serum and urine C1,2C	Types I and II collagen degradation	Knee: D(u) Hip: none	Exploration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint[12]	Competitive-inhibition
Serum and urine C2C	Type II collagen degradation	Knee: E(s), D(u) Hip: B(s)	Demonstration: changed significantly in one pharmacologic trial meeting primary clinical endpoints[11]	Competitive-inhibition
Serum and urine Coll2-1 and Coll2-1NO2	Type II collagen degradation	Knee: D(s),B(u),P(u) Hip: D(s)	Exploration: not used to date in published pharmacologic trial	Competitive-inhibition
Serum CPII	Type II collagen synthesis	Knee: D(s) Hip: B(s)	Exploration: nonsignificant change in one pharmacologic trial that met primary	Competitive-inhibition

			clinical endpoint[12]	
PIIANP	Collagen synthesis	Knee: BPD Hip: none	Exploration: not used to date in published pharmacologic trial	Competitive-inhibition
Urine/serum NTX-1	Bone resorption	Knee: P(u),E(u) Hip: P(s)	Demonstration: changed significantly in one pharmacologic trial that met primary clinical (WOMAC) endpoint[13]	Competitive-inhibition
Urine/serum CTX-1	Bone resorption	Knee: B(u), D(s/u), P(u) Hip: none	Exploration: not used to date in published pharmacologic trial	Competitive-inhibition
Serum CS846	Cartilage aggrecan synthesis /turnover	Knee: P Hip: none	Exploration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint[15] but changed associated with concurrent JSN	Competitive-inhibition
Serum MMP-3	Protease involved with joint tissue degradation	Knee: E Hip: none	Characterization: changed significantly in two pharmacologic trials that met primary clinical endpoints [11,14]	Sandwich for total MMP-3 assay

[+]This list does not include many emerging biomarkers that may prove useful in the future nor cytokines and chemokines that are also worthy of consideration; *these are general recognized processes for which these biomarkers are known. This is very preliminary information at this time and should not be considered definitive but rather in evolution; *per van Spil[15]; Cibere 2009[8]; Conrozier 2008[16]; Kraus 2010.[17] References in Table as follows: [9-11,13,14,18].

Table 1 abbreviations: CTX-II=carboxy-telopeptide of type II collagen; COMP=cartilage oligomeric matrix protein; HA=hyaluronan; C1,2C=collagenase-generated neoepitope of types I and II collagen collagenase; C2C= collagenase-generated neoepitope of type II collagen; Col2-3/4m= type II collagen denaturation epitope; CPII/PIICP=type II procollagen carboxy-propeptide; PIIANP=type IIA procollagen amino propeptide; NTX-I=N-telopeptide of type I collagen; CTX-I=carboxy-telopeptide of type I collagen; CS-846=aggrecan chrondroitin sulfate 846 epitope; MMP=metalloproteinases-3 (stromelysin).

Table 2. Other OA-related biomarkers qualified for various OA outcomes				
Biomarker	**Process (preliminary)**	**BIPEDS Classifications**	**Surrogacy Based on Human Clinical Trials (preliminary)**	**ELISA assay type**
Serum KS	Cartilage catabolism, aggrecan	Knee: BPED Hip: none	Demonstration: changed significantly in one pharmacologic trial meeting primary clinical endpoints[15]	Competitive-inhibition (not commercially available)
Serum YKL-40	Catabolic; macrophages, cartilage, synovium, cells of epithelial origin	Knee: BE Hip: D	Demonstration: changed significantly in men one pharmacologic trial meeting primary clinical endpoints[16]	(not commercially available)
Urinary TIINE	Cartilage catabolicsm type II collagen	Knee: BP Hip: none	Exploration: paradoxical response[17]	(not commercially available)
Serum OC	Anabolic bone turnover	Knee: BPED Hip: none	Demonstration: changed significantly in one pharmacologic trial meeting primary clinical endpoints[15]	ELISA
Urinary Glc-Gal-PYD	Catabolic synovium	Knee: BD Hip: none	Exploration: insignificant change in one pharmacologic trial meeting	HPLC

			primary clinical endpoints[10]	
Urinary PYD	Catabolic bone turnover	Knee: BED Hip: none	Demonstration: changed significantly in one pharmacologic trial meeting primary clinical endpoints[15]	HPLC
Uurinary DPD	Catabolic bone turnover	Knee: BED Hip: none	Demonstration: changed significantly in one pharmacologic trial meeting primary clinical endpoints[15]	HPLC

Table 2 abbreviations: KS-keratan sulfate; YKL-40=human cartilage glycoprotein 39; uTIINE (mAbs 9A4/5109) urinary type II collagen collagenase-generated neoepitope; OC=osteocalcin; Glc-Gal-PYD=glucosyl-galactosyl-pyridinoline;MMP=matrixmetalloproteinases:-3(collagenase-3); PYD=pyridinoline; DPD=deoxy-pyridinoline.

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Table 3. *B*urden of disease, *I*nvestigational, *P*rognostic, *E*fficacy of Intervention, *D*iagnostic, and *S*afety classification scheme of the major types of biomarkers

B	To provide a global measure of disease burden from all joints and skeletal and soft tissue components thereof
	Potentially to discriminate between mono- and polyarticular OA
	To identify patients with high burden of active disease for inclusion into clinical trials of DMOADS expected to improve later stage disease
	To help identify patients with low burden of active disease but with no or limited tissue alterations or structural alterations for inclusion in clinical trials of DMOADS expected to prevent progression of early OA
	To balance treatment arms in a DMOAD trial for metabolic activity or stage of disease that would not otherwise be obvious from usual randomization criteria
	To identify where in the body the burden of disease lies and aid in patient stratification,

	made possible when joint-specific biomarkers or patterns of biomarker expression are discovered
I	To explore novel biomarkers that could be informative in future preclinical and clinical trials
	To contribute to biomarker data packages that support qualification of a biomarker or biomarker set for a particular outcome
	To further understand the pathobiology of OA
	To further understand the MOA of a DMOAD
P	To select subjects likely to progress rapidly ('high-risk' patients by biomarker measurement) to reduce the length of time required to see an effect of a DMOAD in a clinical trial and to improve the chances of observing efficacy
	To select subjects likely to progress rapidly ('high-risk' patients by biomarker measurement) for purposes of stratification (prognostic value)
	To select subjects likely to progress rapidly ('high-risk' patients by biomarker measurement) who would benefit most from therapy with structure modifying agents (predictive value)
	To select subjects for primary prevention trials (screen for at risk for developing OA to demonstrate reduction of incidence)
	To select patients likely to respond to a given drug for inclusion in a clinical trial. For instance, patients with high levels of an MMP-13 specific collagen cleavage product could be selected for inclusion in a trial of an MMP-13 inhibitor (predictive value)
	As a companion diagnostic, to select likely responders for treatment with a marketed product (predictive value)
	To provide predictive evidence that disease processes have been beneficially impacted by serving as an early indicator of a later trial outcome or response to therapy; this category of markers would therefore form a specific subset of efficacy of intervention markers described below
E	To demonstrate that a drug is having the desired immediate downstream biochemical effect (mechanistic value)
	To understand the pharmacodynamics of a drug intervention and the relationship between pharmacodynamics and pharmacokinetics in order to select the optimal model/s describing this relationship
	To provide a basis for the selection of lead candidates for clinical trials
	To contribute to the understanding of the pharmacology of candidates
	To characterize subtypes of disease for which a therapeutic intervention is most appropriate
	To choose a dose and dose schedule via *ex vivo* and *in vivo* studies
	To support an efficacy endpoint
	To support go/no go decisions in advance of preclinical and clinical studies and trials by improving the translation of preclinical data to humans
	To serve as a surrogate biomarker for delay of structural worsening, reduction of pain,

	or improvement in function
D	To select subjects with molecular pre-radiographic OA for primary prevention trials
	To identify patients with different disease subtypes
	To identify individuals unlikely to have OA as controls in case-control studies
S	To support other more generalized organ system safety indicators in preclinical and clinical trials
	To monitor for local and systemic adverse effects both early and advanced
	To set therapeutic dosages that do not impact on physiology

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Devices Working Group Recommendations

The Initiative Steering Committee agreed that a working group to consider implications for the development of devices as therapeutics in the treatment of patients with OA was important. Thus, as mentioned earlier, this working group was devised and the questions posed to them included the following:

- How to measure efficacy with a device; is it the same as for a pharmacologic treatment or should there be different measures?
- How to determine relative risk to relative benefit; what is an acceptable control arm for such studies?
- What are the optimal outcomes parameters for evaluation?
- Are the parameters substantially different with respect to different joints under study?
- Short-term vs long-term benefit
- Complications and their prevention
- Clinical indications
- Cost factors vs conservative therapy
- What is the research agenda required to inform each of the above questions?

Background

TJR is one of the most successful and cost-effective treatments for significant OA of the hip and knee. Both physician and patient directed measurements provide prospective and

retrospective data that validate these. Survival estimates for hip and knee arthroplasty are above 90% at 10 to 15 years after surgery.[10-13] Joint replacements have been used in almost every synovial joint, though results for other joints have not been as successful as hip and knee replacement. However, newer designs and techniques are evolving rapidly, and current implants for replacing other joints have outcomes that are approaching those of hip and knee arthroplasty.

Spinal OA is a significant healthcare problem in the US causing severe disability in patients and enormous costs to society. New products are being developed for spinal pathologies, but presently these products have met with variable outcomes in clinical use. These new technologies include cervical and lumbar disc replacement, lumbar dynamic internal fixation stabilization, facet replacement, and interspinous distraction devices.

Hyaluronans have been used intra-articularly as an approach to the treatment of knee OA.[5] The treatment modality is directed toward pain relief, but recent studies suggest that hyaluronans may also have a disease-modifying effect on the articular cartilage. Implantable biologic devices such as cell-based treatments for repair of articular cartilage have also recently been introduced with variable results, but including significant pain relief and improved function.

The introduction of many devices to the marketplace has progressed through the 510(k) premarket clearance route, often including reasonable, standardized preclinical studies, followed by general release after approval by the FDA.[1-4] Occasionally, the FDA will require a short-term clinical trial as part of a 510(k) clearance, however, typically only after commercialization are randomized controlled trials, registries, and retrospective reviews performed to assess further the efficacy of the device. Henrik Malchau presented to the Hip Society in 1999 a comprehensive approach to device approval, a phased innovation process of preclinical study followed by rigorous quantitative metrics to assess the true effectiveness of the device. Preclinical metrics could be established through existing standards produced by ASTM or ISO and other guidelines developed appropriately for each device. Examples of rigorous clinical metrics would include not only validated physician and patient directed clinical assessment tools, but also quantitative measures to assess functional abilities of the patient. These could include kinematic studies, unique quantitative measures such as radiostereometric analysis (RSA) methodologies, or more simple tools such as muscle testing and the sit-to-stand and 6-minute walk tests. Ultimately,

clinical outcomes for any device including biologics are best established through postmarket surveillance using perhaps implant registries. For example, the Swedish Hip and Knee Registries have been quite successful in assessing the outcome of devices as used by a broad spectrum of surgeons in sufficient numbers of patients so as to impact practices toward a more cost-effective device. This comprehensive approach, including the development of registries, could also be used for implantable biologic devices.

How to measure efficacy with a device, is it the same as pharmacologic treatment or should it be different measures.

Recommendations: Devices, especially orthopedic devices, do not fit into the definition of efficacy used for pharmacological treatment on two important points. First, the time course for showing efficacy in the device is usually much longer, since the intention of the device is to have a very long lasting action such as pain relief and return of function over a period of years or more. Performance in the early time course may reflect the variables associated with the surgical procedure and not the performance of the device itself. The second efficacy usually has a broader interpretation than for pharmacological treatments. As such the compromise for joint replacement has been to pick a reasonable time frame (ie, 2 years) and to pick efficacy outcomes that cover a range of items (eg, hip or knee scores that encompass pain and function). Although one might adjust the time frame and pick a different outcome measure such as patient- or surgeon-derived validated instruments, the general approach that has been accepted by the FDA, by device manufacturers, and by journal reviewers and editors should remain. It is important to differentiate efficacy of the implant from efficacy of the surgical procedure. An implant that is efficacious has a relatively low failure rate across a large section of surgeons. Additional work needs to focus on what specific hard endpoints can be assessed to determine failure modes. HA-based viscosupplements are currently indicated for the use and treatment of pain related to OA of the knee that is unresponsive to simple analgesics.[5,7,8] These products require clinical safety and effectiveness data as part of their FDA Premarket Approval (PMA) application to obtain FDA approval.

Because of the indication for treatment of pain, viscosupplements have efficacy endpoints that are very similar to what would be expected for pharmacologic OA pain treatments. However, viscosupplements and biologic devices differ from pharmacologic treatment in

that the treatments are local and the effect is sustained with pain-relief for 6 to 12 months in the treated joint. The FDA draft guidance for biologic products and devices such as HA viscosupplements which have a local effect should be adjusted to allow measurements specific to the treated joint or area. For example, in patients with OA in more than one knee or hip joint, the patient should be able to report on pain, function, and stiffness in the treated joint alone. There are several approaches to address these issues such as enrolling patients with a single joint disease (although there are relatively few of those and how to extrapolate results to patients with more than one joint involved but only one joint treated), treating all affected joints, analyzing patients separately based on whether all symptomatic OA was treated or not, and finally using subscales that are more specific for the treated joint such as WOMAC A-1 pain on walking for treatment of OA knee pain with a medical device.

How to determine relative risk to relative benefit; what is an acceptable control arm for such studies?

Recommendations: This is an area that addressed the regulatory pathway for devices with particular emphasis on the 510K approach vs true application of the intent for Classification around the concept of special controls for Class II devices. It is important for the device manufacturers to work closely with the FDA and the clinical community to adopt special controls aimed at minimizing risk while providing an avenue for maximizing benefit. The goal should be to encourage manufacturers with truly new technology to claim its benefits and then minimize risk by meeting minimum standards while establishing with the FDA what additional data (preclinical, clinical, and postmarket) are needed to show the claimed improvements. Active control groups are important, however, the specific defined control groups should be developed in consultation between the FDA, device manufacturers, and the clinical community. Minimal standards will be obtained from the existing American Society for Testing and Materials International (ASTM) and International Organization for Standardization (ISO) standards. It is possible that a claimed improvement of the new device over existing devices, (eg, improved wear performance or kinematics or fixation) can be tested with existing standards. However, if a suitable test method does not exist to evaluate the new claim, the manufacturer should, if possible, use tests that have been developed in the scientific community and published in the literature or, alternatively, tests specifically developed by the company should be used. Changing over to a relative risk

vs benefit would enhance the present 510K pathway, which in many circumstances is used by device manufacturers to circumvent the more difficult Class III pathway.

It is clear that there is a risk associated with every device and every procedure. As stated above, in the circumstances of a new Class II device, the risks should be minimized by comparing with a predicate device plus utilizing additional tests to demonstrate the safety and efficacy of any new claims of the new device. However, risk is not constant for a given device for every patient. For example, the risk of loosening and wear is higher with heavier and more active patients.[14] Yet, it is unrealistic or even impossible to design every device to function indefinitely without problems in the "worse case scenario." In this circumstance, the patient-physician relationship is central in importance.

HA-based supplements, since they are indicated for pain relief, require a patient reported outcome. In order to adequately assess safety and effectiveness, the patient and other reporters need to be blinded to treatment selection. An appropriate control would need to incorporate an intra-articular or sham injection and be perceived by the patient as being the same as an intra-articular injection. Currently viscosupplement trials have included the following treatments and the control in order to blind the patients to treatment. Intra-articular injections of phosphate buffered saline, approved viscosupplement, glucosteroid, and the sham injection. It is appreciated that intra-articular phosphate buffered saline has a beneficial effect in many patients that may last several months, and this should be considered a comparator rather than a placebo. Depending on the type of clinical trial design (eg, noninferiority to an active available pain relief product or superiority to a nonactive treatment or an active treatment), any of these control options are acceptable.

What are the optimal outcome parameters for evaluation?

Recommendation: Pain relief, restoration of function (ie, range of motion [ROM], 6-minute walk), assessment of radiographs and/or other images, complications and complication rates, and revision and revision rates are all approaches to defining outcomes. Patient directed self-assessment outcomes are critical in that they give a specific measure of

performance in relation to patient expectations independent of evaluation by medical staff. Further, independent living, work status may also be economically better indicators of restoration of function. There are a number of instruments that have been validated and define outcome measures from either physician derived or patient directed measures. These include Harris Hip Score, the new Knee Society Scoring System, and specific indices such as the WOMAC index. The number of quality of life measures that are important in determining the effectiveness of medical treatments, including biologic devices, include the SF-36 or medical outcome study short form, the quality of life evaluation, and the health assessment questionnaire. In the near future OARSI OMERACT virtual total joint replacement outcome measures may also be helpful.

The optimal outcome tools for evaluation of HA-based viscosupplements are those tools that can detect pain, functional, or global assessment improvement occurring in a single target treatment joint. Examples of instruments that are useful are those above and also include specific pain management such as the VAS, subsets of the WOMAC A and A-1 scales, new emerging patient directed study instruments such as the patient global assessment (PTGA), the physician global assessment (Clinical Observer Global Assessment [COGA], and Lequesne's Algofunctional Index. The OARSI OMERACT Responder Rate may be of use. Until now the most prevalent primary endpoint is a simple VAS pain measurement in the treated joint as well as patient reported outcome tools in the WOMAC and patient global assessment instruments. Outcome measures of biologic devices may require specific structural outcome measures such as MRI biomarkers to assess their efficacy. These are being effectively discussed in other working groups. All of the above measures incorporate validated and verifiable physical therapy outcome tools and can be used to measure a benefit of other surgical approaches to the treatment of OA.

Are the parameters substantially different with respect to different joints under study?

Recommendation: There are similar criteria across different joints. These include pain relief, restoration of function in terms of independent living, and return to productive employment, and a re-operation rate within 10 years of the incident procedure. However, there are specific parameters and criteria for success directly related to each joint. These parameters are best reflected in the numerous validated assessment tools both from the

physician and the patient point of view that had been developed by the specific societies addressing each anatomical area. For example, the upper extremity, the glenohumeral joint is addressed by a number of specific shoulder assessment tools including the Western Ontario Osteoarthritis Scale for the shoulder. The Ankle Osteoarthritis Scale (AOS) for the ankle is another example of joint-specific joint assessment tools.

The general concepts for HA-based viscosupplements are the same for each joint in terms of pain and function improvement measurement and patient global assessment. As above, there are specific measurement tools that have been designed specifically for load bearing joints or for nonload bearing joints. These specific tools should be considered on a case-by-case basis for specific joints. Some examples of these tools are listed below:

- VAS or NRS pain measurement
- WOMAC A pain subscale using a VAS or NRS scale
- WOMAC A1 pain on walking on a flat surface subscale using a VAS or NRS scale
- PTGA—patient global assessment
- COGA—physician global assessment
- Acetaminophen consumption
- WOMAC function subscale
- Lequesne's function subscale
- KOOS
- In the near future, OARSI-OMERACT virtual TJR outcome measure
- OARSI-OMERACT responder rate

How should short-term vs long-term benefits be balanced in the assessment?

Recommendation: Devices used for joint reconstruction have a goal of a long-term success of the procedure. Short-term benefits are, of course, important in regard to complications; however, the ultimate goal of the procedure is long-term benefit and that must be taken into consideration. The 2-year mark with suitable evaluation methods will define problems such

as premature loosening, instability, or inadequate motion. Additional evaluation might be required for Class II devices where special claims are made.

In regard to biologic devices, they are similar to HA-based viscosupplements where the short-term benefits are critical. These products should probably be studied over a 3–6 month period and repeat injections performed to assess safety of repeated injections. Postmarket surveillance is critical in that, although these products benefit certain patients and not others in terms of pain relief or perhaps disease modifying effects, specific responder analysis in regard to the success and failure outcome should be carefully monitored.

How should complications and other AEs and their prevention be assessed?

Recommendations: The complications of orthopedic devices are well documented and numerous studies have provided data on their incidents, causes, and preventive measures.[9] The prevention of device-related complications begins with rigorous preclinical testing as discussed previously. The importance of well-designed programs of such tests prior to even early clinical trials cannot be over emphasized. There is, however, an area of complications that is associated not with device, but introduced by inadequate instrumentation, by surgical factors such as incorrect ligament balancing, poor cement technique, mal-rotations of components, or even by the patients themselves. It is important from the onset to address this subject and to clearly define what complications can be laid on the device and what can be related to surgical or patient issues. If possible the preclinical testing should include studies that expose the sensitivity of devices to such occurrences.

HA-based supplements also have a history in clinical use of definition of well-characterized AEs.[6] The AEs in relation to these treatments are typically divided into those related to the injection procedure itself and those related to the HA material injected into the intra-articular joint space. The same can be said about biologic devices. Although there is significant data for the study of the knee, there are fewer clinical data in other joints such as hip, shoulder, ankle, or carpometacarpal **(**CMC) joint, and new safety issues or signals may exist for these joints. A number of typical complications that occur for the knee include injection site pain, erythema and local complications such as effusion or stiffness, or

potential allergic reaction to the material. However, the severity of these AEs is usually mild-to-moderate, and they resolve spontaneously. There have been no long-term complications reported. Continued postmarket surveillance and standardization of criteria and reporting should continue.

What are the clinical indications?

Recommendation: The clinical indications for joint replacement have been well documented and include limitation of function of any given joint either due to pain or malfunction to justify the risk of surgical intervention and introduction of a foreign body.[15] The long-term goals of joint replacement are relief of pain and restoration of function of the joint. These clinical indications have been well documented and validated. The clinical indications for the use of HA-based viscosupplements include treatment of patients with pain from OA of the knee who have failed to respond to conservative nonpharmacologic therapy and simple analgesics. Presently, there are no viscosupplements approved for nonknee joint involvement in the US. There are a number of clinical trials now being conducted, and hopefully, the use of these treatment modalities will be extended. There are no well documented indications for biologic treatments (ie, devices). Clearly, this is a new area in which the FDA must develop an expertise. In order to accomplish this, collaboration with the scientific community is required.

How should cost factors associated with the device be balanced against conservative therapy?

Recommendation: This is a difficult area of address, although it is a timely topic. Central to understanding this relationship should be a quality oflife estimate so that both economic costs and patient derived satisfaction should be considered in the light of cost saving and quality of life issues that are achieved by undergoing a surgical treatment such as joint arthroplasty, as opposed to just continuing with conservative care. Consideration must be given to other matters such as the relationship of care givers to patients who continue with conservative care and might well be enhanced functionally by a total joint arthroplasty or the use of biologic devices. One problem that exists with both biologic and orthopedic devices is that they do require long-term follow-up so that the device procedure being

investigated becomes very rapidly an old technology. Importantly there is a strong subjective element here, which relates to the patient-physician relationship. A central question is whether a patient is prepared to continue with conservative treatment for an extended time period, meanwhile functioning suboptimally and experiencing some pain because they believe that a total joint or a biologic device has a limited lifetime and they do not want an early revision; or does the patient prefer early treatment with restoration of function and relief of pain but with the risk of a failure of the device requiring revision sometime in the future? There are no well validated studies that address the issue of defining the true risks and benefits of these procedures in the long-term and how they affect the costs of each approach. Because of the increasing cost of medical care in the US, there may become a time where rationing of treatments such as joint arthroplasty will be considered. Careful consideration of the issues of quality of life and its concomitant economic costs must be considered in any decision making process. HA-based viscosupplements are indicated for pain relief and are typically indicated in patients where simple analgesics have failed. Data indicate that HA-based viscosupplement provide long-term, long duration of pain relief with only treatment so that this device may offer a cost effective alternative to daily systemic NSAIDs orally or topically. Further, this treatment modality has a very favorable safety profile and avoidance of AEs associated with other systemic treatments.

What is the research agenda required to inform each of the above questions?

- Meta-analyses of clinical results with current technologies with emphasis on demonstrating safety and efficacy by identifying types of complications, their prevalence, their timing, and their relationship if any to the device. The same should be done for revisions; do not rely on national or Medicare registries, which simply do not contain enough information to make these kinds of efficacy determinations.

- Research into consensus building for all types of outcome measures (patient- and surgeon-derived questionnaires, objective measures like the 6-minute walk, etc). This could be done by meta-analysis. Multi-center prospective studies are needed.

- Research into establishing the efficacy of existing and proposed standards. Many of the tests that have become part of the FDA and ASTM/ISO lexicons are simply not efficient at demonstrating device performance in a clinically meaningful way. Just because standard test technique can be shown to be reproducible through round robin testing doesn't mean it has any bearing on clinical performance. Many of the test standards are simply time consuming and costly without adding much in the way of useful information.
- Establish a National Registry with well defined goals.
- Consensus building in the surgical and scientific community to define clearly the primary modes of device failure. The FDA can then modify the minimum standards that apply to all modes.

For HA-based viscosupplements, a significant number of clinical trials have been conducted on multiple injection viscosupplements used in the knee.[6] These trial results have varied dramatically, and the trial designs have been varied as well. It is important to collect randomized, controlled, double-blind, patient-reported outcomes on these products to establish a class effect to a constant comparator such as a saline injection.

Current trends in viscosupplement development include reducing the number of injections required for treatment, increasing intra-articular residence time through cross-linking, and treatment of other synovial joints beyond the knee such as the hip, shoulder, ankle, TMJ, CMC hand joint, and the facet joint.

Potential research topics for this area might include the following:

- Definition of a responder on a patient reported outcome scale (ie, WOMAC) for a viscosupplement treatment from 3 to 6 months, stating limitation of current OARSI-OMERACT responder rate criteria

- Consideration of whether or not a repeated measure of a landmark analysis is more appropriate for 3 and 6 months viscosupplement trials

- Definition of an appropriate placebo or comparator (ie, saline control, sham injection, PBS control with lidocaine, etc)

- Increased understanding of appropriate injection volumes for different joints and appropriate endpoints measures for different joints

- Increased understanding of the importance of residence time for viscosupplements and MOA of synovial fluid replacement with HA-based viscosupplement material

Conclusions

It is hoped that the answers noted by this Working Group can be helpful in enhancing the FDA process of assessing new devices. An ordered sequential approach to the introduction of any "device" is critical. Additionally, a National Registry is important but should have well defined research objectives, a valid protocol design, clear inclusion, and exclusion criteria, a comprehensive collection of variables necessary to answer the project objectives, mechanisms implemented to track patients and to insure a high level of data integrity, and finally a blinding of data collection personnel and a method to rectify methodological problems. Finally, appropriate dissemination and data sharing procedures must be put in place to benefit the consumers of this information, which includes patients, surgeons, and device manufacturers. The feedback process should result in an enhanced quality of care and cost-effectiveness of any treatment.

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APPENDICES

APPENDIX 1

(Click on above link to return to text)

MEMBERSHIP OF INITIATIVE WORKING GROUPS

Definition of Disease State	***Safety Considerations***
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APPENDIX 2

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4QImaging	Wyeth
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APPENDIX 3

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CONFLICT OF INTEREST

OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

CONFLICT OF INTEREST POLICY

OARSI FDA OA INITIATIVE

I. Introduction

This Conflict of Interest Policy ("the Policy") governs conflicts of interest involving (i) members of the OARSI FDA OA Executive Committee and Steering Committee ("the Committee") and Chairs of the Working Group Committees ("Chairs") (ii) individuals working directly or indirectly with the Working Groups or Committees (iii) others to whom the Committee has delegated significant decision-making authority and (iv) staff supporting the Initiative (collectively, "Interested Persons"). The purpose of the Policy is to protect OARSI's ("the Society") interests as it relates to the work to be undertaken and recommendations to be submitted in regards to the OARSI FDA OA Initiative ("Initiative"). Specifically, this conflict of interest policy is to protect the Society from conflicts by Interested Persons who have entered into or are contemplating entering into a transaction or arrangement that might benefit a private interest by the Interested Person. The Policy is intended to supplement but not replace any applicable state and federal laws governing conflicts of interest applicable to nonprofit corporations.

II. Definition of a "Conflict of Interest"

A conflict of interest exists when an Interested Person has a direct or indirect (through business, investment or family) financial or other interest in a matter that might influence, or that might be perceived to influence, the judgment or actions of the Interested Person while serving within the Initiative. Conflicts of interest may arise under numerous scenarios, including but not limited to the following:

a. An Interested Person receiving or being considered to receive compensation (eg, consulting fees, speaking or writing honoraria, research or institutional support, reimbursement of expenses, etc.) from, or having an actual or potential ownership or investment interest in, an entity offering or proposing to offer products or services to the Society and the Initiative;
b. An Interested Person doing business or having a relationship with any entity doing business or wishing to do business with the Society and the Initiative;

c. An Interested Person who has ownership of a company whose products may be reviewed or recommended within the Initiative recommendations submitted by the Society, and
d. An Interested Person also serving as an officer, director or editorial board or committee member of another nonprofit organization in the general areas of interest to the Society.

III. Disclosure

Interested Persons must disclose all conflicts of interest as defined in Section II above, including those that *might* influence or be *perceived* to influence the actions or decisions of the Interested Person. Therefore, even if one believes that the relationship or other circumstance will not affect one's judgment or conduct, if it could do so or could reasonably be perceived as having the potential for improper influence, then it must be disclosed. Each Interested Person shall complete a Conflict of Interest Disclosure Form annually; such annual disclosures shall be supplemented immediately upon the occurrence of an event or a change in circumstance, which makes a disclosure incomplete or inaccurate. Disclosure forms for all Interested Person's will be reviewed and vetted by the Society's Ethics Committee, shared with the OARSI FDA OA Executive Committee ("Executive Committee") and made available prior to each meeting of the Society's Board of Directors. The Society's Ethics Committee will provide recommendations to the Society's Board of Directors and the Executive Committee for the appropriate resolution of conflicts of interest, including but not limited to, recommendations on an Interested Person's level of participation within the Initiative.

All Interested Persons shall bring to the attention of the Society any actual or perceived conflict of interest involving any other Interested Person.

The Society Board of Directors in coordination with the Executive Committee may request a verbal disclosure by all Interested Persons at the initiation of all meetings to assure that all disclosure information is current.

IV. Procedure Upon a Disclosure

Upon making a disclosure of a possible conflict of interest, the Interested Person must make all requested information available to the Society's Ethics Committee, Society Board of Directors or the Executive Committee, as applicable.

Possible actions that may be taken by the Society Board of Directors in coordination with the Executive Committee include, but are not limited to:

- prohibiting consideration of participation for providing products or services;
- determining, after exercising due diligence, whether the participation related to the Interested Person is the most advantageous transaction or

arrangement for the Society and, if so, whether it is fair and reasonable and in the best interest of the Society;
- requesting all necessary actions to eliminate the conflict of interest, and
- requesting a limited level of participation of the Interested Person or resignation of the Interested Person from the Initiative.

V. Disclosure to the Board of Directors

Upon receiving a disclosure of a possible conflict of interest concerning any Interested Persons or other person having significant decision-making authority, the Society's Ethics Committee shall consider appropriate action and decide whether procedures for a hearing are warranted. If a hearing is warranted, the Ethics Committee, Society Board and Executive Committee shall provide for the due process rights of the Interested Person. If a vote is taken and the Interested Person is a member of the Society Board, that person must recuse and absent him- or herself from the vote. Final actions with respect to conflicts of interest shall, if deemed necessary and appropriate by the Ethics Committee, be reflected in the minutes of the Society Board.

VI. Confidentiality

Except to the extent that disclosure to members of the Ethics Committee, Society Board of Directors and Executive Committee is found to be necessary, all persons receiving a communication from a member or staff pursuant to this Policy shall maintain the confidentiality of the contents of the disclosure, as well as any conclusions made as to whether there is a conflict of interest.

VII. Violations of This Policy

If the Ethics Committee, Society Board of Directors or the Executive Committee has reasonable cause to believe that an Interested Person has failed to make a disclosure required by this Policy, the Interested Person shall be informed of the basis for such belief and shall be afforded an opportunity to explain the alleged failure to disclose. If, after hearing the Interested Person's response and making any further investigation warranted by the circumstances, the Ethics Committee determines that the Interested Person has failed to disclose an actual or potential conflict of interest, appropriate disciplinary and corrective action, up to and including removal from the Initiative will be undertaken.

OARSI FDA OA INITIATIVE
CONFLICT OF INTEREST POLICY
ANNUAL DISCLOSURE STATEMENT

The undersigned person acknowledges receipt of a copy of the "OARSI FDA OA Initiative Conflict of Interest Policy" dated _____ __, 200_. By my signature affixed below I acknowledge my agreement to the letter and spirit of the Policy, and I agree to report to the OARSI Ethics Committee any possible conflicts of interest (other than those stated below) that may develop before completion of the next annual statement.

I hereby disclose, on behalf of myself and members of my family, the following with respect to persons or entities who or which are doing business with, are proposing to do business with, or desire to do business with the OARSI FDA OA Initiative: I receive, or am being considered to receive, compensation (eg, consulting fees, speaking or writing honoraria, research or institutional support - including unrestricted educational grants, equipment or services, or reimbursement of expenses from the following:

I have an ownership interest or patent in the following companies:

I am doing business with or have a business or other relationship with, or am being considered to have a business relationship with, the following:

I serve another (other than OARSI) organization in the general areas of interest to OARSI in the following capacity(ies):

_____ I have nothing to disclose.

Signed: _____ Date: _____

Printed Name: _____

(Rev. 10/08)

Fax this page only to Valorie Thompson (202.244.5854)
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APPENDIX 4

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Assessment of Structural Change (ASC)

1.0 INTRODUCTION

1.1 Current status of guidance for assessing OA disease modification

The development of disease-modifying OA drugs (DMOADs) is faced with many challenges. Since there are currently no DMOADs on the market the development path is unprecedented and the primary endpoint for demonstrating DMOAD efficacy is poorly understood. While arthroplasty represents the actual endpoint of OA progression its use as an endpoint in clinical trials is associated with multiple problems including the variability in rates of surgery, in part related to socioeconomic disparities, different healthcare environments and the relatively low incidence rate of arthroplasties compared with the total OA burden. Alternative clinical endpoints for DMOAD clinical trials have therefore been considered and the FDA previously provided regulatory draft guidelines for use in DMOAD development.[1] The *FDA Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA* draft guidelines defined the current acceptable structural endpoint for DMOAD clinical trials as a slowing in the loss of knee or hip joint space narrowing (JSN) using x-ray.

The current hierarchy of claims for structural outcome as defined by the FDA Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA draft guidance is as follows:

1. Normalize the x-ray (reverse progression)
2. Improve the x-ray (halt progression)
3. Slow JSN by at least a prespecified amount (slow the rate of progression)

1.2 Limitations of current guidance

Since it is widely (but not universally) accepted that alteration in progression of JSN implies preservation of cartilage and consequently clinical benefit, measurement of joint space width (JSW) by x-ray was determined as the most appropriate structural endpoint measure. However, it was recognized that the nature and magnitude of structural changes that are likely to be clinically relevant remain uncertain. Whether parallel clinical outcomes should be included in the claim depends on what JSW outcome is achieved, but collection of these data (including measurement of

pain, a patient global assessment, a self-administered questionnaire, and the time to the need for total joint replacement surgery) was strongly recommended regardless of the anticipated outcome since their assessment is critical for analysis of the overall risks and benefit of a product. Since the concept of structural improvement connotes an element of durability, trials to demonstrate structure improvement were recommended to last at least one year.

There is currently limited evidence as to the validity or likelihood of a product showing benefits in delaying structural progression without associated benefits in improving patient symptoms. Although a product showing a slowing of JSN would be expected to also affect symptoms, it is possible that certain classes of products developed in the future may affect structural progression without associated symptomatic evidence. A claim of structural improvement (ie,, slowing of JSN) might conceivably be dissociated from other claims when the mechanism of action of the product, and/or the size of the effect on slowing of JSN, are suggestive of future clinical benefits. If products are not anticipated to have different effects on these parameters or show only small improvements in JSN without demonstrated effects in symptoms they will not generally be considered for approval or for separate claims. In other words, as long as an observed delay in JSN progression is correlated to an improvement of clinical outcomes it is considered as an appropriate primary endpoint and as a surrogate endpoint for total joint replacement, the critical event characteristic of a medical treatment failure for OA. It is assumed that a delay in JSN will consequently delay the need for total joint surgery, and can hence be interpreted as a treatment success for DMOAD's.

The use of JSN measured by x-rays as a structural endpoint is associated with some concerns. Since disease progression is generally slow, minimal and variable within and between subjects, the use of JSW as an endpoint measurement requires long-term treatment periods (>1 year) and inclusions of large patient numbers. Moreover, the inability of radiographs to visualise cartilage means there is an insensitivity to early and small changes in this tissue. There is difficulty in obtaining high quality reproducible images of OA joints, despite state of the art standardisation of radiographic protocols to reduce the variability related to joint repositioning. MRI studies have demonstrated that JSN represents a complex of hyaline cartilage loss, meniscal extrusion and meniscal degeneration. Although structure is a critical component of OA assessment, the relationships between structure and pain and/or function and between structure and future outcomes (eg, arthroplasty) are not well developed and the definition of a clinically relevant change in JSN has not been established.

The use of JSW alone may not be entirely relevant as an outcome measure for DMOAD efficacy since it fails to allow for OA being a disease of the whole joint. As such, potential early beneficial changes

in other components of the joint are missed by the use of JSN alone as the structural endpoint. Moreover, the insensitivity of JSN to early changes in cartilage and meniscus means that moderate to severe OA knees (K/L>3), which may already represent a stage of the disease too molecularly and biochemically advanced for alteration of disease course by pharmacological intervention, are generally selected for clinical trials to ensure disease progression can be measured and may therefore not be optimal for demonstrating DMOAD efficacy. However, since these patients are more likely to show progression of both JSN and clinical symptoms during the period of a trial, selecting the optimal OA target population is a complex process. Despite the limitations as a measure for DMOAD efficacy, delay in JSN has been demonstrated for a small number of potential DMOADs to date. However the lack of associated symptomatic benefit in these studies has prevented any of these agents from being successfully registered.

Aims of the ASC Working Group

1. For the current tools for assessing structure modification (x-ray, MRI, biomarkers):
   a. What are the performance metrics for each individual feature that they detect?
   b. How can they be used optimally in clinical trials?
   c. What are the relative strengths and weaknesses of these assessment tools?
2. What do these putative tools measure? How to determine change over time?
3. How can rapid structural progression patients be identified? Is that necessary?
4. What is the relationship between symptoms and structural progression? What is the relationship between disability and measured structural change?
5. Could the need for a joint replacement be a clinical outcome, which might supplant imaging as a measurement?
6. What is the research agenda required to inform each of the above questions?

2.0 BACKGROUND ON IMAGING MODALITIES FOR ASSESSING STRUCTURAL CHANGE

2.1 Conventional radiography

The research cited in this section is based on the assumption that the symptomatic manifestations of OA (joint pain and related functional impairment and disability) are, in fact, due to the pathophysiology of OA seen in joint structures. This assumption is supported strongly by epidemiological evidence of an association between the presence of radiographic OA and joint pain/disability in the general population.[2-4] Further, it is assumed that, within the subpopulation of patients with OA, there is a direct relationship between the severity of structural damage of OA and the severity of symptoms, that between-patient variability in symptom severity can be explained by variations in structural severity of OA, and that worsening symptoms of OA can be accounted for by progressive changes of OA in structures of the joint.

While the radiographic evidence of OA seen in bone structures is relatively robust in a two-dimensional image, the joint space (and thereby the apparent thickness of articular cartilage) can be affected easily by changes in the positioning of the joint from examination to examination.[5,6].A reproducible radiographic image of the joint space requires adherence to exacting standards of radioanatomic positioning, which include specifications for flexion and rotation of the joint, as well as for focus and angulation of the central ray of the x-ray beam relative to the joint space.[7,8] Alternative protocols for standardized joint positioning examined in this report fall into two broad categories of procedures: (1) those in which pre-acquisition fluoroscopy is used to guide positioning to achieve reproducible anatomical markers of alignment of the joint space and x-ray beam and (2) those that employ empirically derived standards of optimal radioanatomic positioning without the benefit of confirmation with fluoroscopy.

The detection of OA progression (ie, loss of radiographic JSW) can be confounded not only by changes in joint position due to inadequate positioning standards, but also to error in the measurement of JSW itself. Numerous systems have been developed to evaluate radiographic JSW and detect changes over time. These procedures range from semi-quantitative, ordinal-scale ratings of the severity of JSN to quantitative measurement of JSW as a continuous variable. Since the advent of digital radiography, computerized methods of JSW measurement have become increasingly automated, requiring correspondingly less input (and potential for error) from the reader or software operator. The automation of mensural procedures has been lauded as an advance that has improved the reproducibility of JSW measurements and permitted more sensitive detection of OA progression.[8]

As with any imaging modality, plain radiographs offer only proxies of the joint structures affected by OA. The following recommendations represent the best research evidence to indicate the extent to which measurements of structural damage of OA taken from CR are reproducible, sensitive to change and possess concurrent and predictive validity with respect to symptoms and other outcomes (eg, joint replacement) that are associated with progression of OA.

2.2 Magnetic Resonance Imaging

2.2.1 Acquisition Techniques

Magnetic resonance (MR) imaging uses a powerful magnetic field to align the nuclear magnetization of protons (the hydrogen atoms of water molecules or lipids that constitute most of the tissue in the human body). By altering this alignment using radio frequency (RF) electromagnetic pulses, the vector sum of the nuclear magnetization is made to traverse the RF coil elements (used either for signal transmission or reception or both) and an electric current is induced which can be measured as the MR signal. In this way, MR can be used to generate 2 or 3 dimensional (2D or 3D) images where each voxel (volume element), provides cross-sectional images and soft tissue contrast of the joint in any given orientation (the imaging plane). This is a distinct advantage over 2D projection imaging modalities like radiography. The MR signal intensity depends on many parameters, including but not limited to static magnet field strength, proton density, diffusion, and T1 and T2 relaxation times.

Magnets with a static magnetic field strength of 1.5 Tesla (T) are the most commonly used, although 3T MR systems are becoming increasingly available that provide higher resolution or time savings but not necessarily differing diagnoses. Different pathologies (tissue contrast) can be selected by the proper choice of pulse sequence parameters, in any number of sequences and in any oblique imaging plane (the power of MR over computed tomography). Image sequences and image sequence parameters are chosen in order to provide maximal information (contrast) on the different tissues within the joint (ie, time to echo (TE) or repetition time (TR)). For example, a conventional T1-weighted (T1-w) image (to interrogate tissues with a shorter T1 relaxation an image sequence with a short TR and short TE is employed) usually demonstrates high signal from bone marrow tissue and fat, whilst in a water frequency-selective or fat-suppressed image the signal from the fat tissue in the marrow is reduced such that that signal from higher water-containing areas will be prominent. Commonly a fast spin echo T2-weighted image (long TR, long TE) is used with fat suppression for identifying soft tissue inflammation or bone marrow edema (BME). A

STIR (short tau inversion recovery) sequence also produces fat saturation, although may not be as sensitive for inflammation as frequency-selective suppression.

The intravenously administered paramagnetic contrast agent gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) may be used to increase the contrast between tissues primarily by shortening T1 relaxation where the contrast agent extravasates. Uptake of Gd-DTPA is dependent on tissue vascularity and capillary permeability, and is the most sensitive means to detect or demonstrate inflammation associated with synovitis (more common in rheumatoid arthritis). Traditionally, T1-w gradient echo sequences are often performed as 3D acquisitions to provide detailed delineation of tissues such as cartilage or menisci. These 3D images are also used for quantifying cartilage volume, surface area, and thickness. More recently, fast spoiled gradient echo images and selective water excitation sequences (replacing fat saturation) are used to reduce scanning time for cartilage assessment while potentially increasing resolution.

MR imaging measures the whole joint in OA and can reliably image pathology such as osteophytes, bone marrow edema, sub and periarticular cysts, meniscal tears, ligament abnormalities, synovial thickening, joint effusion, intra-articular loose bodies, synovitis with the addition of contrast agents, and can identify signal abnormalities associated with cartilage defects.

2.2.2 Quantification

Semi-quantitative Scoring Systems

Three semi-quantitative scoring systems for the assessment of knee OA have been published and applied in epidemiological studies to date: the whole-organ MRI score,[9] the knee OA scoring system[10] and the Boston-Leeds OA scoring system.[11] Direct comparison of these systems with regards to longitudinal sensitivity to change and correlation to clinical outcomes has not yet been performed, and the superiority of one system over the others can not be defined. Choice of scoring system for an individual study may thus be determined by a variety of factors, including outcome measure, resources available and available image set since not all features are scorable on all sequences or with any given sequence protocol. In addition to the whole organ scoring systems described above, a number of pathology-specific scoring tools have been developed, offering alternative approaches or addressing those pathologies not adequately covered by the whole organ systems. Examples of such

systems include several SQ grading systems for the evaluation of articular cartilage[12]; systems for assessing synovitis, including a detailed whole-joint synovitis scoring system measuring synovial thickness on T1-weighted, fat-suppressed contrast-enhanced images[13]; and scoring systems for the evaluation of ligaments[14] and bone marrow lesions.[15] The majority of MRI imaging-based SQ assessment to date has focussed on the knee joint, and aside from a recently presented SQ system to assess early hip OA, little information is available regarding MR imaging-based SQ assessment of other joints.[16].

Quantitative Scoring Systems

Quantitative imaging assessment of cartilage morphology exploits the 3D nature of MRI to assess tissue characteristics, such as volume and thickness, or signal as a continuous variable. Water excited (or fat-suppressed) T1-weighted spoiled gradient recalled echo acquisition in the steady state (SPGR) or fast low-angle shot (FLASH) sequences at 1.5 or 3T are the current 'gold standard' for quantifying cartilage morphology,[16,17] although double-echo steady-state (DESS) imaging with water excitation has also gained interest lately due to the faster acquisition time and smaller slice thickness that can be achieved.[18].Quantitative image assessment allows minute changes in cartilage thickness and volume (increases and decreases), which may be missed by the naked eye, to be detected, providing a more powerful measure of these changes than semi-quantitative scoring systems. However, the power of quantitative imaging only holds for those changes which occur homogenously at predictable locations within larger areas and struggles to measure local changes occurring at unpredictable locations within the structure. In these instances SQ scoring remains more powerful (also by assessing other structures within the joint), supporting a complimentary use of both approaches in order to optimally assess the status and progression of OA. Quantitative assessment is also hindered by the specialized software required to generate measurements and can be very time-intensive due to the segmentation by trained technical personnel that is required to identify tissue boundaries and allow measurements to be made.

2.2.3 Strengths and weaknesses

Magnetic resonance imaging, allows unparalleled visualization of all the tissues involved in OA joint pathology, including cartilage, menisci, subchondral bone and other soft tissue. Synovitis can be confirmed with the addition of intravenous contrast agent followed by T1-w imaging. The ability to image in 3-D allows cross-sectional views of the anatomy to be obtained in any given plane, enabling the joint to be evaluated as a whole organ and

eliminating problems of morphological distortion, magnification and superimposition, thereby providing more detailed analysis of change than with other imaging techniques. Moreover, MRI has unlimited image contrast variability resulting in an unparalleled ability to discriminate articular tissues, whilst the lack of ionizing radiation provides a distinct advantage in a clinical setting. However MRI does have its limitations. Patients with pacemakers or imbedded metal foreign objects cannot safely be put inside the magnet. Many patients have problems with claustrophobic reactions, although these issues are improving with the use of extremity MR scanners. The size of the joint being imaged—for example a large knee in an obese patient—may be too large for the cylindrical RF coil typically used, meaning that the joint cannot be adequately imaged. Just as in radiographs, there are artefacts, the commonest one being movement artefact or, at the knee, 'ghosting' due to a pulsatile popliteal artery which can be reduced by variation in the sequence parameters with tradeoffs with chemical shift artefacts and in-plane resolution.

2.3 Ultrasonography

2.3.1 Principles of ultrasonography

Ultrasound imaging of joints utilises high frequency sound waves to provide images of physical structures. The range of suitable frequencies is around 2-15 MHz, whereas the audible range of sound for humans is less than 20 000 Hz.[19] In simple terms, sound waves are emitted from a source[19], and directed towards the object (joint) to be imaged[19]. The sound waves propagate through matter, with the characteristics of the matter affecting the absorption and transmission of the waves.[19].For example, fluids, such as blood and synovial fluid transmit sound well; but soft tissues tend to result in some absorption and scattering of sound.

Sound waves meeting the interface between two different tissue types is reflected (as echoes) to varying degrees, depending on the characteristics of the two tissues.[19] Returning echos are displayed as a two dimensional image in shades of grey (grey scale: GS) on a monitor[19]. Higher intensity signal is displayed as brighter dots on the screen, and are referred to as hyper-echoic: no or low intensity signal appears blacker and is termed hypo-echoic.

The Doppler effect can be usefully applied to the imaging of joints. The Doppler effect relies on the frequency of sound waves being altered when they encounter a moving object.[19]Hence the frequency of sound waves, returning as echoes from red blood cells

travelling within vessels, are recognised and displayed as colour on a monitor. Both colour Doppler (CD) and power Doppler (PD) can be applied to imaging joints. Power Doppler is perhaps more commonly utilised, as it provides information about the intensity of vascular flow, and is generally thought to be more sensitive to low flow through smaller vessels than CD (which provides information about direction and velocity). Doppler signal within the synovium of joints has been demonstrated to reflect vascularity[20-22] and is considered indicative of active inflammation. Recently there has been some investigation of the role of contrast enhancing (CEPD) agents, which may aid the detection of vascular flow in inflamed tissues.[23]

As mentioned above, the physical properties of sound limit what can be visualised with US. For example, the interface between bone and muscle or fat is highly reflective, meaning sound waves do not penetrate cortical bone well, and are reflected as echoes, preventing visualisation of structures below the cortical surface. Resultantly, features of OA seen with other imaging techniques, such as bone cysts demonstrated with conventional radiography, or bone marrow oedema demonstrated with MRI cannot be appreciated using ultrasonography. Additionally, visualisation of structures relies on an acoustic window (or absence of barrier to sound). For example, the femoral distal cartilage is difficult to image with ultrasonography due to the overlying patella being a physical barrier to ultrasonography, in contrast this cartilage is easily demonstrable with MRI.

2.3.2 Ultrasonography in clinical practice: the pros and cons

Multiple benefits exist to the practice of ultrasonography (US) in the assessment of OA in clinical practice. It is a sensitive and specific method of assessing soft tissue and bone changes (including vascularity). In the clinical setting, US becoming part of the clinical assessment by a trained physician sonographer, can aid diagnosis and management.[24].The method has advantages over CR; it does not require ionizing radiation, can image the joint in multiple planes, and allows dynamic assessment of moving structures[24]. Advantages over CT and MRI include the relative patient friendliness and lower associated costs.[24]

However, significant investments in training, practice and maintenance of competency are required for the physician performing ultrasonography; the quality of images and their subsequent interpretation is dependant on the skills of the practitioner. Additional costs include the clinical time required, and financial costs of hardware and maintenance.[24] Additional limitations result from the physical properties of sound, meaning some

anatomical structures are not well visualized by US (discussed further above). Additionally, US should not be considered a diagnostic test, rather an adjuvant to routine clinical assessment and investigations in the diagnosis and management of rheumatological conditions.[24]

2.3.3 Imaging pathology in OA

US imaging of joints is now well developed in the rheumatological community, and has become part of mainstream practice largely thanks to the development of modern US technologies. However, ultrasound clearly has limitations for assessing joint disease and this is particularly relevant to the assessment of OA, in which cartilage pathology has been considered pathognomonic. The inability of ultrasound to visualise the majority of the articular surface in most joints due to a limited sonographic window and the inability to demonstrate intrinsic bone abnormalities such as marrow lesions, cysts and sclerosis, significantly impact upon the utility of US in assessing OA. However, US can demonstrate synovial pathology, synovial fluid, and boney cortex abnormalities. Most of the evidence relating to the validity of ultrasonography in imaging joints has been undertaken in inflammatory diseases, with less evidence of its validity in OA.

2.4. Other imaging modalities

2.4.1 Computerized tomography

Computerized topography (CT), a cross-sectional digital imaging method based on advance radiographic technology, provides high quality images of cortical bone and soft tissue calcifications. Since the introduction of helical multidetector CT systems, multiplanar reconstructions in any given plane with equal quality to the original plane can be achieved. CT has a higher sensitivity in the detection of intraarticular bone fragments and soft-tissue abnormalities in peripheral joints than conventional techniques,[25] however the orientation of the cartilages and subchondral cortices in the hip make it less amenable to CT imaging. Since cartilage is a nonradioopaque structure, its direct visualization by CT or radiographic technology is not possible. It has been shown, however, that spiral CT arthrography of the knee and shoulder is able to image the articular surface in an excellent manner.[26-29] Penetration of contrast medium (CM) within deeper layers of the cartilage surface indicates an articular-sided defect of the chondral surface. Conspicuity of focal morphologic changes can be achieved as a result of the high spatial resolution and the high attenuation difference between the cartilage substance and the CM within the joint. In the assessment of dysplastic hips at risk for OA, the role of arthrography has been established for the assessment of the

acetabular labrum.[30] Grading systems for CT are mainly based on the integrity of cartilage surface and depth of cartilage defects.[12,31]

Grade	Arthroscopic findings	CT Arthrography
0	Normal	Smooth surface and normal thickness of cartilage
1	Fibrillation without cartilage loss and cartilage softening	Smooth surface and normal thickness of cartilage
2	Substance loss less than 50% of cartilage thickness	Penetration of contrast in cartilage to less than 50% in depth
3	Substance loss more than 50% of cartilage but not down-to-bone	Penetration of contrast in cartilage to more that 50% in depth
4	Down-to-bone cartilage loss	Penetration of contrast down to subchondral bone

Strengths and weaknesses

CT arthrography is the most accurate method for the evaluation of cartilage thickness, thanks to its spatial resolution and high contrast between the low attenuating cartilage and its high attenuating deep (subchondral bone) and superficial (contrast material filling the joint boundaries). CT arthrography can also provide excellent imaging of subchondral bone sclerosis and osteophytes, enabling detailed imaging of osseous changes. However, it is insensitive to changes of deep layers of cartilage without surface alterations, provides low soft tissue contrast and can not detect subchondral bone marrow edema-like lesions. In addition, because the transaxial scan orientation parallels the joint space of many joints in the body, such as the hip, imaging of these joints can be more problematic. A further drawback to CT imaging is the exposure of the patient to ionizing radiation.

2.4.2. Nuclear Medicine

2.4.2.1. Radionuclide scintigraphy

Radionuclide scinitigraphy uses radiopharmaceutic agents, such as ^{99m}Tc-hydroxymethane diphosphate, to visualise skeletal metabolism, and to identify areas of increased bone activity which are often localised around OA arthritic joints.[32].Investigations of OA in the hand have demonstrated that increased bone uptake can occur in the absence of radiographic changes and is a predictor of subsequent radiological damage.[33,34] In the knee, Dieppe and coworkers demonstrated that abnormal scinitigraphy predicted subsequent joint space loss in patients with established knee OA, suggesting that activating of the subchondral bone may determine cartilage loss.[35] Although radiographic scinitigraphy principally detects changes in bone metabolism, the initially isotope distribution is dependent on blood flow and vascular permeability. Thus, early increased uptake is indicative for synovitis whilst late increased uptake reflects joint pain and osteophyte growth.[36]

Strengths and weaknesses

Radionuclide scinitigraphy shows excellent sensitivity, is inexpensive and readily available. However, drawbacks include a lack of agents the specifically target articular cartilage and exposure of patients to ionizing radiation.

2.4.2.2. 2-^{18}Fluoro-2-deoxy-D-glucose positron emission tomography

Positron electron tomography (PET) can be used to detect foci of inflammation, infection and tumours by visualisation of glucose metabolism in target tissues. A recent pilot study in knee OA, demonstrated increased uptake in periarticular regions, the intercondylar notch and areas of subchondral bone marrow corresponding to MRI-detected bone marrow lesions.[37]

Strengths and weaknesses

PET scanning shows high sensitivity and resolution, and provides and opportunity to combine molecular and anatomic imaging in one image. However, PET scanners currently have limited availability and are hampered by their relative expense and the exposure of patients to ionizing radiation.

APPENDIX 5

CONVENTIONAL RADIOGRAPHIC JOINT SPACE NARROWING

3.1 Methods

Search technique

- PICO: patients-intervention-controls-outcomes

Patients

- Knee/Hip/Hand OA (whatever the criteria)
- With analysis of X Rays by metric measurement of joint space width (either cross sectional or longitudinal)
- Joint space measured either manually or by computer based methods

Intervention

- Any intervention or without intervention (cross sectional or longitudinal studies).

Controls

- Any control or without controls.

Outcomes

Psychometric properties, as defined in the OMERACT filter.[38]

1. Validity : "truth":
    - Cross-sectional or longitudinal relationship between joint space width metric measurement and/or joint space loss and clinical (pain, functional disability, WOMAC, Lequesne, others) or arthroscopic parameters. Correlation with MRI findings was not evaluated since this was performed by the MRI working group.
    - Predictive validity for symptoms, arthroscopic changes, surgery in particular knee/hip replacement surgery
2. Reliability : reproducibility (inter and intra reader) with intra-class coefficient of correlation (ICC).
3. Responsiveness or sensitivity to change: analysed by change of joint space width with time standardized response mean (SRM).

Quality assessment of articles

Down criteria.

Search strategy

In Medline PUBMED and Embase database

Search terms: ((Osteoarthritis[MeSH] and (knee OR hip OR hand)) AND (x-ray OR radiography OR diagnostic imaging OR radiology OR disease progression) AND (joint space OR JSW OR disease progression)

Limits

- no limit by publication date
- languages: French, English, Spanish and German
- limited to humans

Quality control on searches in PUBMED January 13 2009: all 30 relevant articles taken at random in the reviewer's personal library were found with the search terms.

Search strategy approved by the OARSI/FDA assessment of structural change (ASC) group.

Screening and extraction

All abstracts were read by one reviewer. Full-length articles of all abstracts considered as probably relevant or of unknown relevance were obtained. A full-text review of the articles was performed using a data abstraction form approved by the ASC group. The abstracts of all potential relevant citations referenced in the full-text review were screened, and full-text were obtained if probably relevant or of unknown relevance (manual search).

Criteria for exclusion were studies reporting results on OA joints other than knee/hip/hand as appropriate, or combined results on target joint and other joint OA without discriminating for target joint, no radiographic evaluation or radiographic data not reported, radiographic structural degradation not evaluated by metric measurement of joint space (thus excluding studies in which joint space was evaluated with an atlas), secondary OA, case reports. Reviews and systematic literature analysis were not included but were obtained for quality control and manual search.

Statistical analysis

Pooled reliability. Intra and inter-reader ICCs were weighted by the sample size and pooled. For knee, pooled ICCs were obtained for all studies and separately for different radiographic techniques: extended

views, semi-flexed or flexed views, x-rays obtained without the aid of fluoroscopy, x-rays obtained with the aid of fluoroscopy, manual or computer-based measurement.

Responsiveness. Analysis included articles in which the SRM were available or could be calculated. For randomized clinical trials (RCTs), only the placebo arms were entered. Pooled annual mean change of joint space width, pooled annual standard deviation of the change, and pooled SRM were obtained for minimum joint space metric measurement. For knee, the analyses were performed for all studies and separately for different radiographic techniques: extended views without fluoroscopy, extended views with fluoroscopy, semi-flexed or flexed views without fluoroscopy, semi-flexed or flexed views with fluoroscopy, manual or computer-based measurement.

3.2 Knee

3.2.1 Objectives

- To perform a systematic literature review regarding the psychometric properties (concurrent and predictive validity, reliability, responsiveness) of metric measurement of femoro-tibial joint space in knee OA.
- To evaluate differences in psychometric properties of the numerous acquisition and assessment techniques
- To evaluate whether rapid progression patients could be identified.

3.2.2 Results

The search was performed in March-April 2009 and actualized in August 2009. A total of 998 articles were selected (PubMed 807, Embase 59, manual search 132). One reviewer read the abstracts, which led to a selection of 285 articles, then performed a full-text review, resulting in the inclusion of 82 articles. The main cause for non inclusion was joint space evaluated using an atlas rather than by metric measurement.

3.2.2.1 Concurrent validity

[Click here to return to your place in the text, p 40 (Concurrent Validity/Conventional Radiography/Knee).]

[Click here to return to your place in the text, p 45.]

Data were extracted from 20 articles. For more details, the reader can refer to the radiography tables (pp 168–259).

1) Correlation between femoro-tibial joint space metric measurement and arthroscopic findings

Joint space was correlated with arthroscopic findings in 3 cross-sectional studies, either used as a continuous or dichotomous (cut-off = 2 mm) variable.

- Medial and lateral joint space (weight-bearing extended views without fluoroscopy) were strongly and moderately correlated with the SFA (Société Française d'Arthroscopie) 0-100 medial and lateral grading (r = - 0.59 and -0.39, respectively, *P* <0.01) and to the SFA grade (r = -0.48 and -0.31, respectively, *P* <0.01).[39].

- The sensitivity, specificity, and accuracy of joint space <2 mm for predicting severe grade IV chondropathy on arthroscopy were good. For medial joint space, they were 73%, 82%, and 78% (extended view without fluoroscopy); and 78%, 76%, and 77% (45° flexion view without fluoroscopy). For lateral joint space, they were 42%, 99%, and 93% (extended view without fluoroscopy); and 83%, 96%, and 95% (45° flexion view without fluoroscopy).[40]

- The sensitivity and specificity of a major joint space narrowing (JSN), defined as difference with unaffected knee ≥2 mm, for prediction of a grade 3 or 4 arthroscopic score were 25% and 96.3% (extended view) and 85.7% and 100% (45° flexed view) for medial JSN, and were 30% and 91.5% (extended view) and 0% and 100% (45° flexed view) for lateral JSN.[41]

- The 1-year changes in medial joint space were correlated with the 1-year changes in arthroscopic SFA grading (r = 0.4, *P* = 0.01) and with the examinator's overall assessment of chondropathy (r = 0.38, *P* = 0.02), but not with the changes in 0-100 SFA score (r = 0.16, *P* = 0.35).[39]

2) Correlation with MRI findings: see MRI report

3) Correlation between femoro-tibial joint space metric measurement and symptoms

a) Correlation between joint space metric measurement and symptoms in the general population

There was an association between the presence of knee pain and the presence of femoro-tibial JSN in 3 studies, some association in one, and no association except when femoro-patellar OA JSN was associated in a fifth study.

- The medial and lateral minimal JSW (semi-flexed view) were lower in knees with pain vs without pain (2.9 ± 24.4 and 4.3 ±.0.24 mm in patients with pain, 3.3 ± 44.9 and 4.4 ±.0.0 mm in patients without pain, *P* <0.0001 and = 0.0013). Similar results were obtained for joint space area. The relationship persisted on multivariate analysis (odds ratio of medial JSN for pain = 1.66, 95% CI = 1.49-1.87).[42]

- In another study, the relationship increased with decreasing joint space. The odds ratio (OR) of minimal medial and lateral joint space < 2 mm (extended view without fluoroscopy) for the presence of knee pain were 29.8 and 1.4, respectively (both: 5.5). With cut-off of 3 and 4 mm, the OR were 5.5 and 0.9, respectively (both: 2.1) and were 2.0 and 0.6, respectively (both: 1.5).[43]

- In another study, the association increased with decreasing joint space. The OR of decreased medial joint space (extended view without fluoroscopy) for the presence of pain were 2.2 (95% CI = 1.35-3.59) with a cut-off of 2 mm (joint space ≤ 2 mm vs > 2 mm) and 8.96 (95% CI = 2.41-33.2) with a cut-off of 1 mm. The relationship was lower with lateral joint space: the OR of decreased lateral joint space for the presence of pain were 1.33 (95% CI = 0.90-1.95) with a cut-off of 3 mm and 1.77 (95% CI = 0.77-4.07) with a cut-off of 1 mm.[44]

- In a study in which pain, function and joint space measurement were categorized in quartiles, there was some relationship between joint space and symptoms: radiographic grade 0 vs 1 and 0 vs 2, no relationship, grade 3 vs 0, OR = 4.06 (95% CI = 1.97-8.4) for pain, and OR = 2.48 (95% CI = 1.25-4.92) for function.[45]

- In a fifth study, pain and function were not different in subjects with vs without tibiofemoral joint space narrowing (either medial, lateral, or both), except in the subpopulation of patients with tibio-femoral and femoro-patellar JSN (*P* <0.01).[46]

b) Correlation between joint space metric measurement and symptoms in knee OA patients

Data were obtained from three articles, which included four populations. In all, joint space was not correlated with disability. There was no correlation between pain and joint space in two populations, and some correlation in a third one. Joint space was not related to quality of life (QOL) in one population.

- There was no difference in baseline pain, function, QOL, and some gait parameters (stride length, velocity) between patients with joint space (semi-flexed) above or below the median of the population (1.9 mm) in 126 patients included in a RCT.[47]

- There was no correlation between disability and minimal joint space measurement (extended view) in a cross-sectional study involving 51 patients (r = 0.17, *P* = 0.24).[48]

- When categorized in quartiles, the joint space measurement was not correlated with function in populations from 2 RCTs. With respect to pain, there was some relationship in one population (x-ray grades 1 vs 0, NS; grade 2 vs 0 NS; grade 3 vs 0: OR = 4.06, 95% CI = 1.97-8.4) but not in the other one.[45]

- Finally, another study reported that joint space metric measurement was influenced by pain when x-rays were performed using a standing fully extended technique, but not when using a semi-flexed view with fluoroscopy. In the same patients, evaluated after treatment washout and after resumption of therapy, the mean change in joint space between repeated measurement was 0.2 ± 0.06 mm (*P* <0.005) in flaring knees and - 0.04 ± 0.04 in nonflaring knees (*P* = 0.0053 vs flaring knees) when evaluated with extended views, and was 0.08 ± 0.05 mm in flaring knees and 0.02 ± 0.05 in nonflaring knees (*P* = 0.08 vs flaring knees) when evaluated using semi-flexed views.[49]

c) Correlation between baseline symptoms and subsequent joint space metric measurement loss in knee OA patients

Data were obtained from nine studies. Results were conflicting.

- In a 30-month RCT, there was a weak correlation between the 16 and the 30-month joint space loss and baseline pain: r = 0.221,
  P <0.0001 for 16 months JSN and r = 0.13, *P* <0.05 for 30 months)[50] (+ author's personal communication).

- In an ancillary study using data from some of the patients included in the placebo arm of the above mentioned RCT, a baseline WOMAC pain > 44 predicted further JSN ≥ 0.5 mm at 16 and 30 months with 77% and 65% sensitivity and 59% and 62% specificity.[51]

- In a cohort, there was a moderate correlation between the 6-year joint space loss and baseline pain (r = - 0.37, *P* = 0.001).[52]

- In a 3-year RCT, there was a weak correlation between the 3-year changes in joint space metric measurement and baseline function and stiffness (r = 0.28, *P* = 0.02 and r = 0.31, *P* = 0.008, respectively). On the contrary, there was no correlation between the 3-year JSN and baseline pain (r = 0.18, *P* = 0.12).[53] However, in another article from the same author on the same population, there was no relationship on multivariate analysis.[54]

- In a 2-year RCT, baseline pain was not correlated with the further joint space loss, either in the placebo and the treated groups.[55]

- In a 4-year cohort, the baseline total WOMAC score was not related to subsequent joint space loss.[56]

- In two 1-year RCTs, baseline pain and Lequesne's index were not related to further progression (defined as a decrease in medial joint space ≥ 0.5 mm.[57]

- In a 2-year RCT, baseline pain did not predict join space loss.[58]

d) Correlation between changes in joint space metric measurement and changes in symptoms in knee OA patients

Data were obtained from 4 studies.

- In a 30-month RCT, the rate of joint space narrowing over 30 months was related to the percentage of semi-annual assessment in which 50-foot walk pain was ≥ 20% more severe than that reported 6 months previously.[50]

- In the placebo group of a 3-year RCT, the 3-year joint space narrowing was weakly correlated with the 3-year changes in pain (r = - 0.29, *P* = 0.017 for change in mean joint space, r = -0.24, *P* = 0.044 for change in minimal joint space), but was not correlated with the 3-year changes in function (r = -0.19, *P* = 0.11 for change in mean joint space, r = -0.14 *P* = 0.31 for change in minimal joint space) and 3-year change in stiffness (r = - 0.22, *P* = 0.06 for change in mean joint space, r = - 0.05, *P* = 0.67 for change in minimal joint space).[53]

- In a 1-year RCT, the changes in total WOMAC, WOMAC pain and WOMAC function increased with increasing loss of joint space. The mean changes in WOMAC total was -5.9, in patients with any loss of JSW, and was +1.4 in patients with JSW loss of ≥ 40%. The mean changes in

WOMAC pain was -4.6, in patients with any loss of JSW, and was +6 in patients with JSW loss of ≥ 40%. The mean changes in WOMAC function was -6.3, in patients with any loss of JSW, and was +2.3 in patients with JSW loss of ≥ 40%.[59]

- In a 1-year RCT, there was no relationship between changes in pain and changes in joint space width, in the subgroup with baseline JSW ≥ and < 4.6 mm.[60]

4) Summary

- The joint space metric measurement was moderately or strongly associated with arthroscopic findings. The 1-year change in joint space was moderately associated with the 1-year changes of some arthroscopic findings (but not with others).

- In the general population, the results were heterogeneous but most suggested that there is an association between the presence of knee pain and of knee OA.

- In the knee OA population, the results were heterogeneous but most suggested that there is no cross-sectional association between the knee pain and joint space metric measurement. In addition, in all studies, no association between the disability and joint space metric measurement was observed. It must be stated that most of the evaluated studies did not use a semi-flexed or flexed technique with fluoroscopy.

- In the knee OA population, baseline joint symptoms might be weakly correlated to further joint space loss, but results are heterogeneous.

- In the knee OA population, changes in joint symptoms might be weakly correlated to changes in joint space loss, but results are heterogeneous.

- Comment: joint pain is influenced by numerous factors, including patients-related factors. A beautiful recent study showed that the relationship between pain and joint space is increased when the patients are their own controls[61]. This study was not included in the present analysis, since joint space was not evaluated using metric measurement. However, it might suggest that the above collected results on correlations between pain and joint space obtained from longitudinal data are more valid than those obtained from cross-sectional studies.

3.2.2.2 Predictive validity

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Data could be extracted from 11 articles.

1) Prediction of the evolution of symptoms in knee OA patients

Two studies were evaluated. The results were conflicting:

- In a RCT comparing a 8-week physical therapy individual treatment, format group program vs control, pain function and QOL improved markedly less after physical therapy in patients with baseline joint space below 1.9 mm, versus patients with baseline joint space above 1.9 mm. Mean change in pain were 5.63 and 11.0, mean change in function were 2.6 and 9.1, mean change in SF36 physical were 1.4 and 4.5, mean change in SF36 mental were 1.3 and 2.8.[47]

- In a 3-year RCT, baseline joint space measurement was not correlated with the 3-year changes in WOMAC scores (total and subscales) in the treatment as well as in the placebo groups,[53]

2) Prediction of treatment efficacy

Data were extracted from five studies

- The percentage of success of arthroscopic debridement was higher in patients with baseline joint space ≥ 3 vs ≤ 2 mm. The mean postoperative pain score was 14.7 ± 4.4 in patients with baseline medial JSW ≤ 2 mm, and was 33.2 ± 1.9 in patients with baseline medial JSW ≥ 3 mm, $P = 0.0001$. The arthroscopy was considered as successful in five out of 16 (31%) knees with baseline JSW ≤ 2 mm and in 63 out of 91 (69%) of knees with baseline JSW ≥ 3 mm.[62]

- Pain function and QOL improved markedly less after physical therapy in patients with baseline joint space below 1.9 mm, versus patients with baseline joint space above 1.9 mm. Mean change in pain was 5.63 in patients with baseline joint space below 1.9 and 11.0 in those with baseline joint space above 1.9. Mean change in function was 2.6 and 9.1, mean change in SF36 physical was 1.4 and 4.5, mean change in SF36 mental was 1.3 and 2.8.[47]

- In a 3-year RCT, baseline joint space did not predict symptomatic efficacy. The changes in WOMAC total were significantly different between treatment and placebo groups in patients in the lowest quartile of baseline mean JSW (< 4.5 mm) as well as in those in the highest quartile (> 6.2 mm).[53]

- In another RCT, baseline joint space influenced the structural effect of the evaluated treatment. In patients with baseline joint space above the median of the population, the 1-year joint space loss was lower in the treatment group compared to the placebo group (0.13 vs 0.55 mm, *P* = 0.02) while there was no difference between groups in patients with baseline joint space below the median of the population.[60]

- In another RCT, joint space loss was increased in placebo patients in an analysis removing those with a baseline joint space < 1 mm, while it did not change the results in the treatment group.[55]

3) Prediction of arthroscopic changes

Two articles were found. However, some patients might be common between these studies.

- In one study, baseline joint space metric measurement did not predict 1-year changes in examinator's arthroscopic overall assessment of chondropathy. There was however a trend toward a lower baseline joint space in those whose chondropathy worsened. Baseline JSW was 4.3 ± 1.2 mm in patients whose arthroscopy VAS improved (n = 5), 4.9 ± 1.8 mm in patients whose arthroscopy VAS remained stable (n = 13) and 3.7 ± 1.5 mm in those whose arthroscopic findings worsened (n = 23) (*P* = 0.09).[39]

- In the second study, the mean baseline joint space was lower in patients with a further 1-year progression of the arthroscopic score (SFA scoring system) compared to non progressors (mean baseline JSW = 3.1 ± 1.3 in subsequent progressors vs 4 6 ± 1.7 in subsequent nonprogressors (*P* = 0.002).[63]

4) Prediction of further joint surgery, including total joint replacement

Data were extracted from four studies

- In a 5-year cohort following a 3-year randomized trial, the joint space loss during the first 3 years was correlated with further 5-year knee surgery (either joint replacement or debridement/menicectomy) (*P* = 0.006). The best predictive cut-off value was a 0-3 initial change of 0.7 mm (RR = 5.15, efficiency = 79). However, surgery was not always performed on the original target knee of the RCT.[64]

- In a 5-year cohort following two 3-year randomized trials (including the one above), a 0.5 mm or more joint space loss during the 3-year trial was predictive of further joint replacement: 4 out 15 patients (26.7%) with an initial joint space loss above 0.5 mm

underwent a knee surgery during the 5 years following, 9 out of 118 patients (7.6 %) in those with a previous joint space loss below 0.5 mm (P = 0.019, RR = 3.5, 95% CI = 1.23-9.97). It is not clear in the article whether the operated joint was the trial index knee or not.[65]

- In the above mentioned study in which the percentage of success of arthroscopic debridement was higher in patients with baseline joint space ≥ 3 vs ≤ 2 mm, the success of arthroscopy was highly predictive of further joint replacement.[62]

- In a 2-year cohort of 28 patients, neither baseline joint space nor changes in joint space were associated with joint replacement (5 patients operated).[66]

5) Summary

- There are not sufficient data to conclude on the predictive validity of joint space metric measurement on the evolution of symptoms in knee OA patients.

- Although data are sparse and heterogeneous, the symptomatic and structural efficacy of knee OA treatment might be decreased in patients with lower joint space metric measurement.

- The further arthroscopic changes might be more important in knee OA patients with lower baseline joint space. However, the data are too sparse and heterogeneous to conclude.

- The amount of joint space might be predictive of further knee surgery. However, the data are sparse, heterogeneous thus, again, no definite conclusion is possible.

- Comment: in surveys, surgeons usually state that they are weakly or moderately influenced by x-rays when deciding whether joint replacement is indicated or not. [67,68] However, it has been shown that, in reality, the amount of JSN is a major predictive factor of the decision, at least for hip replacement.[69] Thus, the validity of prediction of joint replacement as an outcome to evaluate the predictive validity of joint space narrowing is questionable. On the other hand, the reasons why joint space influences the surgeons' decision remain unclear. If these reasons are differential diagnosis (some surgeons might consider that pain and functional impairment are certainly due to OA in patients with severe joint space narrowing, but might be due, at least in part, to another disease in those with mild joint narrowing), optional treatments (the surgeons might consider that an additional or complementary medical treatment is less likely to be efficient in patients with severe joint narrowing), and/or

disease's potential evolution (OA is frequently a waxing and waning disease, and surgeons might consider that a spontaneous clinical improvement is less likely observed in patients with severe joint loss), joint replacement might be considered as a valid outcome.

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3.2.2.3 Reliability

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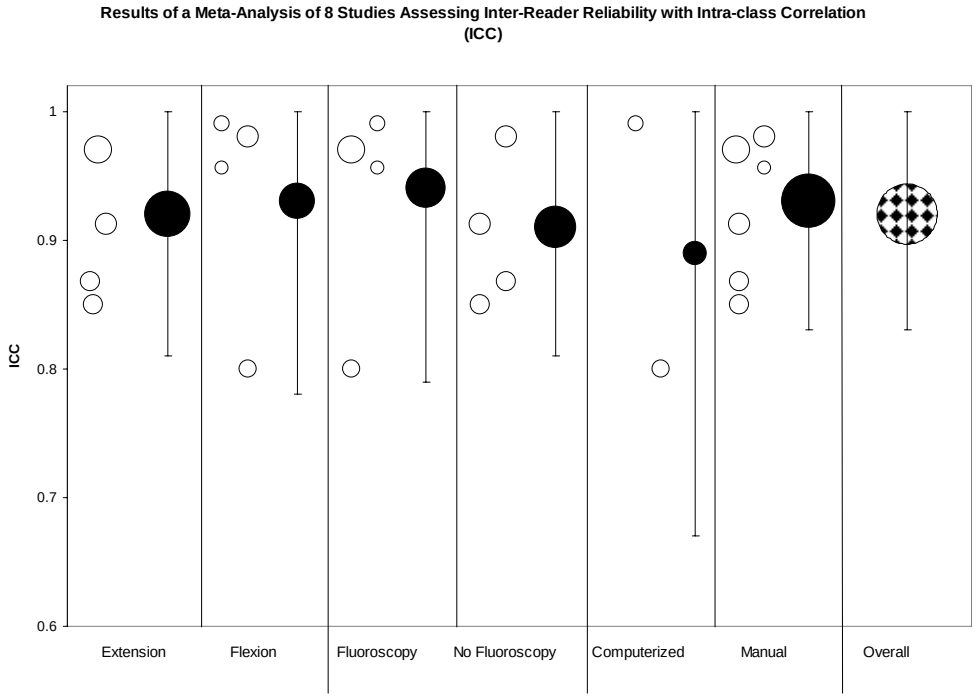
Data were obtained from 25 studies, 3 of those providing results for 2 different radiographic techniques. The inter-reader intra-class coefficient of correlation (ICC) were available in only 8 studies (mean sample size of 61) and the intra-reader ICCs in 17 (mean sample size of 42). Among the 8 studies in which inter-reader ICCs were available, 4 used extended views (mean sample size = 76) and 4 used semi-flexed or flexed views (mean sample size = 45); 4 used fluoroscopy (mean sample size = 57) and 4 did not (mean sample size = 64); 6 measured joint space manually (mean sample size = 68) while in the other 2, joint space measurement was computer-based (mean sample size = 40).

Results for inter-reader reliability are presented in the following figure. Overall, there was an excellent inter-reader reliability, independent of the technique used..

Figure 1



3.2.2.4 Responsiveness

[Click here to return to your place in the text, p 44.]

1) Pooled changes and standardized response means

Data were extracted from 47 articles (22 cohorts, 25 RCTs), including 7 studies evaluating different radiographic techniques. In the RCTs, structural assessment analysis was performed as an intention to treat analysis in 13 studies, a completer analysis in 11 studies, and was unreported in the last one. Among the 47 studies, SRMs for change in minimal joint space width were available in 40. The mean sample size was 97. Six studies used extended views with fluoroscopy (mean sample size = 80), 8 used extension views without fluoroscopy (mean sample size = 98), 15 used semi-flexed or flexed views with fluoroscopy (mean sample size = 118), and 11 used semi-flexed or flexed views without fluoroscopy (mean sample size = 75). Results are shown in the following figures:

Figure 1

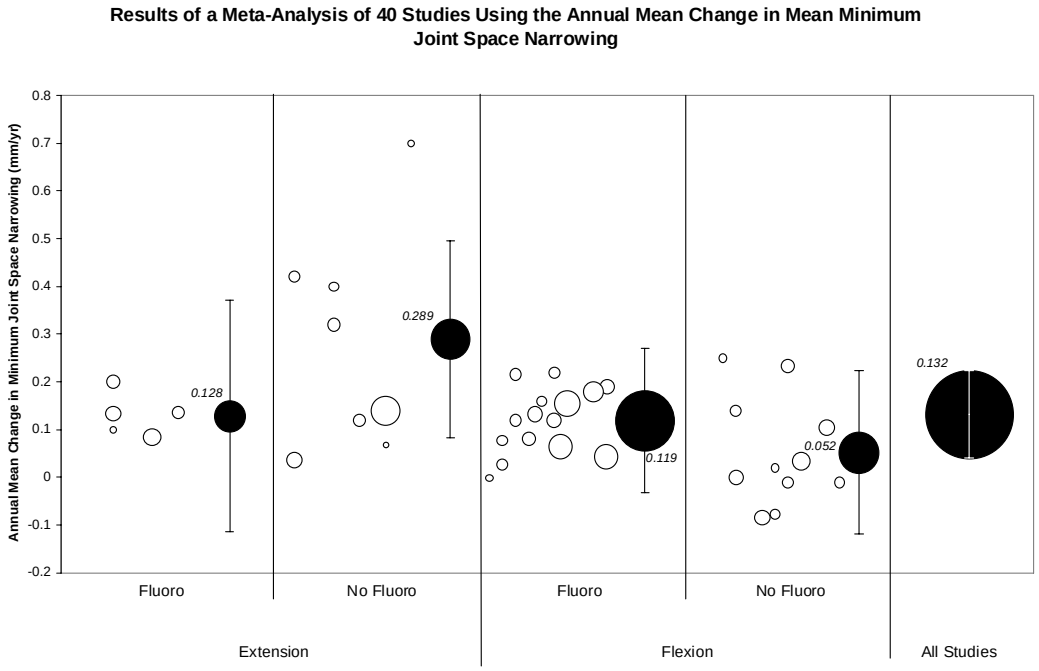


Figure 2

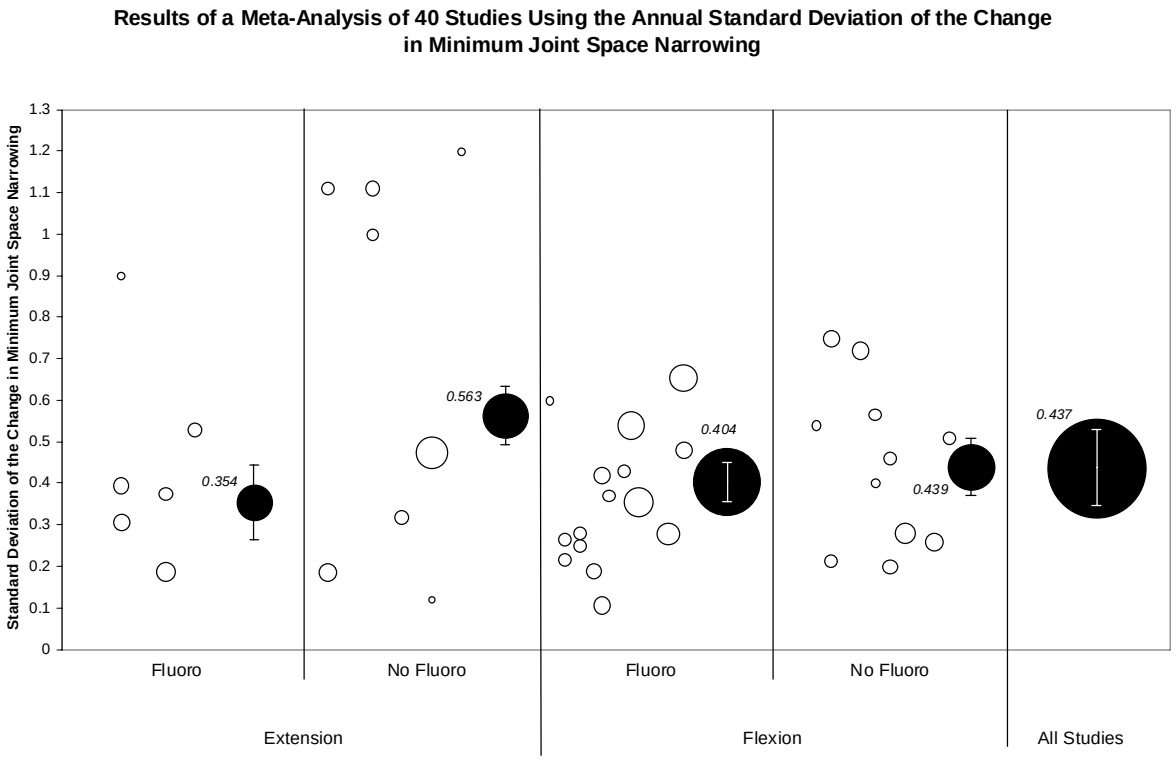
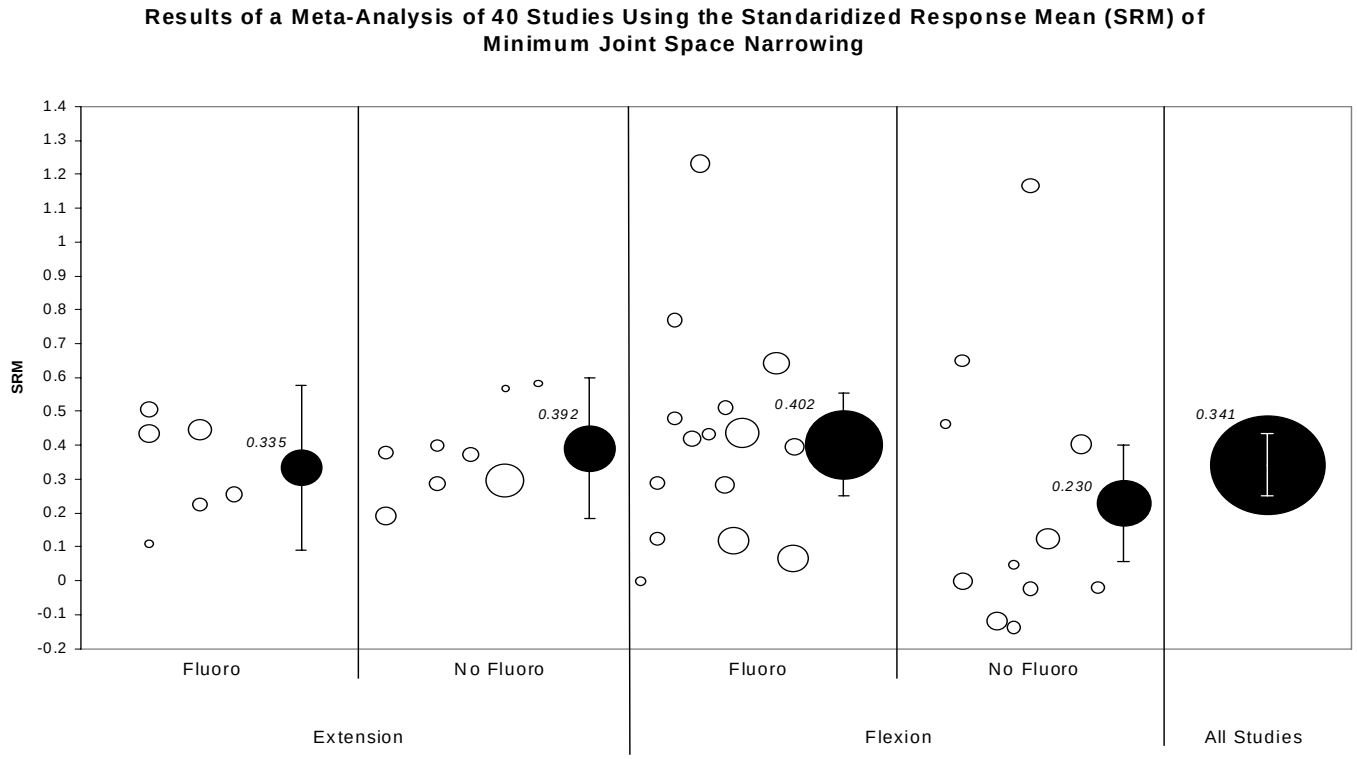

Results of a Meta-Analysis of 40 Studies Using the Annual Standard Deviation of the Change in Minimum Joint Space Narrowing
Standard Deviation of the Change in Minimum Joint Space Narrowing
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.354
0.563
0.404
0.439
0.437
Fluoro
No Fluoro
Fluoro
No Fluoro
Extension
Flexion
All Studies

Figure 3



Overall, the pooled annual joint space loss was 0.132 mm, with a pooled annual standard deviation of 0.437 and a pooled SRM of 0.341. The pooled annual joint space loss tended to be higher in studies using extended views without fluoroscopy, while the pooled SRM tended to be higher in studies using semi-flexed or flexed views but with overlap in confidence intervals.

[Click here to return to your place in the text, p 37 (Responsiveness, Conventional Radiography/Knee.]

2) Head to head comparisons between x-ray or measurement techniques

a) X-ray techniques

Six studies were analyzed

- A 2-year prospective study compared in the same patients the extended view and a semi-flexed view (the schuss view). Fluoroscopy was used in both. The schuss view was more responsive, whatever the outcome evaluated (minimal joint space, mean joint space or joint area). The 2-year decrease in minimal joint space was 0.17 ± 0.75 mm for extended views (NS, SRM = 0.23) and was 0.24± 0.5 mm for the schuss view (P = 0.007, SRM = 0.48). The 2-year decrease in mean JSW was 0.14 ± 0.78 mm for the extended view (NS, SRM = 0.17) and was 0.25 ± 0.55 mm for the schuss view (P = 0.009, SRM = 0.45). The 2-year decrease in joint area was 2.5 ± 13.3 mm^2 for the extended view (NS, SRM = 0.18) and 3.8 ± 9.0 mm^2 for the schuss view (P = 0.02, SRM = 0.42).[70]

- In a 1-year prospective study, conducted by the same team, the schuss view tended to be more responsive than the extended view. In this study, fluoroscopy was performed only for the schuss view. The 1-year decrease in joint space was 0.17 ± 0.37 mm for the extended view (NS, SRM = 0.47) and was 0.41 ± 0.7 mm for the schuss view (P < 0.05, SRM = 0.58) (Piperno, Osteoarthritis Cartilage 1995).

- Two flexed or semi-flexed techniques (ie, the schuss and the fixed-flexion views) were compared in the same patients in a 1-year prospective study. The schuss was performed with fluoroscopy, the fixed-flexion without. The results favoured the schuss view: the 1-year decrease in minimal medial joint space was 0.22 ± 0.43 mm for the schuss view (P = 0.0002, SRM = 0.51), while the minimal medial joint space remained stable when evaluated with the fixed-flexion view (mean increase of 0.01 ± 0.46 mm, P = 0.92, SRM = -0.022).[71]

- A 14-month prospective study compared 2 semi-flexed techniques (ie, the MTP semi-flexed postero-anterior view and the semi-flexed antero-posterior view). Fluoroscopy was used only in the latter. The results, although non significant, were in favour of the semi-flexed antero-posterior with fluoroscopy: with the MTP view, the mean minimal joint space increased (+ 0.09 ± 0.66 mm, P = 0.33, SRM = - 0.14), while with the semi-flexed antero-posterior view with fluoroscopy, the mean minimal joint space decreased (- 0.09 ± 0.31 mm, P = 0.1, SRM = 0.29).[72]

- A 1-year prospective study compared the schuss view with fluoroscopy and the fixed-flexion view without fluoroscopy, and compared a modified schuss view without fluoroscopy vs the

fixed-flexion view without fluoroscopy (actually, some patients in the schuss without fluoroscopy did undergo baseline schuss with fluoroscopy). The results favoured the schuss view. The 1-year decrease of joint space with the schuss and fluoroscopy was 0.16 ± 0.37 mm (SRM = 0.43), while there was an increase of mean joint space with the fixed-flexion (0.01 ± 0.51 mm, SRM = -0.02), *P* = 0.007 one technique vs the other. The 1-year decrease of JSW was 0.25 ± 0.54 mm with the schuss without fluoroscopy (SRM = 0.46) while it was 0.02 ± 0.4 mm with the fixed-flexion (SRM = 0.05), *P* = 0.005 one technique vs the other.[73]

- The extended view was compared to a flexed postero-anterior view in a 1-year study. Fluoroscopy was used for both techniques. The results were comparable with SRM of 0.1 for the extended view and 0.0 for the flexed view.[74]

b) Alignment of medial tibial plateau

Several studies have suggested that responsiveness is a function of the quality of serial medial tibial plateau alignment.

- In a 1-year prospective cohort, the SRM was 0.68 if baseline and follow-up intermargin distance (IMD) were both ≤ 1.2 mm, 0.23 if one IMD was ≤ 1.2 mm and the other was > 1.2, and 0.39 if baseline and follow-up IMD were > 1.2 mm.[75]

- In a 2-year prospective cohort, the SRM was 0.4 if IMD was accurately reproduced (difference between baseline and 24-months IMD ≤ 1 mm), and 0.56 in knees with serial satisfactory alignment (baseline and 24-months IMD ≤ 1 mm).[76] Progression, defined as joint space loss > 0.4 mm was observed in 37.5 % of knees with serial satisfactory alignment, vs 28.4%.[77]

- In a study using data from 3 longitudinal cohorts (mean follow-ups = 2.6, 3.0 and 2.3 years), the mean loss in minimal medial joint space was 0.67 ± 0.70 mm in knees with serial satisfactory alignment vs 0.32 ± 1.32 mm in others (*P* = 0.004 for mean and 0.006 for SD).[5]

c) Measurement technique

Five studies were evaluated

- In a 2-year prospective study, there was no difference in responsiveness between assessment of change of minimal joint space, mean joint space and joint area, both when using extended views with fluoroscopy and schuss view with fluoroscopy (SRM = 0.23, 0.17 and 0.18 for the extended views; 0.48, 0.45 and 0.42 for the schuss view).[70]

- In the second study, a RCT comparing naproxen and licofelone, the SRM of minimal joint space and mean joint space were also comparable (SRM = 0.7 and 0.66 in the naproxen group; 0.59 and 0.64 in the licofelone group).[78]

- In a 3-year RCT (extended view with fluoroscopy), the SRM of assessment of minimal joint space and of mean joint space were again comparable, both in the treatment (mean change in minimal joint space = 0.07 ± 0.76, SRM = 0.09; mean change in mean joint space = 0.06 ± 0.81, SRM = 0.07) and in the placebo group (mean change in minimal joint space = 0.4 ± 0.92, SRM = 0.43; mean change in mean joint space = 0.31 ± 0.84, SRM = 0.37.[79]

- In a 1-year RCT, the responsiveness of minimal joint space, mean joint space, and joint area were, again, similar (0.29, 0.27, and 0.25 in the placebo group, 0.048, 0.007 and 0.013 in the treated group.[80]

- In a 2-year RCT, the SRM of minimal joint space measurement and mean joint space were 0.125 and 0.23, respectively, in the placebo group, and were -0.09 and 0 in the treated group.[55]

d) Analysis method

Table 1: X-ray based SRM on JSN

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Analysis (Radiographic View/Method of Measurement/Follow-up Time)	Number of Studies	SRM
Extension/Computerized/1 year or less	1	0.29 (0.04, 0.54)
Extension/Computerized/1-2 years	1	0.23 (0.13, 0.32)
Extension/Computerized/> 2 years	0	N/A
Extension/Manual/1 year or less	5	0.37 (0.30, 0.44)
Extension/Manual/1-2 years	1	0.51 (0.42, 0.59)
Extension/Manual/> 2 years	5	0.39 (0.26, 0.51)
Flexion/Computerized/1 year or less	10	0.20 (0.06, 0.34)

Flexion/Computerized/1-2 years	7	0.28 (0.15, 0.40)
Flexion/Computerized/> 2 years	3	**0.77 (0.20, 1.34)**
Flexion/Manual/1 year or less	1	0.00 (-0.26, 0.26)
Flexion/Manual/1-2 years	1	-0.14 (-0.29, 0.02)
Flexion/Manual/> 2 years	4	**0.68 (0.26, 1.09)**

- Responsiveness of x-ray depends greatly on study timeline: longer studies offer better data on responsiveness.

- JSN should not be used to assess treatment efficacy over short periods of time.

- Computerized reading reduces the measurement error leading to somewhat better responsiveness compared to manual read responsiveness in short-term studies on flexion, although responsiveness is still poor.

- In studies longer than 2 years, advantages of computerized vs. manual read are much less apparent.

- While JSN represents composite domain (cannot differentiate loss of cartilage from loss of meniscus), the following positive aspects of using JSN based on x-rays in RCTs should be noted:
  - X-rays are inexpensive, easy to administer, do not lead to patient population restriction (compared to MRIs where those with claustrophobia, metal implants, and morbid obesity may not be eligible).
  - JSN-based outcomes will be hard to evaluate in studies of duration shorter than 2 years, but in studies of longer duration the magnitude of responsiveness may lead to feasible sample sizes, if efficacy is at least 50% (see Table 1).

3) Summary

- The pooled analysis differentiated different radiographic techniques (ie, extended views with or without fluoroscopy and flexed or semi-flexed techniques with or without fluoroscopy). However, there are numerous different techniques, in particular for semi-flexed and flexed views, which were not possible to analyse separately.

- The pooled responsiveness was low, whatever the used radiographic technique, and without significant differences between techniques.

- However, the head to head comparisons suggest that responsiveness is higher with the semi-flexed views with fluoroscopy in comparison with other techniques.

- There are concordant data which suggest that satisfactory serial medial tibial plateau alignment allows obtaining a better responsiveness.

- Head to head comparisons suggest that there is no difference in responsiveness between assessments of change of minimal joint space, mean joint space, and joint area.

4) Prediction of "slow" and "fast" losers

a) Biomarkers

- Serum hyaluronic acid (HA) was evaluated in 4 studies, with 3 suggesting prediction of joint space loss. In a 5-year longitudinal cohort, baseline serum HA level was higher in patients with vs without subsequent progression (P = 0.007). Progression was defined as a decrease in joint space ≥ 2 mm in any compartment OR total knee replacement (11 out 26 progressors).[81] In the same cohort, followed-up 8 years, baseline serum HA remained related to progression, and there was a trend toward a relationship between serum HA 3 years prior to baseline and progression. However, the definition of progression was unchanged, and the sensitivity was low (sensitivity and specificity of 3-year HA for progression with a cut-off of 117.3 ng/ml = 46 and 87%; sensitivity and specificity of baseline HA for progression, with a cut-off of 150.0 ng/ml = 38 and 89%).[82] In an ancillary study of a 3-year RCT, the baseline HA was not correlated with the further percentage change in minimal and mean JSW, but the 1-year change in HA was (r = 0.27, P = 0.02 for changes in mean joint space, r = 0.24, P = 0.04 for changes in minimal joint space).[83] A 2-year prospective study demonstrated a correlation between baseline serum HA and 2-year JSN (r = 0.56, p < 0.005).[84]

- Serum cartilage oligomeric matrix protein (COMP) was evaluated in 5 studies, with conflicting results. In a 5-year longitudinal cohort, the baseline COMP was not related to progression, but the 1-year changes in COMP was (P <0.001, sensibility and specificity of the 1 year increase in COMP to predict progression = 70 %, 95% CI = 50-90% and 78%, 95% CI = 63-93%). Progression was defined as a decrease in joint space ≥ 2 mm in any compartment OR total knee replacement.[85] In the same cohort with an increased number of patients, the mean baseline serum COMP was increased in subsequent progressors vs non progressors (14.12 ± 3.39 vs 12.62 ± 3.25 U/l, P = 0.036).[86] In an

ancillary study of a 3-year RCT, the baseline COMP did not correlate with the further percentage change in minimal and mean JSW (Bruyere, J Rheumatol 2003). In the placebo arm of a 3-year RCT, there was no correlation between baseline serum COMP and further 3-year change in mean JSW, but the baseline serum COMP was higher in further progressors, defined as a decrease in joint space > 0.5 mm for either knee (4.92 ± 1.05 vs 3.96 ± 0.94 mg/ml, $P < 0.05$) (Vilm, *Osteoarthritis Cartilage.* 2005). In a 2-year study, there was no correlation between baseline serum COMP and the further 2-year joint space loss.[84]

- Urinary crosslinked C-telopeptide (CTX-II) was evaluated in 6 studies. In a 5-year longitudinal cohort, there was a trend toward a higher baseline CTX-II in further progressors, and the 5-year mean levels of CTX-II were higher in progressors. Each SD increase of 5-year mean CTX-II was associated with a relative risk of progression of 2.02 (95% CI = 1.20-3.41). Progression was defined as a decrease in joint space ≥2 mm in any compartment OR total knee replacement.[87] In an ancillary study of a two 1-year RCTs, there was a trend toward a relationship between baseline urinary CTX-II and 1-year change in joint space (r = - 0.27, $P = 0.056$), and the baseline urinary CTX-II was increased in subsequent progressors (1-year decrease in medial joint space ≥0.5 mm) vs subsequent non progressors, $P = 0.04$.[57] In another study by the same team in another population, the baseline and 0-6 months absolute and relative changes in CTX-II were related to progression (defined as a 2-year decrease in minimal medial joint soace ≥ 0.6 mm), after adjustment for BMI, gender, pain, presence of hip OA, knee crepitus, treatment, and baseline JSW ($P = 0.0003$, 0.0049 and 0.0063). When defining low and high levels of CTX-II (cut-off = 150 ng/mmole creatinine) at baseline and 6 months, the relative risk for progression (high level at baseline and 6 months as reference) was 0.57 (95% CI = 0.39-0.85) for high/low levels, 0.77 (95% CI = 0.43-1.36) for low/high levels, 0.36 (95% CI = 0.21-0.63) for low/low levels.[88] In a cohort with a mean follow-up of 6.6 years, the authors described an association between quartiles of baseline CTX-II and further progression (first quartile used as reference: OR second quartile = 0.9, 95%CI = 0.6-1.5; OR third quartile = 1.1, 95%CI = 0.7-1.7; OR fourth quartile = 1.1, 95%CI = 0.7-1.7) (progression defined as a decrease of joint space of at least 1.0 mm in any compartment, similar results with cut-off of 1.5 and 2.0 mm).[89] In a 4-year longitudinal study, there was no correlation between baseline CTX-II and further joint loss.[56]

- Plasma and urine samples from the 30-month randomized placebo controlled trial of structure modification with doxycycline were assayed for stromelysin (MMP-3), CS846 (proteoglycan aggrecan turnover), biomarkers of the collagenase cleavage of Type II collagen C2C, Types I and II

collagens C1,2C; Type II collagen synthesis CPII; cross-linked C-telopeptide of Type II collagen CTX-II and Type II collagen neoepitope uTIINE.[1-5] ***Only*** plasma stromelyin showed that baseline level as a significant predictor of JSN[1] Serial levels of plasma MMP-3, CS846 and uTIINE only reflected concurrent JSN.[1,3,4]

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- In a 2-year prospective cohort, baseline serum pentosidine was strongly related to further 2-year joint space loss ((r = 0.56, *P* <0.005).[84]

- In a 4-year cohort, there was a moderate correlation between baseline synovial procollagene II C propeptide (PIICP) and further joint space loss (r = 0.440, 95% CI = 0.282-0.575, *P* <0.001). Patients with baseline synovial PIICP ≥3.8 ng/ml had a rate of joint space loss twice as those with PIICP <3.8 (1.04 ± 0.62 vs 0.50 ± 0.40, *P* = 0.001).[90]

- The serum N-propeptide of type IIA collagen (PIIANP) was evaluated twice. In a 5-year longitudinal cohort, there was a trend toward a higher baseline PIIANP in progressors, and the 5-year mean levels of PIIANP were higher in progressors. Each SD increase of 5-year mean PIIANP associated with a relative risk of progression of 1.75 (95% CI = 1.02-3.01). Progression was defined as a decrease in joint space ≥ 2 mm in any compartment OR total knee replacement. [87] In an ancillary study of two 1-year RCTs, there was a trend toward a relationship between baseline serum PIIANP and 1-year change in joint space (r = 0.29, *P* = 0.059), and the baseline serum PIIANP was not statistically different in progressors (1-year decrease in medial joint space ≥0.5 mm) vs nonprogressors (17.8 ± 5.7 mg/ml in progressors and 20.1 ± 5.4 in nonprogressors, *P* = 0.2).[57]

- The baseline osteocalcin did not correlate with further joint space loss in a 3-year RCT[83] and a 4-year cohort[56] but in the 3-year RCT, the 1-year change in osteocalcin was weakly correlated with the 3-year change in mean JSW (r = -0.24, *P* = 0.04) as well as minimal JSW (r = -0.31, *P* = 0.01).

- In the placebo arm of a 3-year RCT, the baseline urine type II collagene propeptide Coll 2-1 and Coll-1 NO2 were not correlated with further joint space loss, but there was a weak negative correlation between the 3-year change in mean JSW and the 0-1 year changes in Coll 2-1 (r = -0.31, *P* = 0.03) and Coll 261 NO2 (r = -0.31, *P* = 0.03).[91]

- In an ancillary study of two 1-year RCTs, the baseline uncoupling index (Z-score CTX-II – Z-score PIIANP) was moderately related to further joint space loss (r = - 0.46, *P* = 0.0016) (Garnero, *Arthritis Rheum.* 2002).

- Baseline serum keratane sulphate,[83,92] urinary pyridinoline and deoxypyridinoline[83,91], serum CTX-I and glucosyl-galactosyl-pyridinoline,[56] serum metalloproteases 9 and 13, serum tissue inhibitor of metalloproteases,[84] urinary N-terminal crosslinking telopeptide of type I collagene[88] did not correlate with further joint space loss.

Baseline x-rays

Baseline radiographs were evaluated in 16 studies (metric measurement of joint space in 11 studies, joint space grades in 2, osteophytes grades in 1, and KL in 4).

- The relationship between continuous baseline joint space and subsequent progression (yes or no) was evaluated in 3 studies (2 from the same team). In an ancillary study of two 1-year RCTs, the baseline joint space was not related to the 1-year progression (decrease in joint space ≥0.5 mm).[57] In a 5-year cohort, the baseline joint space was predictive of disease progression (no progression,

mean = 4.0 ± 2.0, progression, mean = 2.0 ± 2.0, *P* <0.001), but there was no more relation in multivariate analysis.[81] In the last study by the same authors, the mean baseline JSW was similar in 5-year progressors and non-progressors (progression defined by at least 2 mm JSW decrease OR joint replacement).[87]

- The relationship between a bichotomized baseline joint space and further joint loss was evaluated in 2 studies. In a RCT, the 18-month joint space loss was higher in patients with baseline JSW <2.3 mm compared to those with baseline joint space >2.3 mm: the change was 0.12 mm (placebo) and 0.06 mm (NSAIDs) in patients with baseline JSW >2.3 mm, and was 0.37 mm (placebo) and 0.66 mm (NSAIDs) in those with baseline joint space <2.3 mm. However, there were only a small number of patients and no statistical comparison between the 2 groups was provided (Buckland-Wright, *Ann Rheum Dis*. 1995). In a second RCT, the 12-month joint space loss was higher in patients with baseline JSW ≥4.6 mm compared to those with baseline JSW <4.6 mm. The change was 0.55 ± 1.04 mm (placebo) and 0.13 ± 1.05 mm (treatment) in patients with baseline JSW ≥4.6 mm, and was +0.20 mm (placebo) and 0.06 mm (treatment).[60]

- Continuous joint space loss was correlated with continuous baseline JSW in 6 studies, with conflicting results. In 3 studies, a 2-year[58] a 4-year cohort,[90] and a 2-year RCT[55] there was no correlation between baseline joint space and further joint loss. The 3 other studies did find a correlation. In a 3-year RCT, there was a weak correlation both in the placebo (r = -0.34, *P* = 0.003) and the treated (r = - 0.28, *P* = 0.019) groups, the higher baseline joint space, the higher the joint loss.[54].In a 6-year prospective cohort, there was a weak correlation between baseline joint space and joint loss (r = - 0.25, *P* = 0.03).[52] In a 4-year cohort, there was a weak correlation (r = 0.31 and 0.35 for the medial right and left medial compartment, *P* <0.0001, with those with higher baseline joint space experiencing the most severe joint space loss). The relationship was no more significant when the analysis was restricted to medial knee OA.[56]

- Joint space loss was correlated with baseline KL in four studies. In a 2-year RCT, the joint space loss was greater in knees with KL 3 than with KL 2 (placebo group, mean joint space loss = 0.273 in baseline KL 2 and 0.523 mm in baseline KL III). It is noteworthy that the same study did not find any relationship between baseline joint space and joint space loss[58] On the contrary, in a 3-year cohort, joint space loss was higher in patients with baseline KL 2 vs KL 3 and KL 1. The mean joint space loss was 0.22 ± 0.52 (SRM = 0.43) for baseline KL 0 (93 subjects), 0.25 ± 0.69 (SRM = 0.35) for baseline KL 1 (38 subjects), 0.51 ± 0.59 (SRM = 0.86) for baseline KL 2 (13 subjects), 0.32 ± 0.75 (SRM = 0.43) for baseline KL 3 (55 subjects), and 0.09 ± 0.30 (SRM = 0.29) for baseline KL 4 (18

subjects).[93] In a 30-months RCT including only patients with KL 2-3, the sensitivity and specificity of baseline KL 3 for 16-month progression were 71% and 57%, and for 30-month progression were 65% and 64%.[51] In another study, the 24-months joint space loss was greater in patients with baseline KL 3 than in those with baseline KL 2 (0.523 and 0.273 mm). In a 5-year RCT, joint space loss was 0.22 ± 0.74 mm for baseline KL 0 or 1 (SRM = 0.30), 0.33 ± 0.85 mm (SRM = 0.39) for baseline KL2, 0.49 ± 0.89 mm (SRM = 0.55) for baseline KL 3, 0.38 ± 1.26 mm (SRM = 0.30) for baseline KL 3. The statistical significance was not provided.[94]

- Joint space loss was correlated with baseline joint space evaluated using an atlas in two studies. In a 2-year cohort, there was no association between baseline joint space grade and progression (joint loss >0.4 mm). However, there was a relationship in knees with satisfactory serial medial tibial plateau alignment (baseline JSN OARSI grade 1 vs 0: OR = 14.7, 95% CI = 2.6-82.4, grade 2-3 vs 0: OR = 11.0, 95% CI = 1.3-90.7).[77] In the second study, the 37-month joint space loss was 0.14 ± 0.53 mm for baseline grade 0, and 0.50 ± 0.67 mm for baseline joint space grade ≥1. It was 0.36 ± 0.76 mm for baseline grade 1 and 0.63 ± 0.66 mm for baseline grade 2, *P* <0.001 for trend across the 3 categories, NS for grade 2 vs 1.[95]

- Joint space loss was correlated with baseline osteophytes (atlas) in one study. In a 2-year cohort, there was no association between baseline osteophyte grade and progression (joint loss >0.4 mm). However, there was a relationship in knees with satisfactory serial medial tibial plateau alignment (baseline femoral osteophyte score, par increase in grade, OR = 3.9, 95% CI = 1.1-13.3, baseline tibial osteophyte score, per increase in grade, OR = 2.4, 95% CI = 0.6-9.2).[77]

Malalignment

Two studies evaluated the relationship between malaignment and subsequent loss in metric measurement of joint space. In both, there was a relationship between the lower limb mechanical axis and subsequent joint space loss.

- In a prospective cohort, there was a moderate relationship between the 6-year joint space loss baseline mechanical axis (r = 0.41, *P* <0.001).[52] In an 18-months prospective cohort, there was a strong relationship between a greater varus alignment and a greater subsequent 18-month change in medial joint space (r = 0.52, 95% CI = 0.4-0.62), and a moderate relationship between a greater valgus alignment and a greater subsequent 18-month change in medial joint space (r = 0.35, 95% CI = 0.21-0.47).[96]

Demographic characteristics

- Age was not related to further joint space loss in nine studies. However, in one of these studies, the analysis restricted to knees with satisfactory serial medial plateau alignment demonstrated a trend toward a higher frequency of progression in subjects aged 60 or more (OR vs <60 = 3.0, 95% CI = 0.9-10.4).[77] The influence of satisfactory serial medial plateau alignment was evaluated in another article: age was not related to joint space loss in two cohorts, and was in a third one (r = 0.39, *P* = 0.02).[5]

- Gender was evaluated in five studies. There was no relationship in three. In a fourth study, there was no relationship in two cohorts, and joint space loss was higher in men in the third one (men: joint space loss = 0.92 ± 1.92, women: 0.09 ± 1.22, *P* = 0.0007). However, when restricted to knees with satisfactory medial tibial plateau alignment, there was no relationship between gender and joint space loss.[5] In a fifth study, female sex was associated with a more rapid loss, but only in patients with serial satisfactory medial tibial plateau alignment (OR for women vs men = 4.7, 95% CI = 1.4-15.4).[77]

- The BMI was evaluated in 11 studies. Eight did not find any correlation with joint space loss. Among these eight studies, there was a trend toward a relationship when analysis was restricted to patients with satisfactory serial medial tibial plateau alignment.). In a 2-year cohort, BMI was not related to further progression (decrease in joint space >0.4 mm) in the whole population, but there was a trend toward a relationship in patients with satisfactory serial medial tibial plateau alignment (OR for baseline BMI ≥ vs < 30 = 2.9 (95% CI = 0.4-21.0).[77] In another study, the relationship between baseline BMI and joint space loss increased when analysis was restricted to knees with satisfactory MTP alignment (r = 0.13, *P* = 0.1, vs r = 0.06, *P* = 0.51 when analysing all knees).[5] In a 4-year cohort, there was a weak correlation between joint space loss and baseline BMI (r = 0.260, 95% CI = 0.0084-0.419, *P* <0.005).[90] In a cohort with 6.6 years mean follow-up, BMI was not related to subsequent progression when defined as a joint space loss ≥1mm. However, when progression was defined as joint space loss ≥1.5 mm, there were 3.6% progressors in patients with baseline BMI ≤25; 7.5% in patients with BMI between 25 and 25.7 (OR = 2.3, 95%CI = 0.7-7.7), and 11.2% in patients with baseline BMI > 27.5 (OR vs ≤25 = 3.2, 95%CI = 1.1-9.7).[97] In a 2-year RCT, the baseline BMI significantly interacted with treatment, with the structural effect of treatment being more important in patients with higher BMI (*P* = 0.03).[98] Finally, in a 5-year cohort, the baseline weight/height ratio was predictive of progression (0.42 ± 0.08 in nonprogressors, 0.49 ± 0.08 in progressors, *P* = 0.0048).[81] However, a study on the same cohort did not find relationship between BMI and progression[87] with progression defined as decrease of JSW ≥2 mm in any compartment OR total knee replacement.

Others

Symptoms: see validity

- In a 6-year cohort, there was a strong correlation between 6-year joint space loss and knee adduction moment (r = 0.62, *P* <0.0001).[52]

- Bone scanning was related to joint space loss in three studies. In a 5-year cohort, a loss of joint space ≥2 mm was observed in 0 out of 55 knees with no scan abnormality and in 14 out of 65 knees with scan abnormality.[35] In a 30-month RCT, the medial tibial uptake was moderately related to 16 and 30 months JSN (r = 0.28 and 0.30). However, there was no more statistical correlation after controlling for age, BMI and KL. The 30-month JSN was more rapid in patients with Tc-MDP uptake in the medial tibia in the lower tertile = 0.10 ± 0.11 vs 0.46 ± 0.18 mm in the middle and upper tertiles (*P* = 0.045) but, again, the correlation disappeared after controlling for KL.[99] In the placebo group of the same RCT, a bone scan uptake in the middle and upper tertiles of the distribution predicted a joint space loss >0.5 mm with a 65% sensitivity and a 36% specificity (16 months), and a 74% sensitivity and 40% specificity (30 months).[51]

- Disease duration was not related to joint loss in three studies.[81,58,57]

- In a 5-year cohort, previous surgery and number of other joint sites involved were not related to further progression.[81]

- In two 1-year RCTs, the chondropathy score on arthroscopy were not related to further progression.[57]

- In a 4-year cohort, baseline bone mineral density was not related to joint space loss.[56]

- In a 2-year cohort, the presence of hand OA and the number of OA affected joint groups were not related to further progression (defined as joint space loss >0.4 mm). However, when analysis was restricted to knees with satisfactory medial tibial plateau alignment, there was a trend toward a relationship between further progression and hand OA (OR for presence vs absence of hand OA = 2.1, 95% CI = 0.4-11.1), and there was a relationship between progression and the number of sites affected (OR for OA joint sites, per increase in site = 3.1, 95% CI = 1.2-8.3).[77]

- In an 18-month cohort, there was no relationship between knee antero-posterior laxity and joint space loss.[100]

Summary fast and slow losers

Some biomarkers, in particular serum HA and urinary CTX-II, might be related with joint space loss. In the aim of selecting fast losers for inclusion in trials, thresholds with acceptable sensitivity and specificity need to be established. The relationship is more convincing with biomarkers longitudinal determination than with baseline biomarkers, which suggests that biomarkers might be of a greater relevance when used as a surrogate outcome than when used as an inclusion criterion to select fast losers.

A higher baseline joint space narrowing or a baseline KL 3 grade might be predictive of more rapid joint space loss. However, the results are conflicting and, for baseline joint space metric measurement, the most relevant threshold needs to be established.

Malalignment is strongly or moderately associated with joint loss. This relationship might be due to an increase in the knee adduction moment. However, since the adduction moment cannot be evaluated everywhere, malalignment might be a better criteria to select fast losers in trials.

There is no evidence that demographic data allow prediction of change in metric measurement of joint space. Female sex and high BMI might be predictors, in particular in subjects with a satisfactory serial tibial plateau alignment, but data are sparse and most studies did not find any relationship.

Two studies suggest that a joint uptake on bone scan is predictive of further joint loss. However, this relationship might be related to structural degradation.

Comments on predictors of joint loss:

- Data suggest that 1) semi-flexed or flexed views with fluoroscopy, and satisfactory serial tibial plateau alignment, enable better responsiveness to be obtained, 2) predictors of joint space loss are more easily discriminated in patients with satisfactory serial tibial plateau alignment. Most studies did not use semi-flexed or flexed views with fluoroscopy and did not separately evaluate patients with satisfactory serial tibial plateau alignment, leading to difficulties in the interpretation of the literature.

- Relevant thresholds of acceptable sensitivity and specificity are lacking. Moreover, it should be useful to define what constitutes an acceptable sensitivity and specificity (increasing specificity

with decreasing sensitivity would lead to a more powerful selection of fast losers, but would increase difficulties of inclusion, decreasing specificity with increasing sensitivity would lead to the opposite).

- There are no data to support the concept that inclusion of fast losers in trials is relevant: responsiveness would be increased, but data are needed on the effect of rate of joint space loss on treatment effect.

3.3 Hip

3.3.1 Objectives

To perform a systematic literature review regarding the psychometric properties (concurrent and predictive validity, reliability, responsiveness) of metric measurement of coxo-femoral joint space in hip OA.

3.3.2 Results

3.3.2.1 Concurrent validity

1) Cross-sectional relationship with symptoms

a) Correlations in the general population

- In a population-based study (3595 participants), the presence of hip pain was associated with minimal joint space (≤2.5 mm, OR = 2.4, 95% CI = 1.7-3.4, ≤2.0 mm, OR = 4.5, 95% CI = 2.9-7.0; ≤1.5mm, OR = 6.6, 95% CI = 3.6-12.2), as well as with the presence of morning stiffness (≤2.5 mm, OR = 1.6, 95% CI = 1.2-2.1, ≤2.0 mm, OR = 1.7, 95% CI = 1.2-2.6; ≤1.5 mm, OR = 2.0, 95% CI = 1.1-3.7), with the presence of moderate disability (≤2.5 mm, OR = 2.7, 95%CI = 2.0-3.7, ≤2.0 mm, OR = 3.7, 95% CI = 2.4-5.9; ≤1.5 mm, OR = 5.3, 95% CI = 2.9-9.8) and the presence of severe disability (≤2.5 mm, OR = 3.0, 95%CI = 2.0-4.4, ≤2.0 mm, OR = 4.1, 95% CI = 2.5-7.0; ≤1.5 mm, OR = 6.1, 95% CI = 3.1-12.1).[101]

- In a population-based study (3208 participants), a minimum joint space ≤2 mm was significantly associated with self-reported pain in or around the hip joint during the previous 12 months.[102]

- In a population-based study (women aged over 65), 46.5% of the 745 women with radiographic hip OA (936 hips) reported hip pain on most days for at least 1 month.[103]

b) **Correlations in subjects with hip pain**

- In a population of 195 patients presenting with new episodes of pain in primary care, 30% had a minimum joint space ≤2.5 mm, with 14% having a minimum joint space ≤1.5 mm. More severe OA was associated with a longer duration of hip pain (pain duration <3 months, 28% with ≤2.5 mm and 7% with minimal joint space ≤1.5 mm; pain duration = 3–12 months, 25% with ≤2.5 mm and 13% with minimal joint space ≤1.5 mm; pain duration >12 months, 43% with ≤2.5 mm and 26% with minimal joint space ≤1.5 mm, *P* = 0.02).[104]

- In a population of 220 patients consulting for hip pain, a pain duration ≥3 months (OR = 2.34, 95% CI = 1.26-4.32) and the presence of morning stiffness (OR = 2.0, 95%CI = 1.15-3.62) were associated with a minimal joint space ≤2.5 mm on univariate analysis. On multivariate analysis, pain duration ≥3 months showed an independent relationship. In the same population, the presence of morning stiffness (OR = 2.6, 95% CI = 1.12-6.06), but not pain duration ≥3 months, was associated with the presence of a minimal JS ≤1.5 mm. This relationship was not observed on multivariate analysis. The relationship between pain intensity and joint space was not evaluated.[105]

- In 735 subjects from a community-based cohort, categorical joint space width (cut-offs of 2.5, and 3.0 mm) was not related to pain, but a minimum joint space <2.5 mm was associated with functional impairment, categorized in quartiles (OR = 1.67, 95% CI = 1.0-2.78 compared to joint space >3 mm).[106]

c) Correlations in hip OA patients

- In a population of 41 hip OA patients seen prior to hip joint replacement, the functional impairment, as evaluated by the Lequesne's index, correlated with minimal joint space in the operated hip (r = -0.57, *P* <0.05) as well as in the contralateral hip (r= -0.70, *P* <0.05) and correlated with the sum joint space (lateral + superior + axial), in the operated hip (r = -0.63, *P* <0.05) as well as in the contralateral hip (r= -0.71, *P* <0.05).[107]

- In 508 patients included in a 3-year RCT, the baseline clinical parameters (pain, disability, patients' overall assessment), explained only 0.4% of the variability of the baseline radiological joint space width (*P* = 0.44).[108]

- In the same 3-year RCT, categorical joint space width (cut-offs of 1.5, 2.5, and 3.0 mm) was not related to pain or function.[106]

2) Longitudinal relationship with symptoms

- In 458 patients included in a 3-year RCT, a baseline Lequesne's index (0-24) >10 and more than 90% of painful days during the month preceding the entry visit were independent predictors of subsequent 1-year change in minimal joint space on multivariate analysis. These parameters, as well as other predictors (age at entry greater than 65 years, female gender, supero-lateral migration of the femoral head, unilateral hip OA, KL ≥3, greater mobility) explained only 15% of the variability of the change in joint space (P <0.0001). When defining radiological progression as a 1-year joint space loss of at least 0.6 mm, a Lequesne's index greater than 10 was an independent predictor of progression (OR = 2.66, 95%CI = 1.46-4.83).[108]

- In the same population, the level of clinical parameters (pain, disability, patients' overall assessment) and the amount of symptomatic treatment during the 1-year follow-up explained 20% of the 1-year changes in joint space (P <0.0001).[108]

- In a study of 745 women aged over 65 with radiographic hip OA (936 hips), followed for a mean of 8.3 years, the mean joint space loss was 0.50 ± 0.63 mm in those with baseline hip pain and 0.35 ± 0.55 in those without (P = 0.0345), and the percentages of progression (ie, of decrease in minimal joint space) ≥0.5 mm were 53.7% in hip with pain and 30.7% in hips without (OR for progression = 1.9, 95% CI = 1.4-2.6, P <0.001).[103]

- In a prospective cohort (1904 subjects with hip OA at baseline, defined as KL ≥1 with a mean follow-up of 6.6 years) the authors evaluated predictors of progression, defined as joint space loss ≥1.0 mm or total hip replacement. A radiological progression was observed in 13.1% of the subjects, among whom 35.8% had joint replacement. On multivariate analysis including clinical variables, a disability index score ≥0.5 (moderate disability, OR = 1.9, 95% CI = 1.4-2.6) and the presence of hip pain (OR = 2.6, 95% CI = 1.9-3.7) were predictors of progression. In the model including clinical and radiological variables, the presence of hip pain (OR = 2.4, 95% CI = 1.7-3.5) was a predictor of progression. In the 411 patients with hip pain, a disability index score ≥0.5 was a predictor of progression in the clinical (OR = 3.1, 95% CI = 1.7-5.9) but not in the clinical and radiological model.[109]

3) Summary

- The results suggested that, in the general population as well as in the general population with hip pain, there is an association between the presence of hip symptoms and of hip OA.

- In the hip OA population, the results were too sparse and heterogeneous to allow any conclusion.

- In the hip OA population, baseline joint symptoms are moderately correlated to further joint space loss.

- Comment. 1) Joint pain is influenced by numerous factors, including patient-related factors. A beautiful recent study showed that the relationship between pain and joint space is increased when the patients are their own controls, at least for the knee.[61] This might suggest that the above collected results on correlations between pain and joint space obtained from longitudinal data are more valid than those obtained from cross-sectional studies. 2) OA is a waning and waxing disease. Thus, again, the correlations between pain and joint space obtained from longitudinal data might be more valid than those obtained from cross-sectional studies. 3) Most studies did not adjust for the analgesic and non steroidal anti-inflammatory drugs consumptions, which might alter the associations, at least with pain.

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3.3.2.2 Predictive validity

1) Prediction of further pain and disability

In a 3-year RCT, the baseline minimal joint space, and the 1 year and 2 year changes in minimal joint space were associated with pain (P = 0.029, 0.0004, and <0.0001, respectively) and Lequesne's index (P = 0.004, <0.0001, and <0.0001, respectively) at 3 years on univariate analysis. The baseline minimal joint space, the 1-year and 2-year changes in minimal joint space were associated with the mean values of pain (P = 0.043, 0.0001, and 0.0001, respectively) and Lequesne's index (P = 0.006, <0.0001, and <0.0001, respectively) during the third year on univariate analysis. On multivariate analysis, baseline minimal joint space was not associated with pain and the Lequesne's index at 3 years, but the 1-year (P = 0.003 and <0.0001, respectively) and 2-year changes (P <0.0001 and <0.0001, respectively) in joint space were. Similar results were observed for mean pain and Lequesne's index during the third year (JF Maillefert and M Dougados personal communication).

2) Prediction of further joint space loss

- In a retrospective study of 69 osteoarthritic hips from a case registry of patients who had undergone total hip replacement for OA (mean radiological follow-up of 81.2 ± 59.9 months), the mean joint space at entry was not related to further annual joint space loss.[110]

- In a prospective cohort (1904 subjects with hip OA at baseline, defined as KL ≥1) with a mean follow-up of 6.6 years, the authors evaluated predictors of progression, defined as joint space loss ≥1.0 mm or total hip replacement. A radiological progression was observed in 13.1% of the subjects, among whom 35.8% had joint replacement. On multivariate analysis, a baseline minimal joint space ≤2.5 mm was a predictor of progression (OR = 1.9, 95% CI = 1.2-2.9). However, when the analysis was restricted to the 411 subjects with hip pain at baseline, joint space was no longer a predictor of progression (but KL grade ≥2 was, with an OR of 24.3).[109] In 458 patients included in a 3-year RCT, a baseline joint space <2.0 mm was an independent predictor of a further 0-1 year radiological progression, defined as a 1-year joint space loss of at least 0.6 mm (OR = 2.11, 95% CI = 1.30-3.44).[108]

3) Prediction of total hip joint replacement

- In a population-based study (3595 participants with a mean follow-up of 6.6 ± 0.5 years), a minimal joint space ≤2.5 mm was associated with further total hip replacement (left hip, positive predictive value = 15.4%, OR = 22.6, 95% CI = 11.8-43.0; right hip, positive predictive value = 17.2%, OR = 18.6, 95% CI = 10.7-32.3).[101]

- In a cohort of 195 patients with a new episode of hip pain, recruited by GPs, followed-up for a median duration of 36 months, the baseline minimal joint space was predictive of being put on a waiting list for joint replacement during the follow-up. Using a Cox regression model, the authors generated an overall 0-6 composite score for prediction of being put on a waiting list. In this score, the weight of minimal joint space measurement was 2 (joint space >2.5 mm = 0, joint space 1.5-2.5 mm = 1, joint space < 1.5 mm = 2).[111]

- In a cohort of 224 subjects aged > 50 years with hip pain, followed-up for a mean 2.7 ± 0.25 years (193 subjects) then 5.8 ± 0.3 years (163 subjects), a baseline joint space <2.5 mm was a predictor of further joint replacement on univariate (OR for further 3 years joint replacement = 6.6, *P* <0.01; OR for further 6 years joint replacement = 7.1, *P* <0.01), but not on multivariate analysis (in which KL ≥2 was predictor).[112]

- In 506 patients included in a 3-year RCT, a baseline minimal joint space width <2 mm was associated with a total hip replacement during the 3 following years (relative risk = 1.85, 95% CI = 1.18-2.90), and the first year change in minimal joint space was associated with total hip replacement during the 2 following years: the relative risk of being operated were 2.89; *P* <0.01 (no

worsening vs worsening <25%), 2.09, *P* = 0.07 (worsening < 25% vs worsening between 25 and 50%), and 5.3, *P* <0.0001 (worsening between 25% and 50% vs over 50%).[113]

- In 423 patients included in the same RCT, and followed-up for an additional 2 years, a decrease of minimal joint space of at least 0.2 mm during the first year predicted joint replacement during the 4 following years with sensitivity and specificity of 75% and 68%, and a decrease of at least 15% predicted further joint replacement with a sensibility and specificity of 74% and 78%. In 385 patients, a decrease of minimal joint space of at least 0.4 mm during the first 2 years predicted joint replacement during the 3 following years with sensitivity and specificity of 68% and 67%, and a decrease of at least 20% predicted further joint replacement with a sensitivity and specificity of 70% and 68%.[114]

- The patients included in the same 3-year RCT were followed up for 7 additional years. In multivariate analysis, including demographic characteristics, as well as baseline clinical and radiological parameters, the baseline joint space was predictive of joint replacement during the following 10 years (OR = 0.562, 95% CI = 0.424-0.746), the change in minimum joint space between baseline and 1 year was predictive of joint replacement during the following 9 years (OR = 0.198, 95% CI = 0.113-0.347), and the change in minimum joint space between baseline and 2 years was predictive of joint replacement during the following 8 years (OR = 0.231, 95% CI = 0.140-0.380). Using ROC curves, the baseline minimum joint space, the 1-year and 2-year changes in minimum joint space predicted further joint replacement with area under the curve of 0.687, 0.739, and 0.738, respectively (JF Maillefert and M Dougados personal communication).

3) Summary

- In our unpublished personal data, there was a strong association between 1- and 2-year changes in minimal joint space and further pain and disability in hip OA patients.

- The amount of joint space narrowing might be predictive of further joint space loss, but data are heterogeneous.

- The amount of joint space narrowing and the rate of joint space loss are predictive of further hip replacement.

- Comment: in surveys, surgeons usually state that they are weakly or moderately influenced by x-rays when deciding whether joint replacement is indicated or not.[67,68] However, it has been shown

that, in reality, the amount of JSN is a major predictive factor of the decision, at least for hip replacement.[69] Thus, the validity of prediction of joint replacement as an outcome to evaluate the predictive validity of joint space narrowing is questionable. On the other hand, the reasons why joint space influences the surgeons' decision remain unclear. If these reasons are differential diagnosis (some surgeons might consider that pain and functional impairment are certainly due to OA in patients with severe joint space narrowing, but might be due, at least in part, to another disease in those with mild joint narrowing), optional treatments (the surgeons might consider that an additional or complementary medical treatment is less likely to be efficient in patients with severe joint narrowing), and/or disease's potential evolution (OA is frequently a waxing and waning disease, and surgeons might consider that a spontaneous clinical improvement is less likely observed in patients with severe joint loss), joint replacement might be considered as a valid outcome.

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3.3.2.3 Reliability

Data were obtained from 12 studies, one of those providing results for 2 different radiographic techniques. The inter-reader intra-class coefficient of correlation (ICC) were available in only seven studies (mean sample size of 41) and the intra-reader ICCs in eight (mean sample size of 41).

Table 1. Summary of hip reliability measures from radiographs using random-effects pooling

Measure	Number of Studies	Mean Sample Size	Estimate	95% Confidence Interval
Intra-reader CV	2	8	4.52	1.66, 6.76
Inter-reader CV	2	35	2.98	1.71, 4.25
Intra-reader ICC	8	41	0.94	0.83, 1.00
Inter-reader ICC	8	41	0.88	0.80, 0.96

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3.3.2.4 Responsiveness

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1) Pooled changes and standardized response means

Data on minimal joint space were extracted from 12 articles (7 cohorts, 5 RCTs). In the RCTs, structural assessment analysis was performed as an intention to treat analysis in three, a completer analysis in two. Among the 12 studies, SRMs for change in minimal joint space width were available in 10. The mean sample size was 164. Results are shown in the following table.

Table 1. Summary of hip responsiveness from radiographs using random-effects pooling of the standardized response mean (SRM) of the minimum joint space narrowing

Analysis	Number of Studies	Mean Sample Size	SRM	95% Confidence Interval
Overall	11	164	0.66	0.41, 0.91
Study design				
RCT	4	111	0.35	0.12, 0.57
Cohort	7	194	0.83	0.49, 1.16
Analysis				
Completers	8	176	0.80	0.50, 1.10
ITT	3	132	0.30	0.06, 0.55
Measurement Technique				
Computer	4	40	1.12	0.64, 1.59
Manual	7	234	0.47	0.31, 0.62

- Did not perform an analysis by fluoroscopy because 10 of the 11 studies did not use that technique

2) Prediction of "slow and fast losers"

- This analysis was not performed, since a systematic review of the literature was published recently.[115] In this analysis, progression was associated with age, joint space width at entry, femoral head migration, femoral osteophytes, bony sclerosis, KL grade 3, baseline hip pain, and Lequesne's index score ≥10. Evidence was weak or inconclusive regarding associations between other radiographic or clinical features, biomarkers, and use of non steroidal anti-inflammatory drugs.

3.4 Hand

3.4.1 Objectives

3.4.2 Results

A total of 108 articles were selected. One reviewer (JFM) performed a full-text review, resulting in the inclusion of 50 articles.

The studies were very heterogeneous, in particular in the methods used to assess hand OA, which made it impossible to perform any pooled analysis. Thus, results will be briefly presented individually and then summarized. For more details, the reader can report to the tables.

Scoring methods for hand OA

Numerous different methods have been proposed to assess hand OA. The methods differ in the number and localisation of the scored joints, the scored radiographic features, the respective importance given to each individual feature and the way of scoring. Moreover, these methods have been used to assess individual hand joints, to assess groups of hand joints (usually using the highest individual joint grade of the group, sometimes the mean or the sum of individual joints grades), and to assess global hand OA, through total hand scores (ie, sum or mean of the individual joints grades). In this report, we will separate results on total hand scores (including number of OA joints) from other results.

The KL scoring system is a well known method. Joints are scored on a 0-4 scale: no OA, doubtful, minimal, moderate and severe.

The original KL system has been modified by several authors. The Framingham modified KL grading defines grades as follows: 0 = none, 1 = questionable osteophyte(s) and/or questionable JSN, 2 = definite small osteophyte(s) and/or mild JSN, 3 = definite moderate osteophyte(s) and/or moderate JSN of at least 50%, cysts and sclerosis may be present, 4 = large osteophytes and/or severe joint space narrowing, cysts or sclerosis may be present. In Dahaghin's modified KL, grade 3 takes only into account the presence of JSN.

The OARSI scoring system evaluates individual radiographic features (IRF) of each joint. Osteophytes and JSN are graded 0-3 according to an atlas.

In the method proposed by Lane, 0-2 summary grades are attributed to distal interphalangeal (DIP), proximal interphalangeal (PIP), thumb interphalangeal (IP), first carpometacarpal (1st CMC) joints (0 = normal, 1 = mild osteophytes and/or narrowing, 2 = moderate-severe osteophytes and/or moderate/severe narrowing), as well as to trapezoscaphoid (TS) joints (0 = normal, 1 = mild narrowing, 2 = moderate-severe narrowing). Five IRF can also be scored: osteophytes 0-3, JSN 0-3, sclerosis 0-1, cysts or

erosions 0-1, deformity 0-1. JSN is only graded 0-2 for IP and CMC, and TS is scored only for JSN 0-2 and sclerosis 0-1.

Other atlases for IRF scoring are available: Burnett, Spector, Thomas and modified (each joint scored for osteophytes 0-3, JSN 0-3, sclerosis 0-3, cysts 0-3, subchondral erosion 0-1, attrition 0-1, and remodelling 0-1).

The Kallman's system evaluates 22 joints: DIP, PIP, 1st CMC, TS. All joints are scored for osteophytes (0-3), JSN (0-3), subchondral bone sclerosis (0-1), subchondral bone cysts (0-1), lateral bony deviation(≥ 15¨, 0-1) and collapse of central joint cortical bone (0-1). The metacarpophalangeal (MCP) joints are not considered. First CMC and TS are not scored for collapse of cortical bone, and TS are not scored for osteophytes or lateral deformity.

The Verbruggen's anatomical phase progression system evaluates the 4 DIP, 4 PIP and 4 MCP of both hands, leading to 24 joints evaluated. Thumb joints are not considered. Scores are attributed to of each individual joint. Normal joint = 0, stationary = 1.2, joint space loss = 4.2, erosive = 6.8, remodelled = 7.8.

The Verbruggen's anatomical lesion progression system is a particular method, since it evaluates longitudinal changes. The evaluated joints are the 4 DIP, 4 PIP and 4 MCP of both hands, leading to 24 joints evaluated. Thumb joints are not considered. Scores are attributed to changes of each individual joint. Osteophytes: appearance = +1, disappearance = -1, increase in size = +0.5, decrease in size = -0.5; Joint space: narrowing = +1, widening = -1, subchondral cysts: appearance = +1, disappearance = -1, increase in size = +0.5, decrease in size = -0.5

Others methods have been occasionally used, and will be further described when necessary.

3.4.2.1 Concurrent validity

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The analysis included 26 manuscripts.

1) Correlation between hand pain and x-rays

a) Total hand scores (sum or mean)

- In a population-based study (3355 participants), the summed pain score (0-3 for all DIP, PIP and MCP, then sum of the scores) correlated with the radiological sum score (sum of the DIP, PIP and MCP KL scores) (r = 0.26, *P* = 0.0005).[116]

- In a population-based study (522 participants), the AUSCAN pain score was associated with DIP (r = 0.32, *P* <0.001) and CMC (r = 0.35, *P* <0.001) scores (DIP and CMC scores = sum of OARSI osteophyte and JSN scores of each joint). After adjustments for age, sex, Heberden's node score and other row score, the relationship was significant but low: r = 0.17 (*P* <0.003) for DIP and 0.14 (*P* <0.024) for CMC.[117]

- In a study evaluating 192 subjects, the AUSCAN pain score was associated with the osteophyte (r = 0.27*) and JSN (r = 0.26*) scores (osteophytes and JSN scores = sum of the OARSI osteophyte and JSN scores of DIP, PIP and 1st CMC).[118] (NB. Values were not provided in the article; data provided from communication with authors.)

- In the same study, the baseline pain was higher in patients with vs without JSN progression over 2 years (7.6 ± 4.9 vs 5.8 ± 4.5*, mean difference adjusted for age, gender and family effect = 1.8 points, 95% CI = 0.2-3.4). No such difference was seen for osteophyte score. The 2-year changes in pain score were not associated with progression of JSN or osteophyte scores (increase in at least 1 in the total score).[118]

- Another population-based study (1127 participants) did not observe any difference in the number of OA joints (KL ≥2 in DIP, PIP, MCP and wrist) between subjects with or without nocturnal joint pain.[119]

- A population-based study (3906 participants) observed a significant association between an increase in the number of joints with OA and pain (OR = 1.1, 95%CI = 1.1-1.2).[120]

b) Joint scoring without total score

i) Is the presence of radiographic hand OA associated with pain?

Presence or absence of pain

- A population-based study (3906 participants) observed a modest association between radiographic hand OA (defined by at least 1 joint with KL ≥2 in at least 2 out of the 3 following group joints: DIP, PIP, 1st CMC/TS) and the presence of hand pain: OR = 1.9, 95% CI = 1.5-2.4. In a multivariate analysis (including demographic characteristics but also other diseases such as rheumatoid

arthritis, stroke, Parkinson's disease, etc), positive radiographic OA was a poor predictor of hand pain ($r^2 = 0.005$).[121]

- Another study (3595 participants) observed a modest association between radiographic OA of any finger joint (KL ≥2) or symmetrical DIP OA (KL ≥2 in at least 2 DIP symmetrically) and the presence of pain (OR = 1.38, 95% CI = 1.14-1.67, and OR = 1.68, 95% CI = 1.34-2.10, respectively).[122]

- In a study of 67 subjects recruited in a geriatric institution, there was no significant difference in the proportion of those manifesting pain among those with OA (KL ≥2) and those without OA.[123]

- Another population-based study (1411 participants) observed an adjusted-relative risk of hand pain for those with radiological OA (at least 1 hand or wrist joint with KL ≥2 or at least 2 with KL ≥1) of 1.91 (95% CI = 1.52-2.41).[124]

Level of pain

A population-based study (592 participants) did not observe any significant difference in the level of pain (AUSCAN) between subjects with vs without radiographic hand OA (KL ≥2 in any DIP, PIP and 1st CMC): mean pain = 5.4 in subjects with no OA, 5.8 in subjects with thumb OA only, 5.7 in subjects with other fingers OA only, 6.5 in subjects with combined fingers and thumb OA, $P = 0.077$.[125]

ii) Is radiographic hand OA severity associated with pain?

Presence or absence of pain

- In a population-based study (3355 participants), a correlation was observed between the presence of self-reported pain of the thumb and radiographic evaluation of the 1st CMC joint (KL grading, JSN, osteophytes, cysts and sclerosis) $P < 0.001$). Self-reported pain was present in 15.7%, 24.4%, 40.2%, and 52.4% of patients with KL 0, 1, 2, 3, and 4, respectively. KL grading was associated with self-reported pain in a multivariate logistic regression analysis including age, sex and BMI: OR = 1.478, 95% CI = 1.325-1.649.[126]

- In a population-based study (543 women dentists or teachers), the adjusted (age and occupation) prevalence ratio of pain was 1.70 (95% CI = 1.44-2.01) in KL 2 OA DIP, PIP, and MCP, and 5.17 (95% CI = 4.34-6.16) in KL 3-4 OA, vs no OA.[116]

- In a population-based study (2292 participants), the prevalence of pain during the last week increased with the KL grading of DIP, PIP, MCP, CMC, wrists and hands (*P* <0.05 or 0.01 for all except for MCP in females).[127]

- In another population-based study (1411 participants), the prevalence of pain increased significantly with increasing levels of maximum grade of KL radiological OA: grade 0, 24%; grade 1, 31%; grade 2, 43%; grade 3, 46%,; and grade 4, 60% (*P* <0.0001).[124]

- Another population-based study (1041 participants) observed that pain among joints with KL 2, 3 or 4 in men and women was 1.4 and 2.0, 2.7, and 3.4, 5.0, and 4.3 times higher than among joints with KL <2.[128]

- In a population-based study evaluating 967 women, the prevalence of symptoms (had ever experienced pain or stiffness) in the interphalangeal joints (IP of thumb excluded) increased with KL grade: 15.2% in KL 0-1 joints, 48.7% in KL 2, 80.9% in KL 3-4 (*P* < 0.01), and the prevalence of pain of the 1st CMC joint (painful or have been painful in the past) increased with the KL grade: 10.6% in KL 0-1 joints, 34.2% in KL 2, 65.1% in KL 3-4, *P* <0.01.[129]

- In a study on 160 subjects from two population-based cohorts, there was a significant correlation between joint complaints (pain and stiffness) and radiographic OA grade (OA grade = the grade of the most severely affected hand joint): KL 1: 8% with joint complaints, KL 2: 12%, KL 3-4: 29%.[130]

- In a second article on the population in which a modest association was demonstrated between radiographic hand OA, defined by at least 1 joint with KL ≥2 in at least two out of three group joints (DIP, PIP, 1st CMC/TS) and presence of hand pain (Dahaghin, *Ann Rheum Dis.* 2005, p 99-104, see above), defining OA as KL ≥3 did not change the association (OR = 1.8, 95% CI = 1.3-2.5), but the association was stronger with the cut-off point of KL ≥4 (OR = 3.6, 95% CI = 2.2-5.8).[120]

Level of pain

- In a population-based study (543 women dentists or teachers), the intensity of pain was associated with DIP, PIP and MCP OA score: prevalence ratio of mild pain = 1.93 (95% CI = 1.54-2.41) for KL 2 OA and 4.92 (3.77-6.43) for KL 3-4 OA; prevalence ratio of at least moderate pain = 2.21 (95% CI = 1.58-3.10) for KL 2 OA and 11.73 (8.95-15.38) for KL 3-4 OA.[116]

- In a study on 40 women with hand OA (ACR criteria), the AUSCAN Pain score was related to the KL score of DIP, PIP, MCP, and CMC (r = 0.459, *P* = 0.003). The mean AUSCAN Pain scores (0-4) were 1.17 ± 0.52 in patients with KL 2, 1.60 ± 0.76 in KL 3, 1.91 ± 0.58 in KL 4 (*P* = 0.013 KL 2 vs 4, NS for KL 3 vs 2 and vs 4).[131]

- In a population-based study (3355 participants), the summed pain score (0-3 for all DIP, PIP, and MCP, then sum of the scores) correlated with the number of joints with KL ≥2 (r = 0.28, *P* = 0.0005).[126]

2) Correlation between hand disability and x-rays

a) Total hand scores (sum or mean)

- In a study evaluating 67 subjects, the sex-adjusted grip strength was related to the average KL grade of all joints (DIP, PIP, MCP, 1st CMC, wrists) and with the number of affected joints (KL ≥2) (*P* <0.001).[123]

- In the same study, there was a trend toward a relationship between the Jebsen test (time to perform 7 maneuvers such as writing and lifting) and the number of OA joints and severity of OA, but the mean time was not statistically different between those with and without hand OA (no other data).[123]

- In a study on 23 patients, the mean radiographic score (sum of KL grade of DIP, PIP, MCP, 1st CMC) was not correlated with a hand function index (sum of Z-scores of time to achieve 15 tasks + 10), nor with hand strength, and the number of joints with OA was correlated with upper extremity HAQ score (r not provided).[132]

- In a study evaluating 700 subjects with KL ≥2 in at least 1 DIP joint, the sum of KL grades of DIP, PIP, MCP, and CMC was correlated with a lower right hand grip strength and pinch strength (nonstandardized parameter estimates = -0.67 and -0.16, *P* <0.001 and <0.001) (similar results for left hand) in bivariate as well as in multivariate analysis controlling for demographic and clinical variables (*P* <0.05).[133]

- In a population-based study (522 participants), the AUSCAN function score was associated with DIP (r = 0.52, *P* <0.001) and CMC (r = 0.48, *P* <0.001) scores (DIP and CMC scores = sum of OARSI osteophyte and joint space narrowing scores of each joint). After adjustments for age, sex,

Heberden's node score and other row score, the relationship was significant but low: r = 0.15 (*P* <0.012) for DIP and 0.19 (*P* <0.001) for CMC.[117]

- In the same study, grip strength associated with DIP (r = - 0.53, *P* <0.001) and CMC (r = 0.48, *P* <0.001) scores. After adjustments for age, sex, Heberden's node score, and other row score, r = - 0.12 (*P* <0.012) for DIP and - 0.09 (*P* <0.01) for CMC.[117]

- In a study evaluating 192 subjects, the AUSCAN function score was associated with the osteophyte (r = 0.30*) and JSN (r = 0.20*) scores (osteophytes and JSN scores = sum of the OARSI osteophyte and JSN scores of DIP, PIP and 1st CMC).[118] (NB. Values not provided in the article, data obtained by communication with the authors).

- In the same study, the 2-year change in function score was not associated with progression of JSN or osteophyte scores (increase in at least 1 in the total score).[118]

- In a study evaluating 89 hand OA patients, there was no relationship between the Kallman's index total score and the Cochin disability index (Spearman r = 0.14).[134]

- In a further study by the same team on 116 hand OA patients, there was no statistically significant relationship between the Kallman score and the Cochin disability index (r = 0.199 in the whole population, 0.162 in the predominant thumb base pain and disability group, 0.347 in the predominant DIP and PIP pain and disability).[135]

- In a study evaluating 57 patients with nodular generalized OA, the total modified Thomas's radiographic score was related to dexterity (r = 0.28, *P* <0.02), buts not to light pinch, heavy pinch, tripod pinch, lateral grip and power grip. In 52 subjects with no hand symptoms and normal examination, the total radiographic score was related to time to complete for light and heavy pinch (r = 0.29 and 0.27, *P* <0.02 and 0.03), and the right thumb base score was related to dexterity (r = 0.35, *P* <0.006). In 10 patients with nodular generalized OA, there was no difference in summed radiographic score between those with or without pain, trick, difficulty or inability.[136]

- A population-based study (3906 participants) observed a modest association between the presence of hand disability (HAQ) and the number of joints of the dominant hand with OA (OR = 1.1, 95% = 1.0-1.2).[120]

b) Individual joint scoring without total score

i) Is the presence of radiographic hand OA associated with disability?

Presence or absence of disability

- A population-based study (3906 participants) observed a modest association between radiographic hand OA (defined by at least 1 joint with KL ≥2 in at least 2 out of the 3 following group joints: DIP, PIP, 1stCMC/TS) and the presence of HAQ: OR = 1.5, 95% CI = 1.1-2.1. In a multivariate analysis (including demographic characteristics but also other diseases such as rheumatoid arthritis, strokes, Parkinson's disease etc.), positive radiographic OA was a poor predictor of hand disability (r^2 = 0.000).[120]

- In another study (3595 participants), there was no association between 1st CMC OA and baseline overall disability (ordinary daily activities such as difficulty in moving about the house, getting in and out of bed, dressing and undressing, walking 400 m, carrying a shopping bag, etc) (adjusted OR = 0.80, 95% CI = 0.63-1.01).[137]

Level of disability

- A population-based study (592 participants) did not observe any significant difference in the level of disability (AUSCAN) between subjects with vs without radiographic hand OA (KL ≥2 in any DIP, PIP and 1st CMC): mean function score = 8.3 in subjects with no OA, 8.6 in subjects with thumb OA only, 8.2 in subjects with OA in fingers only, 10.5 in subjects with combined fingers and thumb OA, (*P* = 0.018, but not significant when adjusted for age and gender).[125]

- In a study evaluating 67 subjects, the right hand grip strength was 117.3 mm Hg in males with hand OA vs 140.5 without OA, 74.4 in females with hand OA vs 93.8 without OA. The left hand grip strength was 114.9 mm Hg in males with hand OA vs 127.3 without OA, 71.5 in females with hand OA vs 72.2 without OA, *P*-values not provided).[123]

ii) Is radiographic hand OA severity associated with disability?

- In a second article on the population in which a modest association was demonstrated between radiographic hand OA (defined by at least 1 joint with KL ≥2 in at least 2 out of the 3 following group joints: DIP, PIP, 1st CMC/TS) and presence of hand disability,[121] defining OA as KL ≥3 or as KL ≥4 did not change the association (OR = 1.6, 95% CI = 1.1-2.5, and OR = 1.6, 95% CI = 1.1-2.5).[120]

- In a study on 100 postmenopausal women with hand OA, the functional limitation (Dreiser's index), as well as the grip and pinch strength, increased with KL grade of OA: Dreiser's index = 6.6 ± 5.6 in

grade 4, 4.7 ± 4.8 in grade 3, 1.2 ± 1.4 in grade 2, *P* <0.05 grade 4 vs 2 and vs 3 and grade 3 vs 2; right grip strength = 13.5 ± 4.2 in grade 4, 19.8 ± 6.4 in grade 3 and 21.7 ± 4.9 in grade 2, *P* <0.05 grade 4 vs grade 2 and grade 3; right pinch strength = 3.9 ± 1.2 in grade 4, 6.56 ± 2.2 in grade 3, 6.6 ± 1.7 in grade 2, *P* < 0.05 grade 4 vs grade 2 and grade 3; similar results for left strength.[138]

- In a study on 40 women with hand OA (ACR criteria), the AUSCAN function score (r = 0.394, *P* = 0.012) and the grip strength (r = -0.322, *P* = 0.043, 36 patients right-handed and 1 ambidextrous) were related to the KL score of DIP, PIP, MCP and CMC. The mean AUSCAN function scores (0-4) were 1.36 ± 0.53 in patients with KL2, 1.86 ± 0.68 in KL3, 1.97 ± 0.70 in KL4, *P* = 0.026 KL 2 vs 4, NS for KL 3 vs 2 and vs 4. On the contrary, the left grip strength was not related to KL grade.[131]

3) Correlation between hand physical examination and x-rays

- In a study of 23 patients, the mean radiographic score (sum of KL grade of DIP, PIP, MCP, 1st CMC) correlated with the Clinical OA index (sum of the tenderness or pain on motion, osteophytes and crepitus (0-3) of all joints) (r = 0.53, *P* = 0.001) and with total range of motion score (sum of ROM scores of all finger joints) (r = 0.44, *P* = 0.008).[132]

- In a study of 40 women with hand OA (ACR criteria), the joint tenderness was not correlated with KL.[131]

- In a study evaluating 3595 subjects, there was an association between radiographic 1st CMC OA and the physical status of the carpometacarpal joint of the ipsilateral thumb, including restriction of movement, pain with movement, swelling and tenderness. Subjects with any of these findings had a threefold risk of having radiographic signs of OA (KL ≥2) in the right hand (OR = 3.29, 95% CI = 2.03-5.33) and a twofold risk in the left hand (OR = 2.16, 95%CI = 1.34-3.51).[137] In a study evaluating 541 women, the sensitivity and specificity of DIP bony swelling for DIP KL ≥2 were 49 and 90%, the sensitivity and specificity of DIP tenderness for KL ≥2 were 7% and 97, and the sensitivity and specificity of DIP pain on movement for KL ≥2 were 1% and 99%. Similar results were observed for PIP and CMC, except higher sensitivities of CMC swelling, tenderness and pain on movement (19%, 26%, and 22%).[139]

- In a population-based study (1127 participants), there was no difference in the number of OA joints in males with or without joint swelling, and there was an increased number of OA joints in women with vs without joint swelling (9.10 vs 3.91, *P* <0.005).[119]

- In a study evaluating 498 subjects with finger nodes, the OR of Heberden's node for underlying joint space narrowing and osteophytes (OARSI atlas) were 1.72 (95% CI = 1.47-2.02) and 5.15 (95% CI = 4.37-6.08), respectively. The OR of Bouchard's node for underlying joint space narrowing and osteophytes were 1.62 (95% CI = 1.37-1.91) and 2.98 (95% CI = 2.55-3.47), respectively.[140]

- In a study evaluating 6590 DIP, there was a modest agreement between the presence of Heberden's nodes and the presence of osteophytes: K = 0.36 (95% CI = 0.33-0.39).[141]

- In a study on 160 subjects from two population-based cohorts, the presence of clinical signs (nodular swelling or periarticular enlargement of DIP and PIP, palpable enlargement or instability in the IP1 and 1st MCP, palpable enlargement or squaring of 1st CMC) significantly increased with KL grading (= the grade of the most affected joint in each group) (P <0.01 for PIP and IP, P <0.001 for DIP, MCP 1 and 1st CMC).[130]

- Another study (3595 participants) observed a moderately increased prevalence of restriction in the flexion of fingers 2 to 4 (OR = 1.59; 95% CI = 1.08-2.34) and in the opposing movement of the thumb (OR = 1.42, 95% CI = 1.00-2.03) in OA of any finger joint (KL ≥2), but not in symmetrical DIP OA (KL ≥2 in at least 2 DIP symmetrically).[122]

- In a study evaluating 67 subjects, joint range of motion did not correlate with OA.[123]

4) Others

- In a study of 40 women with hand OA (ACR criteria), the AUSCAN stiffness score and the morning stiffness were not correlated with KL.[131]

- In a population-based study (1127 participants), there was no difference in the number of OA joints in males with or without morning stiffness, and there was an increased number of OA joints in women with vs without morning stiffness (7.11 vs 4.56, P <0.01).[119]

5) Concurrent validity: summary

The following conclusions can be reached from this analysis

- A weak relationship between the level of pain and total hand OA x-ray scores was observed (four positive and one negative studies).

- In the general or general geriatric population, there was a modest (three studies) or no association (one study) between the presence/absence of hand pain and the presence/absence of hand radiographic OA.

- In the general population, the prevalence of pain increased with radiological OA severity (eight studies).

- In the general population (one study) and in hand OA subjects (one study), the pain intensity was related to radiological OA severity.

- Baseline pain was higher in patients with subsequent 2-year JSN progression but not osteophytes (one study). On the contrary, the 2-year change in pain was not associated with the 2-year radiographic progression.

- The relationship between total hand radiological scores and disability scores were unclear, with three studies demonstrating no association, three a modest association, and two with heterogeneous results. On the contrary, a moderate or modest association was demonstrated with grip strength in three out of four studies. Similar results were obtained on the relationship between disability and radiological hand OA presence/absence and severity.

- In one study, the 2-years change in function score was not associated with the 2-year radiographic progression.

- The results on physical examination are difficult to summarize since they are heterogeneous and since some studies do not discriminate the different findings. Globally, physical examination seems to correlate with underlying radiological OA, but the sensitivity might be low. The results on range of motion and nodes are heterogeneous.

3.4.2.2 Predictive validity

[Click on hyperlink above to return to your place in the text, p 43.]

A study (3595 participants) did not find any association between 1st CMC OA and follow-up work disability over a period of up to 17 years (adjusted RR = 0.91, 95% CI = 0.61-1.38 for any 1st CMC OA; 1.47, 95% CI = 0.65-3.31 for 1st CMC grade 3 or 4 OA).[137]

No other data on predictive validity was found.

3.4.2.3 Reliability

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The analysis included 17 manuscripts. Reliability has been considered as low or moderate when the intraclass coefficient of correlation (ICC) or the Kappa (K) coefficient were <0.6, substantial when they were ≥0.6, and excellent when they were ≥0.8.

1) Total hand scores (sum or mean)

- There were only five studies evaluating the reliability of the measurement of total hand scores, including one study evaluating 4 grading systems on the same x-rays (Verbruggen's anatomical phase progression, Kallman, KL, and a global score) and one study evaluating 2 grading systems (Kallman and KL) on the same x-rays. The latter did not allow comparson of the 2 methods as one graded the joints and the others IRFs.

- The KL system (original or modified) was evaluated twice, as the mean score of DIP, PIP, 1st CMC, and TS joints[142] or as the sum score of DIP, PIP, MCP, and 1st CMC joints, normalised on a 0-100 score[143]. The intra and inter-reader reliabilities were found to be substantial in the first study (ICC = 0.80 and 0.74, respectively) and excellent in the second study (ICC = 0.988 and 0.991; 0.951, respectively).

- The OARSI grading was evaluated three times. Two studies by the same team assessed the intra-reader reliability of the sum of OARSI osteophytes and JSN grades of DIP, PIP, MCP, 1st CMC, TS (maximal score = 96 for osteophytes and for JSN) and of DIP, PIP, 1st CMC (maximal score = 60 for osteophytes and for JSN).[118,144] It must be pointed out that these results might come from the same evaluation. The third study evaluated the intra-reader reliability of the sum of OARSI osteophytes and JSN grades of DIP and 1st MCP.[117] Overall, the intra-reader reliability of osteophytes and JSN sum scores was excellent, with ICCs ranging from 0.92 to 0.98. The inter-reader reliability was not evaluated.

- The reliability of the Kallman system was evaluated for the mean score of all IRF of DIP, PIP, 1st CMC, and TS joints[142] and for a global score summing all IRF grades of DIP, PIP, MCP, and 1st CMC joints, normalized on a 0-100 score.[143] The intra-reader reliability of summed IRF was substantial or excellent, with ICCs ranging from 0.74 to 0.84. On the contrary, the inter-reader reliabilities were low to substantial, with low ICCs for some IRF (cysts 0.29, deformity 0.42, collapse 0.56) and good

ICCs for JSN and osteophytes (0.70 and 0.71, respectively). The intra-reader reliability of the normalised summed global score was excellent (ICCs = 0.962 and 0.999), while its inter-reader reliability was substantial (ICC = 0.706).

- The inter-reader agreement of a modified Kallman's IRF grading was found to be usually substantial to excellent, except for sclerosis and narrowing and erosions of CMC.[145]

- One study evaluated the Verbruggen's anatomical phase progression system (sum score of DIP, PIP and MCP, normalised on a 0-100 scale).[143].Both the intra (ICCs = 0.999 and 0.999) and inter-reader reliabilities (ICC = 0.996) were excellent.

- One study evaluated the reliability of a so-called "global scoring" in which the reader had to decide whether or not the joints were osteoarthritic (0-1), resulting in a 0-32 scale which was then normalised (0-100).[143] Both the intra (ICCs = 0.922 and 0.961) and inter-reader reliabilities (ICC = 0.859) were excellent.

- One study evaluated the intra and inter-reader reliability of a 0-2 average summary grade. Intra (ICCs = 0.86 for DIP and 0.81 for PIP) and inter-reader reliabilities (ICCs = 0.85 for DIP, 0.81 for PIP and 0.72 for CMC) were substantial to excellent. The long-term intra-reader reliabilities were also good to excellent.[145]

- In the same study, the interagreement for reliability of IRF scoring was also usually substantial to excellent, except for sclerosis and narrowing and erosions of CMC.

- In the study evaluating four systems on the same x-rays, the Verbruggen's scoring had the best and the Kallman's method the lowest inter-reader reliabilities. The intra-reader reliabilities were comparable, with a tendency for better ICCs for the Verbruggen's system and lower ICCs for the "global scoring", and possibly the Kallman's method (depending on the reader).[143]

a) Reliability of the measurement of change during time

Only one study evaluated the reliability of the measurement of change during time.[143] All methods (Verbruggen's, Kallman, KL and "global scoring") exhibited excellent intra (ICCs ranging from 0.939 to 0.998) and inter-reader (ICCs ranging from 0.995 to 0.999) reliabilities.

2) Individual joint scoring without total score

Kellgren & Lawrence (KL)

- The reliability of KL scoring of individual joints has been evaluated four times.[120,122,131,146]

- Two studies evaluated the intra-reader reliability of measurement of hand joints, which was substantial, with K values ranging from 0.71 to 0.82.[122,131] Both studies also evaluated the Inter-reader reliability of measurement of hand joints, which were moderate to substancial (K = 0.53 and 0.65).

- One study evaluated the intra-reader reliability of measurement of hand joint groups, which was excellent (K ≥0.8) for DIP, PIP, and CMC, except for one of the two readers on DIP (0.58).[146] Two studies evaluated the inter-reader reliability of measurement of hand joint groups, which tended to be lower than intra-reader reliability: K = 0.58 and 0.60 for DIP, 0.72 and 0.61 for PIP, 0.63 for MCP, 0.61 for CMC, 0.74 for 1st CMC + TS).[120,146]

Others

- The intra and inter-reader reliability of individual joints Kallman's osteophytes and JSN IRF scoring was found to be substantial or excellent for DIP, PIP, and CMC (except 1 reader intra for osteophytes DIP).[146]

- The intra and inter-reader reliability of individual DIP joints Burnett's osteophytes IRF scoring was found to be excellent (K = 0.80 for both).[141]

- The coefficients of correlations of inter-reader reliability of individual DIP and PIP joints IRF + sum scores (unknown atlas) ranged from 0.66 to 0.90.[147]

i) Reliability of classifying a joint as OA or not

Some studies did not evaluate the reliability of scoring, but the reliability of classifying joints as osteoarthritic or not. One used the Framingham's modified KL (OA = modified KL ≥2, no OA = modified KL <2). The intra-reader (K = 0.79 and 0.82) and inter-reader (K = 0.65) reliabilities were substantial to excellent.[148] The same study compared the classification obtained with the modified and the original KL and found a high K score of 0.83. In another study using the Altman's classification, the intra-reader reliability was substantial (K = 0.74).[149]

ii) Reliability of the measurement of change during time

Only one study evaluated the reliability of the measurement of change during time.[150] The intra and inter-reader reliability of individual joints Verbruggen's anatomical phase progression system and anatomical lesion progression system were substantial to excellent.

3) Summary

- Although the reliability of total hand scores has rarely been evaluated, it appears to be substantial, and frequently excellent. The inter-reader reliability of the Kallman's system might be lower than that observed with some other scores, but remains substantial.

- The reliability of different scoring methods of individual joints appears usually substantial to excellent. However, the inter-reader reliability of the most frequently evaluated method (ie, the KL method, is moderate or substantial according to the different studies).

- The reliability of the measurement of change during time has been evaluated in two studies. It was excellent for the four evaluated methods in the first study, and was substantial to excellent in the other study.

[Return-to-text hyperlink located at beginning of this section (3.4.2.3 Reliability) on p 150.]

3.4.2.4 Responsiveness

[Click on hyperlink above to return to your place in the text, p 38 (Responsiveness/Conventional Radiography/Hand).]

[Click here to return to your place in the text, p 45.]

The analysis included 17 manuscripts. The SRMs and effect-sizes (ES) were considered as small when <0.5, large when ≥0.8, and moderate between 0.5 and 0.8.

1) Change in score

Eleven manuscripts were analyzed. However, the SRM and/or the ES were not provided in all.

- Data on responsiveness of the Verbruggen's anatomical phase progression system could be obtained in four studies. In a 1-year RCT, the SRMs of the global score for hands were 0.18 and 0.27 (readers 1 and 2, respectively).[143] In a 5-year cohort, the ES were 0.34 for DIP (0.22 at 3 years), 0.44 for PIP (0.26 at 3 years), and 1.04 for MCM (0.09 at 3 years).[151] The annual magnitude of change were 0.794, 0.87, and 0.27 for DIP; 0.62, 0.47 and 0.41 for PIP; 0.49 and 0.13 for MCP (0-62.4 scale).[151,152,153]

- Data on responsiveness of the Verbruggen's anatomical lesion progression system could be obtained in two studies. In a 5-year cohort study, the SRMs were 1.03 and 1.38 (readers 1 and 2) for DIP, 0.90 and 1.28 (readers 1 and 2) for PIP, 0.55 and 0.64 (readers 1 and 2) for MCP.[151] The 3-year magnitude of change were 3.5 and 2.83 (reader 1) for DIP; 2.8 and 2.65 (reader 1) for PIP; 0.5 and 0.43 (reader 1) for MCP (scale from – 8 to + 8).[151,152]

- Data on responsiveness of the Kallman's system could be obtained in two studies. In a 1-year RCT, the SRMs of the global score for hands were 0.26 and 0.29 (readers 1 and 2, respectively).[143] In a 2-year follow-up cohort, the ES was 0.11 in erosive OA and 0.34 in nonerosive OA.[154] The 2-year magnitude of change was 5.0 (erosive OA) and 4.3 (non erosive OA) on a 0-300 scale.[154]

- Data on responsiveness of the sum of KL grading could be obtained in two studies. In a 1-year RCT, the SRMs of the global score for hands were 0.17 and 0.24 (readers 1 and 2, respectively).[143] In an 8-year follow-up cohort, the ES of the global sum score for hands were 0.52 in men and 0.48 in women (for DIP, PIP and MCP scores, see table).[155] The 8-year magnitude of change was 5.1 in men and 5.2 in women (0-32 scale).[155]

- Data on responsiveness of the sum of OARSI grading could be obtained in two studies. When the pairs of radiographs were read without knowledge of chronology, the SRM were 0.00 (JSN) and 0.39 (osteophyte). When they were read with knowledge of chronology, the SRM were 0.38 (JSN), and 0.41 (osteophyte).[156] In a 2-year follow-up cohort from the same authors, the SRMs were 0.34 for JSN (ES = 0.03) and 0.35 for osteophytes (ES = 0.05) (x-rays read without knowledge of the chronology).[118] On a 0-96 scale, the 2-year magnitudes of change were 0.00 and 0.25 (JSN and osteophytes read without knowledge of the chronology), 0.20 and 0.15 (JSN and osteophytes read with knowledge of the chronology).[156] On a 0-60 scale, the 2-year magnitudes of change were 0.3 and 0.4 (JSN and osteophytes).[118]

- Individual data were found in four other studies. In a 1-year RCT, the SRMs of a so-called "global scoring" (the reader decides whether or not the joints are osteoarthritic, resulting in a 0-32 scale which was then normalized on a 0-100 scale) the SRMs were 0.17 and 0.27 (readers 1 and 2, respectively).[143] In a 2-year RCT (naproxen vs naproxen + chondroitine sulphate), the SRM of the number of DIP and PIP joints with erosions was 2.14 in the naproxen group (ES = 2.57, mean annual change = 0.83).[157] In a 4-year cohort, the SRM of individual DIP and PIP joints IRF sum scores (unknown atlas) was 0.24.[147] In a 1-year cohort, the ES of measurement of the osteophytes

number and area of all radiocarpal, ulneocarpal, intracarpal, CMC, MCP, PIP, and DIP joints on microfocal radiography were 0.095 for osteophytes number and 0.083 for osteophytes area.[158]

- Finally, in the study evaluating four systems on the same x-rays, (Verbruggen's anatomical phase progression system, Kallman, KL and "global scoring), there was no significant difference between the SRMs of the different methods.[143]

2) Percentages of progressors

- Data were obtained from eight manuscripts. Most described data from long-term follow-up studies. Consequently there are limited data from cohorts of duration comparable to those of RCTs.

- Four of these studies used the KL system. In all, the definition of progression was an increase in the highest radiographic grade recorded. In a 10-year follow-up cohort, more than half of participants had progression on DIP (54.5 % men and 59.9 % women), around a third progressed on PIP (33.7 % men and 34.9 % women), less than half progressed on CMC (49.9 % men and 41.2 women), and few progressed on the radiocarpal joints (8.1% men and 1.2 % women).[159] Another long-term cohort (mean follow-up of 10 years, range 8-15) obtained comparable results, except for PIP (progression in 47% of hands for DIP, 50 % for PIP, 47 % for CMC).[146] In another long-term cohort (mean follow-up = 9.2 years, range = 5.0-16.3), the time to progression of DIP in 50% of the population was 11.75 years in subjects aged <40 years, 11.16 ± 1.25 in subjects aged 40-60, and 8.34 ± 0.51 in subjects aged >60, and the time to progression of PIP in 50% of the population = 12.26 ± 0.98 years in subjects aged <40 years, 12.13 ± 0.94 in subjects aged 40-60, and 10.01 ± 0.76 in subjects aged >60.[160] Finally, the percentage of hand OA patients who progressed after mean follow-ups of 2.3, 5.8, 9.5, and 13.4 years were 18.2, 31.6, 58.3, and 72.4 for DIP + thumb IP, and were 13.3, 21.1, 23.1 and 21.4 for PIP + 1st MCP.[161]

- The percentage of progressors using the OARSI atlas was provided in two studies by the same author. The definition of progression was different from that used in the KL studies: the 0-3 osteophyte scores and the 0-3 JSN scores of DIP, PIP, MCP, 1st CMC, and TS were summed, and progression was defined as an increase in at least one grade in osteophytes or JSN total scores of the different joint groups. In the first 2-year follow-up study on 20 patients, 5% of patients were progressors for JSN and 15% for osteophytes when radiographic pairs were read unaware of the chronology, while 15% of patients were progressors for JSN and 15% for osteophytes when radiographic pairs were read with knowledge of the chronology.[156] In the second 2-year follow-up

study, evaluating 172 subjects, a radiological progression was observed in 21.5% for osteophyte score and 19.2% for JSN score (reading unaware of the chronology).[118]

- In a long-term cohort (mean follow-up of 10 years, range 8-15), the percentage of progressors according to Kallman's osteophytes and JSN grades (progression = increase in the highest score of the evaluated DIP, PIP and CMC joints) were 39% (DIP), 39 % (PIP), 38% (CMC) for osteophytes, and 39% (DIP), 42% (PIP), 48% (CMC) for JSN. These percentages were comparable to those obtained in the same study using KL.[146]

- In an 11-year follow-up cohort, the Burnett's atlas was used to evaluate the percentage of progressors. DIP and CMC joints were evaluated for osteophytes (0-3 scale) and joint space narrowing (0-3 scale), and progression was defined as an increased grade ≥1 or a new grade 1 or more in an unaffected joint. In a cohort of 222 patients with baseline hand OA according to osteophytes, 72.5% had progressed after 11 years. In a cohort of 308 patients with baseline hand OA according to JSN, 64.0% had progressed after 11 years.[162]

- Finally, in a 67.3-month mean follow-up cohort, in which progression was defined as a definite increase in osteophytosis, joint space narrowing or increase in subchondral bone damage (sclerosis, cysts or erosion) of DIP, PIP, MCP, 1st CMC, wrist joint, and radio-ulnar joint, progression was observed in 3.8% of joints (1.2% of those with no baseline OA and 18.3% of those with baseline OA).[149]

3) Prediction of amount of change

Data were extracted from nine studies.

a) Age

- In a mean 10-year (8-15) follow-up cohort evaluating 59 patients (mean age at follow-up = 69), there was no difference in age between "minor" and "severe" progressors (severe progressors = patients belonging to the third tertile of the difference between the total of all KL grades of all DIP, PIP, and CMC joints).[146]

- In a cohort of 386 males with x-rays taken at least 5 years apart (mean follow-up = 9.2 years, range = 5.0-16.3), the DIP and the PIP time to progression of 50% of the population was lower in the subjects aged >60 than in those aged 40-60 and those aged <40. DIP time to progression of 50% of the population was 11.75 years in subjects aged <40 years, 11.16 ± 1.25 in subjects aged 40-60 (NS

vs younger), and 8.34 ± 0.51 in subjects aged >60 (P <0.01 and 0.02 vs youngs and middle-aged). PIP time to progression of 50% of the population was 12.26 ± 0.98 years in subjects aged <40 years, 12.13 ± 0.94 in subjects aged 40-60 (NS vs younger), and 10.01 ± 0.76 in subjects aged >60 (P <0.01 and 0.05 vs young and middle-aged). The time to increase in the number of DIP OA joints in 50% of the population was lower in olds vs young: 14.97 ± 0.52 years in youngs and 9.4 ± 0.91 in olds, P <0.01 for DIP; 15.73 ± 1.52 yrs in middle-aged and 9.4 ± 0.91 in olds, P <0.01 for PIP. Progression was defined as an increase in the KL grade of the most affected DIP and the most affected PIP joints.[160]

- In a community-based cohort of 23.5-year mean follow-up, the median time for 50% of the cohort to progress by 1 KL grade was 8.9 years in subjects ≥60 years-old, 12.4 years in subjects aged 40-60 and 15.8 years in subjects aged <40. Age increased the risk of progression of both osteophytes and JSN by 5% for each year of life (RR = 1.05, 95% CI = 1.03-1.07). Progression was defined as an increase of at least 1 grade of the most affected DIP and PIP joint.[163]

- In a 2-year prospective cohort (192 participants), middle-age (40-59 years) was associated with JSN and osteophyte progression with RRs of 1.2 (95% CI = 0.6-2.1) and 2.9 (95% CI = 1.0-3.2), compared to patients aged ≥60. In a separate analysis (117 women), women in a early postmenopausal stage (≤10 years) had increased frequency of osteophyte and JSN progression compared to women in a late postmenopausal stage (>10 years): RR for osteophyte progression in early vs late postmenopausal stage = 2.6 (95% CI = 1.0-4.6) for osteophytes and 3.2 (95% CI = 1.0-6.6) for JSN (author's communication, not provided in the article). Progression was defined as an increase of at least 1 in osteophyte summed score or at least 1 in JSN summed score (sum of OARSI osteophytes and of OARSI JSN scores for all DIP, PIP, and 1st CMC joints, range 0-60).[118]

b) Sex

- In a mean 10-year (8-15) follow-up cohort evaluating 59 patients (mean age at follow-up = 69), there was no difference in sex between "minor" and "severe" progressors (severe progressors = patients belonging to the third tertile of the difference between the total of all KL grades of all DIP, PIP, and CMC joints).[146]

- In a 2-year prospective cohort (192 participants), the RRs for osteophytes and for JSN progression were 2.9 (95% CI = 1.0-6.4) and 0.8 (95% CI = 0.3-1.5) in women compared to men. Progression was defined as an increase of at least 1 in osteophyte summed score or at least 1 in JSN summed

score (sum of OARSI osteophytes and of OARSI JSN scores for all DIP, PIP, and 1st CMC joints, range 0-60).[118]

- In a cohort study of 286 subjects with 2 PA radiographs of both hands 10 years apart, the percentages of participants with all joints with KL = 0 were as follows:
  - DIP. Baseline: 65.0% men, 68.7% women, 10 yrs: 21.4% men 14.3% women
  - PIP. Baseline: 81.1% men, 79.3% women, 10 yrs: 52.8% men 56.2% women
  - CMC. Baseline: 58.4% men, 63.0% women, 10 yrs: 27.7% men 39.2% women
  - Radiocarpal joints. Baseline: 85.8% men, 96.7% women, 10 yrs: 82.6% men 96.1% women

- In a study evaluating 263 subjects (127 males and 136 females) evaluated twice 8 years apart, the 8-year evolution of KL scores (sum of KL scores of each joints) were as follows (statistical significance not provided):
  - DIP score: 6.0 ± 5.6 to 8.0 ± 5.8 in men, 8.0 ± 6.0 to 10.1 ± 7.0 in women
  - PIP score: 3.2 ± 2.8 to 4.4 ± 3.1 in men, 4.2 ± 3.5 to 5.7 ± 3.8 in women
  - MCP score: 6.1 ± 2.7 to 7.9 ± 2.4 in men, 6.9 ± 2.6 to 8.0 ± 2.4 in women
  - Total hands score: 15.3 ± 9.8 to 20.4 ± 9.7 in men, 19.1 ± 10.8 to 24.3 ± 11.6 in women.[155]

c) Other demographic characteristics

In a mean 10-year (8-15) follow-up cohort evaluating 59 patients (mean age at follow-up = 69), there was no difference in BMI between "minor" and "severe" progressors (severe progressors = patients belonging to the third tertile of the difference between the total of all KL grades of all DIP, PIP and CMC joints).[146]

d) Baseline x-ray

In a community-based cohort of 23.5 years mean follow-up

- KL 2 (RR = 0.46, 95% CI = 0.27-0.90) and 3 (RR = 0.20, 95% CI = 0.05-0.90) were associated with a reduced risk of KL progression, in comparison with KL grade 1.

- Osteophytes grade 2 were associated with an increased risk of progression of joint space narrowing, compared to osteophytes grade 0 (RR = 3.62, 95% CI = 1.24-10.56).

- Sclerosis was associated with an increased risk of progression of joint space narrowing, compared to no sclerosis (RR = 4.37, 95% CI = 1.53-12.49).

- JSN grade 2 was associated with a reduced risk of joint space narrowing progression compared to JSN grade 1 (RR = 0.32, 95% CI = 0.12-0.84).
- Progression was defined as an increase of at least 1 grade of the most affected DIP and PIP joint.[163]

e) Bone scanning

- In 15 patients with clinical and radiographical hand OA assessed twice 4 years apart for PIP and DIP JSN, osteophytes, sclerosis, bone cysts, and subluxation (total score/joint ranging from 0 to 15), mean 4-year increase of joint score was 2.81 greater in joints showing an initial abnormal bone scan than in joints with normal bone scan (mean = 1.21 ± 2.52 vs 0.43 ± 1.5, P <0.002). When analysis was restricted to joints with OA at baseline, the mean 4-year increase of joints score was 3.62 greater in joints showing an initial abnormal bone scan (mean = 1.16 ± 2.65 vs 0.32 ± 1.99, P <0.01).[147]

- In a 2-year follow-up cohort of 45 patients with symptomatic hand OA (KL ≥2), an increase in the Kallman's score was observed in 21.09% of joints with baseline abnormal bone scan, vs 6.68% of those with normal bone scan (P <0.001).[154]

- In a 67.3-month mean follow-up cohort study evaluating 67 subjects, in which progression was defined as a definite increase in osteophytosis, joint space narrowing or increase in subchondral bone damage (sclerosis, cysts, or erosion) of DIP, PIP, MCP, 1st CMC, wrist joint, and radio-ulnar joint, progression occurred in 46/203 joints (22.7%) with hyperfixation vs 41/2075 (2.0%) without hyperfixation (P <0.0001).[149]

- Baseline bone scan was related to x-ray progression in a fourth study, evaluating14 patients with clinical and radiological features of generalized nodal OA. On the 140 joints with baseline OA, progression was observed in 30/81 (37%) with abnormal baseline bone scan, vs 8/59 (14%) of those with normal bone scan (follow-up between 3 and 5 years). On the 120 DIP and PIP with baseline OA, progression in 24/63 (38%) with abnormal baseline bone scan, vs 8/57 (14%) of those with normal bone scan.[33]

4) Summary

- The responsiveness of global hand OA scores, as evaluated by SRM or ES, was found to be low in most studies.

- Data on the percentages of progressors have mostly been evaluated on cohorts with a longer follow-up than that usually used in RCTs). With the most frequently used definition (increase of the highest KL grade recorded), 50-60% of progressors can be expected after 10 years. There is only one short-term study (mean 2.3 years) that used this definition. Only 18.2% of progressors for DIP + thumb IP, and 13.3% for PIP + 1st MCP were observed. Thus, it can be expected that a RCT of 2–3-year duration aiming at showing a reduction of the percentage of progressors would need to include a huge number of patients.

- There are only two studies, from the same team that used a global hand score to define progression. The 2-year percentages of progressors ranged from 5% to 21.5% for osteophytes and JSN (percentages of progressors defined as increase in osteophyte OR JSN scores not provided). Reading with knowledge of the chronology increased these percentages.

- Prediction of "fast losers": middle-aged and female subjects might progress faster but there are discrepancies in the data, which moreover are sparse, heterogeneous, and not adjusted for confounding variables. Surprisingly, there are very few data on baseline x-rays, which do not allow any conclusion. There are concordant data on the predictive value of bone scans. However, all studies evaluated joints rather than subjects. In addition, no adjustments for confounding variables were done.

Radiography Tables

CONCURRENT VALIDITY Knee

Table 1: Correlation between femorotibial joint space metric measurement and arthroscopic findings

First author	Study design	Inclusion	Exclusion	Number of patients	Characteristics of the patients	X-rays	Arthroscopy score	Results
Ayral J Rheumatol 1996	Cross-sectional	ACR clinical & radiological criteria Inadequate pain control justifying joint lavage	Contraindication to arthroscopy	110 (medial) 82 (lateral)	- Age = 62 ± 8 and 61 ± 11 yrs - 35.5 % males - BMI = 28 ± 4 and 29 ± 6 - Pain (100 mm VAS) = 50 ± 19 and 47 ± 22 - Lequesne's index = 9.3 ± 3.8 and 9.3 ± 4 - KL1 = 36.3 %, KL2 = 27.3 %, KL3 = 17.3 %, KL4 = 9.1 % - JSW = 4.1 ± 1.7 and 5.0 ± 2.1 *	- Bilateral weight bearing, knee fully extended - JSW measured in millimeters	- SFA score (0-100) for each compartment - SFA grade	- Medial JSW correlated to SFA medial score JSW (r = – 0.59, p < 0.01) and to SFA medial grading (r = - 0.48, p < 0.01) - Lateral JSW correlated to SFA lateral score (r = – 0.39, p < 0.01) and to SFA lateral grading (r = - 0.31, p < 0.01)
Ayral J Rheumatol 1996	Longitudinal (1 year) X-Rays and arthroscopy at baseline and 12 months	ACR clinical & radiological criteria Inadequate pain control justifying joint lavage	Contraindication to arthroscopy	41	- Age = 62 ± 8 yrs - 35.6 % males - BMI = 28 ± 4 - Pain (100 mm VAS) = 50 ± 19 - Lequesne's index = 9.3 ± 3.8 - KL1 = 14.6 %, KL2 = 46.3 %, KL3 = 26.8 %, KL4 = 12.2 %*	- Bilateral weight bearing, knee fully extended - JSW measured in millimeters (manual)	- SFA score (0-100) for each compartment - SFA grade - Examinator's overall assessment of chondropathy (0-100 VAS)	- Changes in medial JSW correlated with changes in arthroscopic overall assessment of medial chondropathy (r = 0.38, *P* = 0.02) and arthroscopic grading (r = 0.4, *P* = 0.01) - Changes in medial JSW not correlated to changes in medial arthroscopic score (r = 0.16, *P* = 0.35) - The 1-year arthroscopy evaluated

					- JSW = 4.1 ± 1.7			the medial compartment only
Dervin Clin J Sport Med 2001	Cross-sectional	ACR criteria Age 40-70 yrs Patients symptomatic despite medical management	Inflammatory or traumatic forms of OA	152	- Mean age = 60.5 ± 8.5 yrs - 49 % female - Mean WOMAC pain (0-50) = 24.5 ± 10.5	- Bilateral standing AP and 45° flexion weight-bearing PA without fluoroscopy - Min medial and lateral JSW	SFA grades	- Cut-off JSW = 2 mm - Sensitivity, specificity and accuracy for predicting severe grade IV medial chondropathy (46 patients) = 73, 82 and 78 % for standing AP view and 78, 76 and 77 % for 45° flexion PA view - Sensitivity, specificity and accuracy for predicting severe grade IV medial chondropathy (12 patients) = 42, 99 and 93 % for standing AP view and 83, 96 and 95 % for 45° flexion PA view.

* Some patients were evaluated longitudinally. The authors provide the characteristics of the these patients, and of those not evaluated longitudinally

* SFA: Société Française d'Arthroscopie

Table 2: Correlation between femorotibial joint space metric measurement and arthroscopic findings (2)

First author	Study design	Inclusion	Exclusion	Number of patients	Characteristics of the patients	X-rays	Arthroscopy score	Results
Rosenberg J Bone Joint Surg 1988	Cross-sectional	Patients operated, knee pain ≥ 6 months (53 arthroscopy, 2 total knee replacement)		55	Range 19-70 yrs	- Bilateral standing AP and 45° flexion PA without fluoroscopy - Medial and lateral JSW - Narrowing = difference with unaffected knee	Grades 0-4 0: normal 1:softening & blistering 2: superficial cartilage fibrillation, 3: ulceration involving the deep cartilage zones, 4: Cartilage erosion to subchondral bone	- Cut-off = major narrowing ≥ 2 mm - Sensitivity and specificity of major medial narrowing for grade 3 or 4 = 85.7 and 100 % (45° flexed view), 25 and 96.3 (extended AP) - Sensitivity and specificity of major lateral narrowing for grade 3 or 4 = 80 and 100 % (45° flexed view), 30 and 91.5 (extended AP) :

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Noyes & Stabler scoring system: 0 = normal, 1A = mild softening or discoloration of articular cartilage, 1B = severe softening or discoloration of articular cartilage, 2A = partial thickness defect less than 50 % of the total thickness of the articular cartilage, 2B = partial thickness defect greater than 50 % of the total thickness of the articular cartilage, 3A = full-thickness articular cartilage defect with normal subchondral bone, 3B = full-thickness articular cartilage defect with erosion of subchondral bone

Table 3: Correlation between joint space metric measurement and knee symptoms in the general population (1)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Oka Osteoarthritis Cartilage 2008	Cross-sectional study of subjects included in a nationwide OA cohort	Not provided	1979 knees (594 and 1385 with and without pain) from 1001 persons	- Mean age = 66.7 ± 10.1 (individual treatment) and 66.8 ± 7.5 yrs (group program) - Mean BMI = 229.7 ± 4.6 (individual), 29 ± 5.6 (program) - Mean WOMAC pain 100-0 = 60.7 ± 21 (individual), 62.7 ± 18.4 (group) - Mean WOMAC function 100-0 = 58.7 ± 21.1 (individual), 62.1 ± 19.7 (group). - Mean minimum medial and lateral JSW = 2.0 ± 1.4 and 5.1 ± 1.7 mm (individual), 2.1 ± 1.3 and 4.7 ± 2.0 mm (group).	Baseline weight-bearing semi-flexed radiograph of the most painful knee (obtained in 114 patients)	- Medial and lateral JS Area lower in knees with pain vs without (88 ± 24.4 and 105±.26.8 mm^2 vs 95.7 ± 26.1 and 110.2±.26.1 mm^2, $p < 0.0001$ and = 0.0013) - Medial and lateral minimal JSW lower in knees with pain vs without (2.9 ± 24.4* and 4.3 ±.0.24 mm vs 3.3 ± 44.9* and 4.4 ±.0.0 mm, $p < 0.0001$ and = 0.0013) - Multivariate analysis: female sex, tibiofemoral angle, JSW medial Area (OR = 1.16, 1.05-1.27) and minimal medial JSW OR = 1.66, 1.49-1.87) associated with the presence of pain * Error in the article?
Lanyon ARD 1998	Cross-sectional community study	Postal questionnaire survey, selection of patients with knee pain (= have you ever had pain in or around the knee on most days for at least a month?" and "if so, have you experienced any pain during the last year?" Sex and age match to subjects with no pain	239 with knee pain 213 without pain	No data	- Extended without fluorosopy - Minimal joint space of medial and lateral compartments in either knee	- OR for the presence of pain with 1mm as cut-off: medial non evaluable, lateral = 5.6, both = 19.3 - OR for the presence of pain with 2mm as cut-off: medial compartment = 29.8, lateral = 1.4, both = 5.5 - OR for the presence of pain with 3mm as cut-off: medial compartment = 5.5, lateral = 0.9, both = 2.1 - OR for the presence of pain with 4mm as cut-off: medial compartment = 2.0, lateral = 0.6, both = 1.5 - Most efficiencies between 50 and 56%

Spector Ann Rheum Dis 1993	Cross-sectional community study	Interview and examination of women aged 45-65, selected from a register of general practice in UK	977 women, 1954 knees	Not available	- Extended view without fluoroscopy -Assessment of medial and lateral minimal joint space width (ruler & computer)	- OR for association between knee pain and JSW bellow the 10th and 2nd percentile of the population - Medial JSW obtained with ruler: OR = 2.2 (1.35-3.59) (≤ 2 mm vs > 2mm) and 8.96(2.41-33.2) for knee pain (≤ 1 mm vs > 1mm) - Medial JSW obtained with computer: OR = 1.79 (1.30-2.48) (≤ 3.6 mm vs > 3.6 mm), and 2.94 (0.41-20.9) for knee pain (≤ 3 mm vs > 3mm) - Lateral JSW obtained with ruler: OR = 1.33 (0.9-1.95) (≤ 3 mm vs > 3 mm) and 1.77 (0.77-4.07) for knee pain (≤ 1 mm vs > 1mm) - Lateral JSW obtained with computer: OR = 1.34 (0.95-1.89) (≤ 4 mm vs > 4 mm) and 2.13 (1.03-4.38) for knee pain (≤ 2.4 mm vs > 2.4 mm)

Correlation between joint space metric measurement and knee symptoms in the general population (2)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Szebenyi Arthritis Rheum 2006	Cross-sectional	- Inclusion: patients identified from a population-based study, ACR clinical & radiological criteria for knee OA, self-reporter pain on most days in recent months and any evidence of OA in 1 or both knees - Exclusion: knee joint effusion	167 (344 knees)	- Mean age = 65.5 ± 19.8 yrs - 33 % males - Mean BMI = 30.2 ± 6.5 - 72 % with bilateral knee involvement	- Extended AP, minimal JSW of each compartment (0.5 graduated ruler - No JSN if ≥ 4 mm - Lateral 30° flexion views, JSN yes or no according to OARSI atlas	- Pain (VAS) and WOMAC function score are not higher in subjects with tibiofemoral joint space narrowing (either medial, lateral, or both) but without femoropatellar joint space narrowing, compared to subjects with no joint space narrowing - Increase in pain (VAS) and WOMAC function score in patients with tibiofemoral joint space narrowing (either medial, lateral, or both) and femoropatellar joint space narrowing, vs no joint space narrowing (*P* <0.01)
Gossec Osteoarthritis Cartilage 2008	Community-based cohort	Symptomatic and non symptomatic OA or no OA	735	- Mean age = 67.2 ± 9.5 yrs - 34.3 % males - Mean BMI = 30.4 ± 6.5 - Median WOMAC pain = 15 - Median WOMAC function = 19 - KL: 0-1: 62%, 2: 18%, 3-4: 20%	- Weight-bearing full –extended x-rays, - JSW categorized (cutt-of = 2.0, 3.5, and 5.0 mm	- WOMAC pain and function categorized in quartiles - WOMAC pain related to joint space: (x-ray grades 1 vs 0, NS; grade 2 vs 0 NS; grade 3 vs 0: OR = 4.06 (1.97-8.4). - WOMAC function related to joint space: (x-ray grades 1 vs 0, NS; grade 2 vs 0 NS; grade 3 vs 0: OR = 2.48 (1.25-4.92).

Table 4: Cross-sectional correlation between joint space metric measurement and symptoms in knee OA patients (1)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Fransen J Rheumatol 2001	RCT comparing a 8-week physical therapy individual treatment, format group program vs control	- Inclusion: age ≥ 50 yrs, knee pain on most days on the previous month, evidence of radiographic disease - Exclusion: intraarticular cortisone injection < 2 months, lower limb joint arthroplasty, unstable cardiac comorbidity precluding exercise at 50-60% maximum heart rate, other comorbidities affecting gait	126	- Mean age = 66.7 ± 10.1 (individual treatment) and 66.8 ± 7.5 yrs (group program) - Mean BMI = 229.7 ± 4.6 (individual), 29 ± 5.6 (program) - Mean WOMAC pain 100-0 = 60.7 ± 21 (individual), 62.7 ± 18.4 (group) - Mean WOMAC function 100-0 = 58.7 ± 21.1 (individual), 62.1 ± 19.7 (group). - Mean minimum medial and lateral JSW = 2.0 ± 1.4 and 5.1 ± 1.7 mm (individual), 2.1 ± 1.3 and 4.7 ± 2.0 mm (group).	Baseline weight-bearing semi-flexed radiograph (fluoro?) of the most painful knee (obtained in 114 patients)	- Median JSW = 1.9 mm - No difference in baseline pain, function QOL, and some gait parameters (stride length, velocity) between patients with JSW < or > 1.9
Creamer Rheumatology 2000	Cross-sectional	- Inclusion: outpatients with a diagnosis of knee OA made by their rheumatologist, ACR criteria, , current knee pain ≥ 2 on a 0-10 scale - Exclusion: total knee replacement, significant hip or spinal arthritis, major concurrent illness, inability to attend hospital	51	- Mean age = 65.8 ± 10.4 yrs - 30.4 % males - Mean WOMAC function = 42.1 ± 22.3 - KL: 1: 16.1%,: 2: 33.9%, 3: 33.9%, 4: 16.1%	- Evaluation of one knee/patient (the worse) - Minimal joint space, extended view (fluoro?)	No correlation between disability and minimal joint space measurement (r = 0.17, *P* = 0.24)
Gossec	1- 2-year RCT	1- ACR criteria,	Insole 144,	1- Mean age = 64.4 ± 11.7 yrs	- Insole weight-bearing full –	- WOMAC pain and function categorized in quartiles

Osteoarthritis Cartilage 2008	comparing lateral vs neutral insoles 2- 30-months RCT comparing doxycycline and placebo	pain > 30 after activity, pain at least 1 month during the last 3 months, predominant medial OA on x-rays 2- Subpopulation from the Doxy trial (see above Brandt 2005), x-rays evaluated by a different reader	Doxy 131 (extended) and 298 (semi-flexed)	- 27.8 % males - Mean BMI = 28.44 ± 5.1 - Median WOMAC pain = 52 - Median WOMAC function = 50 - KL: 0-1: 6%, 2: 59%, 3-4: 35% 2- Mean age = 54.3 ± 5.5 yrs - 0 % males - Mean BMI = 36.7 ± 5.1 - Median WOMAC pain = 40 - Median WOMAC function = 42 - KL: 0-1:5%, 2: 66%, 3-4: 29%	extended x-rays, - Doxy: weight-bearing full-extended and semi-flexed AP - JSW categorized (cutt-of = 2.0, 3.5, and 5.0 mm	- Insole study: categorized min JSW not related to WOMAC function but related to pain (x-ray grades 1 vs 0: OR = 2.78 (0.86-8.98), grade 2 vs 0: OR = 3.77 (1.13-12.5) - Doxy study: categorized min JSW not related to WOMAC pain and function, either in extended and SF views

Table 5: Cross-sectional correlation between joint space metric measurement and symptoms in knee OA patients (2)

First author	Study design	Inclusion	Exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Mazzuca Arthritis Rheum 2002	Prospective	- Age ≥ 45 yrs - Radiographic evidence of mild to moderate OA (KL 2 or 3) in 1 or both knees - Washout of NSAIDs and/or analgesics		15	- 27 seven knees with KL 2 or 3, 12 flaring knees (severe or extreme standing knee pain after the washout), 15 nonflaring knees (others)	- Bilateral standing fully extended AP view - Semiflexed AP views using fluoroscopy (each knee imaged separately) - Minimal medial JSW, manual measurement - X-ray after washout and 1-12 weeks (median 4.5) after resumption of therapy	- Mean change in JSW between repeated measurement, extended views 0.2 ± 0.06 (P < 0.005) in flaring knees - 0.04 ± 0.04 in non flaring knees (P = 0;0053 vs flaring knees) - Mean change in JSW between repeated measurement, semiflexed views 0.08 ± 0.05 in flaring knees 0.02 ± 0.05 in nonflaring knees (P = 0.08 vs flaring knees)

Table 6: Are baseline symptoms correlated with subsequent joint loss (metric measurement) in knee OA patients? (1)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Brandt Arthritis Rheum 2005	30-months RCT comparing doxycycline and placebo	Main inclusion: ACR criteria, obese women, 45-64 years, unilateral OA, KL 2 or 3 on one knee, 0 or 1 on the other knee Main exclusion: secondary OA, intraarticular corticosteroid injection < 3 months or hyaluronate < 6 months	431	- Mean age = 54.9 ± 5.6 yrs - 0% males - Mean BMI = 36.7 ± 6.2 - Mean WOMAC pain = 32.5 ± 18 in the former placebo group, 43.2 ± 16.8 - Mean WOMAC function = 45.1 ± 15.3 - Mean minimum medial JSW = 3.62 ± 1.17 mm	Semiflexed AP view with fluoroscopy Manual measure of medial minimum joint space	Correlation between the 16- and 30-months joint space N with baseline WOMAC pain (r = 0.221, p < 0.0001 for 16 months JSN, r = 0.13, p < 0.05 for 30 months) (author's personal communication)
Mazzuca J Rheumatol 2005	Ancillary study from a 30-months RCT comparing doxycycline and placebo	Main inclusion: ACR criteria, obese women, 45-64 years, unilateral OA, KL 2 or 3 on one knee, 0 or 1 on the other knee Main exclusion: secondary OA, intraarticular corticosteroid injection < 3 months or hyaluronate < 6 months	73 patients from the placebo group	Not available for the 73 patients of interest	Semiflexed AP view with fluoroscopy Manual measure of medial minimum joint space	-17 of 73 with 16-months JSN ≥ 0.5 mm, and 23 out of 70 with 16-months JSN ≥ 0.5 mm - Baseline WOMAC pain > 44 predicts further JSN ≥ 0.5 mm at 16 and 30 months with 77 and 65% sensitivity and 59 and 62 % specificity
Miyazaki Ann Rheum Dis	6-year prospective cohort	- Inclusion : patients with primary knee medial OA, more than 50 years, with pain at some daily activity	74	- Mean age = 69.5 ± 7.5 yrs - 21.6 % males - Mean BMI = 24.5 ± 3.3	Semiflexed AP with no fluoroscopy (x-ray beam determined using lateral x-	Significant correlation between 6-year JSL (1.4 ± 1.2) and baseline pain (r = - 0.37,*P* = 0.001)

2002		- Main exclusion: musculoskeletal disorders other than those affecting knees, history of knee trauma, RA, gout, pseudogout, infectious diseases		- Mean pain (0-30, worse to best) = 24.3 ± 4.7 - Mean and min medial JSW = 3.3 ± 1.1 - KL 1: 27%, 2: 29.7%, 3: 31.1, 4: 12.2%	rays) - Minimal medial JSW	

Table 7: Are baseline symptoms correlated with subsequent joint loss (metric measurement) in knee OA patients? (2)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Bruyere Scand J Rheumatol 2002	3-year RCT comparing glucosamine sulphate and placebo	- Main inclusion: ACR criteria, medial OA, age > 50 yrs, primary OA - Main exclusion: secondary OA, knee trauma, BMI > 30	212	- Mean age = 65.6 ± 7.7 yrs - 24 % males - Mean BMI = 27.4 ± 2.7 - Mean WOMAC pain = 36.6 ± 21 - Mean WOMAC function = 41.5 ± 21.6 - Mean mean and min medial JSW = 5.32 ± 1.33 and 3.89 ± 1.28 mm	- Standing fully extended AP with fluoroscopy - Minimal and mean medial JSW	- Baseline WOMAC function (r = 0.28, *P* = 0.02) and stiffness (r = 0.31, *P* = 0.008), but not pain (r = 0.18, *P* = 0.12) correlated to the 3-year changes in mean JSW NB: but (same author, O&C 2003), are not related in a multivariate analysis including baseline JSW in placebo as well as in treatment group
Michel Arthritis Rheum 2005	2-year RCT comparing chondroitine sulphate and placebo	- Main inclusion: 40-85 years, ACR criteria, pain on at least 25 out of the last 30 days, KL 1-3 - Main exclusion: KL 4, secondary OA, traumatic knee lesions, severe comorbidity, intraarticular medications < 1 month	300	- Mean age = 63.1 ± 10.7 (placebo) and 62.5 ± 9.1 yrs (chondroitine) - 52 (placebo) and 49 (chondroitine) % males - Mean BMI = 28.1 ± 5.5 (placebo), 27.2 ± 5.2 (chondroitine) - Mean WOMAC pain = 27 ± 18 (placebo), 25 ± 16 (chondroitine) - Mean WOMAC function = 25 ± 18 (placebo), 21 ± 16 (chondroitine). - Mean minimum and mean JSW = 2.35 ± 0.14 and 3.0 ± 0.15 mm (placebo), 2.41 ± 0.14 and 3.04 ± 0.14 mm (chondroitine).	- Partial flexion (20° PA view) without fluoroscopy - Minimal and mean JSW in the more affected compartment of the target knee	Baseline pain severity had no influence on radiographic progression, either in the placebo or the chondroitine sulphate groups
Gensburger	4-year longitudinal	- Patients with radiographic knee OA recruited in a	125 women	Not available	- Semi-flexed PA view	- In patients with medial OA at baseline, the WOMAC total score and the minimal joint space

Arthritis Rheum 2009	population-based cohort	longitudinal cohort evaluating the determinants of bone loss in women	with knee OA at baseline on x-rays (81 with medial knee OA)		with fluoroscopy - Minimal medial and lateral JSW	width were not predictive of the 4-year subsequent loss in joint space - In the whole knee OA population, the WOMAC total score was not predictive of further joint space loss, but the baseline minimal JSW was (r = 0.31 and 0.35 for the medial right and left medial compartment, p < 0.0001
Garnero Arthritis Rheum 2002	Two 1-year RCT (tenidap vs piroxicam, diacerein vs	Knee OA (ACR criteria), medial knee pain, pain ≥ 30 days in the last 2 months, , failure of prior treatment justifying arthroscopic lavage, minimal medial JSW ≥ 2 mm, medial compartment chondropathy at arthroscopy	75	Baseline: mean age = 63 ± 8, 32 % males, mean BMI = 29.5 ± 4.5, mean disease duration = 58 ± 62 months, mean pain (10 mm VAS) = 51.8 ± 17.5, mean Lequesne's index (0-24) = 8.8 ± 2.96, mean medial joint space = 3.98 ± 1.46 mm	- Extended AP view with fluoroscopy - Minimal medial JSW - Progression = 1-year decrease in medial JSW ≥ 0.5 mm	- 16 progressors and 36 non progressors - No significant difference between progressors and non progressors in pain (VAS), Lequesne's index.

Are baseline symptoms correlated with subsequent joint loss (metric measurement) in knee OA patients? (2)

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Sawitzke Arthritis Rheum 2008	24-months RCT (subpopulation from the GAIT trial)	- ≥ 40 years, knee pain ≥ 6 months, most days of the previous month, KL 2 or 3 - Knees with baseline medial JSW < 2 mm, predominant lateral OA, history of significant knee trauma or surgery excluded from the analysis	357 patients, 581 knees,	mean age = 56.9 ± 9.8, 36.4% males, 53.2 % with BMI > 30, KL2 = 76.9%, KL3 = 23.1%, mean baseline min medial JSW = 4.0 ± 0.96 mm	- Non fluoroscopy semi-flexed PA view - Measurement of minimum medial JSW, using computerized technique - Progressors = joint space loss > 0.48 mm	Baseline pain score did not predict joint space loss (no more detail)

Table 8: Are changes in joint space (metric measurement) and changes in symptoms correlated in knee OA patients?

First author	Study design	Inclusion & exclusion	N	Characteristics of the patients	X-rays	Results
Brandt Arthritis Rheum 2005	30-months RCT comparing doxycycline and placebo	Main inclusion: ACR criteria, obese women, 45-64 years, unilateral OA, KL 2 or 3 on one knee, 0 or 1 on the other knee Main exclusion: secondary OA, intraarticular corticosteroid injection < 3 months or hyaluronate < 6 months	431	- Mean age = 54.9 ± 5.6 yrs - 0% males - Mean BMI = 36.7 ± 6.2 - Mean WOMAC pain = 32.5 ± 18 in the former placebo group, 43.2 ± 16.8 - Mean WOMAC function = 45.1 ± 15.3 - Mean minimum medial JSW = 3.62 ± 1.17 mm	Semiflexed AP view with fluoroscopy Manual measure of medial minimum joint space	Rate of joint space narrowing over 30 months related to the percentage of semiannual assessment in which 50-foot walk pain was ≥ 20% more severe than that reported 6 months previously. No pain increase: 30-months JSN = 0.08 and 0.128, doxy and placebo groups; frequency of increases in pain = 20-39%: 30-months JSN = 0.144 and 0.148, doxy and placebo groups; frequency of increases in pain = 40-59%; 30-months JSN = 0.104 and 0.244, doxy and placebo groups; frequency of increases in pain = 60-100%: 30-months JLN = 0.212 and 0.312, doxy and placebo groups ($P < 0.05$, group 1 vs groups 2-4).
Bruyere Scand J Rheumatol 2002	3-year RCT comparing glucosamine sulphate and placebo	- Main inclusion: ACR criteria, medial OA, age > 50 yrs, primary OA - Main exclusion: secondary OA, knee trauma, BMI > 30	212	- Mean age = 65.6 ± 7.7 yrs - 24 % males - Mean BMI = 27.4 ± 2.7 - Mean WOMAC pain = 36.6 ± 21 - Mean WOMAC function = 41.5 ± 21.6 - Mean mean and min medial JSW = 5.32 ± 1.33 and 3.89 ± 1.28 mm	- Standing fully extended AP with fluoroscopy - Minimal and mean medial JSW	- In the placebo group, relationship between the 3-years joint space narrowing and 3-years changes in WOMAC pain (mean JSW, r = - 0.29, $P = 0.017$; min JSW, r = - 0.24, $P = 0.044$), but not with 3-years changes in WOMAC function (mean JSW, r = - 0.19, $P = 0.11$; min JSW, r = - 0.14 p = 0.31), and stiffness (mean JSW, r = - 0.22, $P = 0.06$; min JSW, r = - 0.05, $P = 0.67$)
Spector Arthritis Res Ther 2004	1-year RCT comparing risedronate 5 or 15 mg one daily vs placebo in	- Inclusion : ACR criteria, 40-80 years, JSW between 2 and 4 mm on semi-flexed views, pain at least on months during the 3 last months, JSW medial > lateral, at		- Mean age = 63.2 ± 8.1 (placebo), 62.9 ± 8.8 (rise 5mg), 63.8 ± 8.3 (rise 15 mg) - 35, 42 and 46 % males	- Semiflexed AP with fluoroscopy - Minimal medial	- The mean 1-year changes in total WOMAC, WOMAC pain and WOMAC function increased with increasing loss of joint space - Mean changes in WOMAC total, pain and function = -5.9, -4.6 and -6.3 in patients with any loss of JSW, the mean changes in

	knee OA	least 1 osteophyte Exclusion: disease that could be responsible of secondary OA, knee surgery history, knee injury, arthroscopy, hyaluronic acid < 6 months, intraarticular steroids < 3 months, non cause of knee pain, bisphosphonate use < 12 months		- Mean BMI = 29.2 ± 3.8, 29 ± 3.9, 29.2 ± 4 - Baseline minimal medial JSW = 3.03 ± 0.49, 2.95 ± 0.49, 3.01 ± 0.57	JSW	WOMAC, +1.4, +6 and +2.3 in patients with JSW loss of ≥ 40%
Jubb Int J Clin Pract 2003	1-year RCT comparing placebo and Hyalgan*	- Inclusion: primary medial knee OA, ACR criteria, KL 2 ou 3 - Exclusion: Valgus and varus deformity, other severe lower limb OA, other cause for knee pain	273	- Mean age = 65.6 ± 8.7 (placebo) and 64 ± 9.1 yrs (Hyalgan*) - 35.8 (placebo) and 28.7 (Hyalgan*) % males - Mean BMI = 30.1 ± 5.1 (placebo) and 29.3 ± 4.7 (Hyalgan*)	- Extended view without fluoroscopy -Assessment of medial JSW (were?)	No relationship between changes in pain (VAS) and changes in joint space width, in the subgroup with baseline JSW ≥ and < 4.6 mm

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Table 9: Predictive validity: is baseline joint space metric measurement predictive of the evolution of symptoms in knee OA patients?

First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Results
Fransen J Rheumatol 2001	RCT comparing a 8-week physical therapy individual treatment, format group program vs control	- Inclusion: age ≥ 50 yrs, knee pain on most days on the previous month, evidence of radiographic disease - Exclusion: intraarticular cortisone injection < 2 months, lower limb joint arthroplasty, unstable cardiac comorbidity precluding exercise at 50-60% maximum heart rate, other comorbidities affecting gait	126	- Mean age = 66.7 ± 10.1 (individual treatment) and 66.8 ± 7.5 yrs (group program) - Mean BMI = 229.7 ± 4.6 (individual), 29 ± 5.6 (program) - Mean WOMAC pain 100-0 = 60.7 ± 21 (individual), 62.7 ± 18.4 (group) - Mean WOMAC function 100-0 = 58.7 ± 21.1 (individual), 62.1 ± 19.7 (group). - Mean minimum medial and lateral JSW = 2.0 ± 1.4 and 5.1 ± 1.7 mm (individual), 2.1 ± 1.3 and 4.7 ± 2.0 mm (group).	Baseline weight-bearing semi-flexed radiograph (fluoro?) of the most painful knee (obtained in 114 patients)	- Median JSW = 1.9 mm - Patients with baseline JSW < 1.9 improved markedly less after treatment than patients with baseline JSW > 1.9 (mean change for pain, function, SF36 PCS and MCS = 5.63 and 11.0, 2.6 and 9.1, 1.4 and 4.5, 1.3 and 2.8
Bruyere Scand J Rheumatol 2002	3-year RCT comparing glucosamine sulphate and placebo	- Main inclusion: ACR criteria, medial OA, age > 50 yrs, primary OA - Main exclusion: secondary OA, knee trauma, BMI > 30	212	- Mean age = 65.6 ± 7.7 yrs - 24 % males - Mean BMI = 27.4 ± 2.7 - Mean WOMAC pain = 36.6 ± 21	- Standing fully extended AP with fluoroscopy - Minimal and mean medial JSW	- No correlation between baseline min and mean JSW and the 3-years changes in WOMAC scores (total and subscales) in the glucosamine and in the placebo groups

				- Mean WOMAC function = 41.5 ± 21.6 - Mean mean and min medial JSW = 5.32 ± 1.33 and 3.89 ± 1.28 mm		

Table 10: Predictive validity: joint space metric measurement for prediction of treatment efficacy in knee OA patients (1)

Prediction	First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Follow-up	Results
Efficacy of arthroscopic debridement in knee OA	Aaron J Bone Joint Surg 2006	Longitudinal cohort	- Inclusion: consecutive patients who underwent arthroscopic debridement for knee OA (ACR criteria), 18 to 70 years old, KL ≥ 2, failure of oral anti-inflammatory medications - Exclusion: previous septic arthritis of the knee, isolated patello-femoral OA, diagnosis other than OA, confounding diagnoses	110	-Mean age = 61.7 yrs - 32.7 % males - Mean BMI = 31.8 - Mean pain = 11.9 (0-50 best to worst Knee Society scoring system) - KL2: 53%, KL3: 29%, KL4: 18%	- Standing AP - Medial and lateral JSW	Mean follow-up = 34 months), range = 24-74)	- Post-hoc definition of arthroscopic success by post-operative pain score ≥ 30 and arthroscopic failure as post-operative pain score ≤ 20 - Baseline JSW ≤ 2 mm, particularly medial was associated with poorer post-operative pain score and higher likehood of treatment failure compared to baseline JSW ≥ 3 mm ($P < 0.001$) - Mean postoperative pain score = 14.7 ± 4.4 and 33.2 ± 1.9 in patients with baseline medial JSW ≤ 2 mm and ≥ 3 mm, respectively ($P = 0.0001$). - Treatment success in 5/16 (31%) knees with baseline JSW ≤ 2 mm vs 63/91 (69%) of knees with baseline JSW ≥ 3 mm.
Efficacy of physical therapy on symptoms	Fransen J Rheumatol 2001	RCT comparing a 8-week physical therapy individual treatment, format group program vs control (after	- Inclusion: age ≥ 50 yrs, knee pain on most days on the previous monthevidence of radiographic disease - Exclusion: intraarticular cortisone injection < 2 months, lower limb joint arthroplasty, unstable	126	- Mean age = 66.7 ± 10.1 (individual treatment) and 66.8 ± 7.5 yrs (group program) - Mean BMI = 229.7 ± 4.6 (individual), 29 ± 5.6 (program) - Mean WOMAC pain 100-0 = 60.7 ± 21 (individual), 62.7 ± 18.4 (group)	Baseline weight-bearing semi-flexed radiograph of the most painful knee (obtained in	8 weeks	- Median of minimum medial JSW = 1.9 - Subjects in the group with medial JSW < 1.9 (mean 0.9) were similar at baseline to subjects with medial JSW > 1.9 (mean = 3.2) in terms of pain, function, QOL, knee extensor muscle strength and gait parameters, but improved markedly

		8 weeks, controls were randomized to one treatment group	cardiac comorbidity precluding exercice at 50-60% maximum heart rate, other comorbidities affecting gait		- Mean WOMAC function 100-0 = 58.7 ± 21.1 (individual), 62.1 ± 19.7 (group). - Mean minimum medial and laterall JSW = 2.0 ± 1.4 and 5.1 ± 1.7 mm (individual), 2.1 ± 1.3 and 4.7 ± 2.0 mm (group).	114 patients)		less after treatment (mean change for pain, function, SF36 PCS and MCS = 5.63 and 11.0, 2.6 and 9.1, 1.4 and 4.5, 1.3 and 2.8

Predictive validity: joint space metric measurement for prediction of treatment efficacy in knee OA patients (2)

Prediction	First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Follow-up	Results
Efficacy of Glucosamine on symptoms	Bruyere, Scand J Rheumatol 2002	3-year RCT comparing glucosamine sulphate and placebo	- Inclusion: ACR criteria, medial OA, age > 50 yrs,primary OA - Exclusion: secondary OA, knee trauma, BMI > 30	212	-Mean age = 65.6 ± 7.7 yrs - 34 % males - Mean BMI = 27.4 ± 2.7 - Mean WOMAC pain and function = 36.6 ± 20.8 and 41.5 ± 21.6 - Mean minimal JSW = 3.89 ± 1.28 mm	- Standing fully extended AP with fluoroscopy - Minimal and mean medial JSW	3 years	- Changes in WOMAC total significantly different between glucosamine and placebo in patients in the lowest quartile of baseline mean JSW (< 4.5, p < 0.05) as well as those in the highest quartile (> 6.2 mm, p < 0.05).
Efficacy of Hyaluronate on structure	Jubb Int J Clin Pract 2003	RCT comparing the structural effects of intraarticular injections of hyaluronate and placebo	-Inclusion: primary knee OA (ACR critera), radiographic involvement of the medial femorotibial compartment KL 2 or 3 - Main exclusion: hip OA or other severe joint disease,	408 included, 273 evaluated in the primary analysis	- Mean age = 65.6 ± 8.7 (placebo) and 64.0 ± 9.1 yrs (hyaluronate) - 35.8 % (placebo) and 28.7 % (hyaluronate) males - Mean BMI = 30.1 ± 5.1	- AP weight-bearing of the index knee - Medial JSW using computer	1 year	- Interaction between baseline JSW and treatment (the outcome of treatment may depend on JSW) on primary analysis (*P* = 0.01) - 1-year joint space narrowing decreased in the hyaluronate vs placebo groups (0.13 vs 0.55 mm, *P*

			psoriasis, sacroiliitis, joint infection, other painful knee conditions, severe concurrent illness, clinically important valgus or varus deformity		(placebo), 29.3 ± 4.7 (hyaluronate) - Meanmedial JSW = 4.5 ± 1.6 (placebo), 4.9 ± 1.5 (hyaluronate).			= 0.02) In patients with baseline JSW ≥ 4.6 mm (median of the population) - No difference in 1-year joint space narrowing in patients with baseline JSW < 4.5 mm
Efficacy of chondroitine on structure	Michel Arthritis Rheum 2005	RCT comparing the effect of chondroitine sulphate and placebo	-Inclusion: age 40-85 years with clinically symptomatic knee OA for at least 25 out of the 30 last days, ACR criteria, KL 1, 2 or 3 - Main exclusion criteria: secondary OA, traumatic knee lesuions, severe comorbidities, previous knee surgery	300 (ITT analysis)	- Mean age = 62.5 ± 9.1 (chondroitine) and 63.1 ± 10.7 yrs (placebo) - 49 % (chondroitine) and 48 % (placebo) males - Mean BMI = 27.7 ± 5.2 (chondroitine), 28.1 ± 5.5 (placebo) - Mean minimum JSW = 2.41 ± 0.14 (chondroitine), 2.35 ± 0.14 (placebo) - Mean mean JSW = 3.04 ± 0.14 (chondroitine), 3.00 ± 0.15 (placebo).	- PA view with 20) flexion - Computer measure of min and mean JSW of the most severe affected compartment of the target knee	2 years	-No influence on structural progression of baseline mean JSW - In the placebo group, the changes in min and mean JSW were increased if the 75 patients with a baseline min JSW < 1 mm were removed (- 0.07 ± 0.56 vs - 0.14 ± 0.57 for min JSW, - 0.14 ± 0.61 vs - 0.20 ± 0.58 for mean JSW) - In the treatment group, removing patients with baseline min JSW < 1 did not change the results.

Table 11: Predictive validity: joint space metric measurement for prediction of arthroscopic changes in knee OA

First author	Study design	Prediction	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Arthroscopy score	Results
Ayral J Rheumatol 1996	Longitudinal (12 months)	12-months arthroscopic changes	- Inclusion ACR clinical & radiological criteria Inadequate pain control justifying joint lavage -Exclusion: Contraindication to arthroscopy	41	- Mean age = 62 ± 8 yrs - 35.6 % males - Mean BMI = 28 ± 4 - Mean pain (100 mm VAS) = 50 ± 19 - Mean Lequesne's index = 9.3 ± 3.8 - KL1 = 14.6 %, KL2 = 46.3 %, KL3 = 26.8 %, KL4 = 12.2 %* - Mean JSW = 4.1 ± 1.7	- Bilateral weight bearing, knee fully extended - JSW measured in millimeters	- Examinator's overall assessment of chondropathy (0-100 VAS)	- No correlation between baseline JSW and changes in arthroscopic findings - Baseline JSW = 4.3 ± 1.2, 4.9 ± 1.8 and 3.7 ± 1.5 in patient whose arthroscopy VAS improved (n = 5), remained stable (n = 13) and worsened (n = 23), respectively (*P* = 0.09)
Georges	Longitudinal (12 months)	12-months arthroscopic progression	Painful knee OA	40	- Mean age = 68 ± 20 yrs - 37 % males - Mean BMI = 27 ± 4 -- Mean pain (100 mm VAS) = 50 ± 19 - Mean Lequesne's index = 8.9 - Mean JSW = 3.9 ± 1.5	- Bilateral weight bearing, knee fully extended - JSW measured in millimeters	- SFA scoring system (0-100) - OA progression = score change > 4.5 (measurement error)	- 18/40 patients with progression - Mean baseline JSW = 3.1 ± 1.3 in further progressors vs 4 6 ± 1.7 in further non progressors (*P* = 0.002)

Table 12: Predictive validity: joint space metric measurement for prediction of knee joint surgery in knee OA patients (1)

Prediction	First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Follow-up	Results
Knee surgery: knee joint replacement and knee joint debridement/ meniscectomy	Bruyere Ann Rheum Dis 2005	Longitudinal cohort following a 3-year RCT	- Inclusion: patients who completed a 3-year randomized trial comparing glucosamine sulphate and placebo, ACR criteria, medial OA, age > 50 yrs,primary OA - Exclusion: secondary OA, knee trauma, BMI > 30	126	- Mean age = 64.7 ± 7 yrs - 30 % males - Mean BMI = 27.3 ± 2.8 - Mean mean medial JSW = 5.4 ± 1.3 mm - Mean min medial JSW = 4.0 ± 1.2 mm	- Standing fully extended AP with fluoroscopy - Minimal and mean medial JSW	- Median = 5 yrs - Mean = 3.8	- Knee surgery in 16 (12.7 %) patients (11 knee replacements and 5 joint debridement/menicectomies - The knee surgery was not always performed in the target knee of the original study(in over 60% only) + it is not clear whether only the JSW of the target knee or of both knees was/were included in the analysis - Mean JSN 0-3 yrs not predictive of further 5-yrs joint surgery (*P* = 0;51) - Min JSN 0-3 yrs predictive of further 5-years knee joint surgery (*P* = 0;006) - Best cut-off value: $\Delta = 0.7$ mm (RR = 5.15, efficiency = 79), but no meaningful differences for cut-off between 0.5 and 0.8 mm
Total knee replacement	Bruyere Osteoarthritis Cartilage 2008	Longitudinal cohort following two 3-year RCT	- Inclusion: patients who completed at least the first year of two 3-year randomized trial comparing glucosamine sulphate and placebo (including the one of the above line)	275	- Mean age = 63.6 ± 6.6 yrs in the former placebo group, 62.9 ± 7.6 yrs in the former active treatment group - Mean BMI = 26.6 ± 2.5 in the former placebo group, 26.6 ± 2.5 in the former active treatment	- Standing fully extended AP with fluoroscopy - Minimal medial	- Mean duration from the last clinic visit = 63 months in the former placebo group and 62 in the former active treatment group	- Total knee replacement in 28 (10.2 %) of the patients - JSN > 0.5 mm during the 3-yrs trial predictor of further total knee replacement (4/15, 26.7 % vs 9/118, 7.6 %, *P* = 0.019, RR = 3.5, 95% CI = 1.23-9.97)

					group - Mean WOMAC pain = 32.5 ± 18 in the former placebo group, 35.6 ± 18.6 in the former active treatment group - Mean WOMAC function = 35.0 ± 18.7 in the former placebo group, 38.8 ± 19.6 in the former active treatment group. - Mean minimum medial JSW = 3.83 ± 1.34 mm in the former placebo group, 3.89 ± 1.32 mm in the former active treatment group.	JSW		- It is not clear whether the joint replacement was always performed in the target knee of the original study ot not (regarding the data from the previous article, the response might be not + it is not clear whether only the JSW of the target knee or of both knees was/were included in the analysis

Predictive validity: joint space metric measurement for prediction of knee joint surgery in knee OA patients (2)

Prediction	First author	Study design	Inclusion & exclusion	Number of patients	Characteristics of the patients	X-rays	Follow-up	Results
Total knee replacement	Aaron J Bone Joint Surg 2006	Longitudinal cohortt	- Inclusion: consecutive patients who underwent arthroscopic debridement for knee OA (ACR criteria), 18 to 70 years old, KL ≥ 2, failure of oral anti-inflammatory medications - Exclusion: previous septic arthritis of the knee, isolated patello-femoral OA, diagnosis other than OA, confounding diagnoses	110	-Mean age = 61.7 yrs - 32.7 % males - Mean BMI = 31.8 - Mean pain = 11.9 (0-50 best to worst Knee Society scoring system) - KL2: 53%, KL3: 29%, KL4: 18%	- Standing AP - Medial and lateral JSW	Mean follow-up post surgery = 34 months (range = 24-74).	- Further knee replacement in 0/62 patients with post-operative pain score ≥ 30 and 17/38 (44.7 %) of those with post-operative pain score ≤ 20 - Post-operative pain score ≥ 30: 31 % if medial JSW ≤ 2 mm vs 69 % in knees with medial JSW ≥ 3 mm - No data on further joint replacement in patients with medial JSW ≥ 3 mm vs ≤ 2 mm but the data above suggest that it might

								have been different.
Total knee replacement	Cicuttini Osteoarthritis Cartilage 2005	Longitudinal cohort	- Inclusion: ≥ 40 yrs, ACR clinical and radiographic criteria for knee OA, radiographic evidence of OA with osteophytes present within the knee - Exclusion: other form of arthritis, contra-indication to MRI, planned knee replacement, unsatisfactory alignement of the medial tibiofemoral joint (anterior & posterior plateau surimposed > 1 mm) on baseline and follow-up x-rays	28	-Mean age = 62.8 ± 9.8 yrs - 43 % males - Mean BMI = 28.6 ± 5.1 - KL 1 10%, KL2 45%, KL3 45% - Mean annual joint space change = 0.24 ± 0.29 mm	- Standing weigth bearing radiograph, knee in full extension - Manual measure of minimal JSW of each knee - Baseline and 2 years later	Two evaluations separated by 2 years, 2 years follow-up after the second evaluation	- Knee replacement: 5/28 (17.9%) - No difference in baseline JSW between patients with or without joint replacement - No difference in 2-years changes in JSW between patients with or without joint replacement

[Click here to return to your place in the text, p 42 (Predictive Validity/Conventional Radiography/Knee).]

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Table 13: Responsiveness: X-ray technique (1)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Vignon Arthritis Rheum 2003	2 –year prospective cohort	ACR criteria, age > 50, knee pain > 6 months, at least 1 definite osteophyte, narrowing of the medial or lateral compartment	- 32 patients (58 knees), baseline mean age = 68.8 ± 8.8, 25 % males - Min baseline JSW = 3.55 ± 1.14 (AP views) and 2.92 ± 1.3 (schuss) mm - Mean baseline JSW = 4.2 ± 1.19 (AP views) and 3.47 ± 1.31 (schuss) mm - Mean baseline joint area = 72.2 ± 23 (AP) and 57.9 ± 22.4 (schuss) mm^2	Standing extended AP-view vs Lyon Schuss view	- Standing extended AP and schuss - Fluoroscopy for both -Computerized measurement of minimal and mean JSW, and joint area - Medial (52 knees) or lateral (6 knees)	- 2 years decrease in min JSW = 0.17 ±0.75 (AP views, NS, SRM = 0.23) and 0.24 ± 0.5 (schuss, *P* = 0.007, SRM = 0.48) mm - 2 years decrease in mean JSW = 0.14 ±0.78 (AP views, NS, SRM = 0.17) and 0.25 ± 0.55 (schuss, *P* = 0.009, SRM = 0.45) mm - 2 years decrease in joint area =2.5 ± 13.3 (AP views, NS, SRM = 0.18) and 3.8 ± 9.0 (schuss, *P* = 0.02, SRM = 0.42) mm^2 - Changes related to satisfactory paired medial tibial plateau alignment (< 1 mm) for schuss, but not extended AP views. Minimal JSW on schuss 0.27 (satisfactory) vs 0.11 (unsatisfactory), similar results for mean JSW and joint area
Piperno Osteoarthritis Cartilage 1995	1-year prospective study	- knee pain > 2 months, evidence of OA on x-ray (JSN and/or osteophytes)	- 10 patients (19 knees)	- Standing extended AP, schuss view	- Fluoroscopy only for schuss view -Computerized measure of medial min and mean JSW	- 1 year decrease in JSW (NB: which one?) = 0.17 ± 0.37 (AP views, NS, SRM = 0.47) and 0.41 ± 0.7 (schuss, p < 0.05, SRM = 0.58) mm
Hellio le Graverand, Ann Rheum Dis 2008	1-year prospective study	- Women > 40 years, BMI ≥ 30, KL 2 or 3, JSW > 2 mm on schuss view - Index knee = more painful, if identical, the one with most x-ray changes	- 62 OA patients, mean age = 57.2 ± 8, mean BMI = 36.9 ± 5.3, mean WOMAC pain score (0 to 20) = 6.3 ± 3.7	- Lyon schuss view vs fixed-flexion (FF)	- Lyon schuss and fixed-flexion (FF) - Fluoroscopy: only schuss - Computerized measurement of minimal medial JSW	- 1-year change in minimal median JSW * Schuss: decrease in mean JSW (0.22 ± 0.43, *P* = 0.0002, SRM = 0.51) * FF: increase in mean JSW (- 0.01 ± 0.46, *P* = 0.92, SRM = - 0.022) - Quality of medial plateau alignment (assessed by intermargin distance) better with Schuss (49 % with aired IMD ≥ 1 mm vs 14%) - FF: 1-year JSW change correlated with differences in IMD between baseline and follow-up x-ray

Mazzuca, Arthritis Rheum 2003	14-months prospective study	Age, ≥ 45, definite unilateral or bilateral knee OA (KL 2-3)	- 49 subjects (43 evaluated twice) - Mean age = 57.7 ± 5.4, 28.6% males, 53% with BMI ≥ 30, - 71 % with radiological bilateral OA - Analysis restricted to 75 knees with KL 2-3 and baseleline min JSW ≥ 1.5 mm	MTP (semi-flexed PA) without fluoroscopy vs semiflexed AP with fluoroscopy	Measure of min medial JSW, manually (MTP) or computerized (semi-flexed PA)	- MTP (without fluoroscopy): increase in mean minimal JSW in the 14-month vs baseline x-ray: + 0.09 ± 0.66 mm (*P* = 0.33) - Semi-flexed AP with fluoroscopy : decrease in mean minimal JSW in the 14-month vs baseline x-ray: - 0.09 ± 0.31 mm (*P* = 0.1)

Responsiveness: X-ray technique (2)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Mazzuca, Osteoarthritis cartilage 2008	1-year prospective study	Definite knee OA, women with BMI ≥ 30, symptomatic uni or bilateral knee OA	74 patients (74 knees), mean age = 58 ± 8, 0% males, mean BMI = 36.7 ± 5.5, KL2 = 45%, KL3 = 55%	Lyon-schuss or modified Lyon-schuss, vs Fixed-flexion (FF)	Fluoroscopy: schuss No fluoroscopy: modified schuss and FF	- 47 knees evaluated using schuss with fluoro and FF. Schuss: 1-year decrease of JSW (0.16 ± 0.37 mm, SRM = 0.43) vs FF: increase of JSW (-0.01 ± 0.51 mm, SRM = -0.02), *P* = 0.007 one technique vs the other - 27 knees evaluated using schuss without fluoro (actually, 12 with baseline schuss and follow-up modified schuss) and FF: Schuss: 1-year decrease of JSW (0.25 ± 0.54 mm, SRM = 0.46) vs FF: decrease of JSW (0.02 ± 0.4 mm, SRM = 0.05), *P* = 0.005 one technique vs the other
Pessis Osteoarthritis Cartilage 2003	1 year	ACR, Knee pain, indication for arthroscopic joint lavage, tibiofemoral JSW ≥ 2 mm	- 20 patients - Mean age = 63 ± 9 yrs - 35 % males - Mean BMI = 30 ± 9 - Mean VAS pain = 49 ± 16 - Mean WOMAC function = 50 ± 17.5 - 35% KL2, 65% KL3	Flexed PA vs extended views	Fluoroscopy in all - Manual measurement of minimal medial joint space	SRM minimal medial joint space, extended view = 0.1 SRM minimal medial joint space, PA flexed view = 0

Responsiveness: X-ray technique (3)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Conrozier Arthritis Rheum 2005	1-year prospective cohort	Age ≥ 40, knee pain ≥ 3 months	- 106 patients, including 73 with OA -- Mean age = 60.9 ± 11.7, mean min JSW in knee OA = 4.1 ± 1.1 mm	Quality of medial plateau alignment (intermargin distance IMD)	- Lyon schuss view - Fluoroscopy - Computerized measurement of minimal JSW and IMD	- Mean decrease in min JSW in knee OA = 0.19 ± 0.48 mm, SRM = 0.4 - If baseline and follow-up IMD are both ≤ 1.2 mm:, change in JSW = 0.34 ± 0.5 mm, SRM = 0.68 - If baseline and follow-up IMD are both > 1.2 mm:, change in JSW = 0.19 ± 0.49 mm, SRM = 0.39 - If one IMD is ≤ 1.2 mm and the other is > 1.2, change in JSW = 0.11 ± 0.48 mm, SRM = 0.23
Botha-Scheepers, Osteoarthritis Cartilage 2007	Prospective longitudinal cohort (GARP), 2-year follow-up	- Probands and siblings with OA at multiple sites - Sibling pairs with at least 1 subject with symptomatic hip or knee OA (not x-ray end stage)	126 knees of 92 patients with baseline KL ≥ 2	Medial tibial plateau (MTP) alignment evaluated by inter margin distance (IMD)	- Fixed-flexion PA with no fluoroscopy - Computerized-assisted semi-automatic measurement of minimal right and left medial JSW	- In OA knees with IMD accurately reproduced (difference between baseline and 24-months IMD ≤ 1 mm): (84% of knees): mean change in JSW = 0.21 ± 0.53 mm (SRM = 0.40) - In OA knees with serial satisfactory alignment (baseline and 24-months IMD ≤ 1 mm): (47% of knees): mean change in JSW = 0.29 ± 0.52 mm (SRM = 0.56)
Botha-Scheepers,	Prospective longitudinal cohort	- Same as above + exclusion of patients without	- 83 patients, median age= 59.6 (IQR: 55.3-66.6), 19.3 % males, median BMI = 26.4	- MTP alignment evaluated by IMD	- Fixed-flexion PA with no fluoroscopy	- Progression: 28.4 % of knees and 37.5% of knees with serial satisfactory MTP

Osteoarthritis Cartilage 2008	(GARP), 2-year follow-up	symptomatic knee OA (pain or stiffness on most days the previous month + osteophytes) in at least 1 knee	(IQR: 24.9-29.8) - 109 knees including 48.6% with a medial OARSI +JSN grade of 0	- others (see specific sections)	- Computerized semi-automatic measure of minimal right and left medial JSW - Progression = JSL > SDD (0.4 mm)	alignment (see definition above) - Others: see specific sections
Mazzuca, Arthritis Rheum 2001	Data from 3 longitudinal cohorts (mean follow-ups = 2.6, 3.0 and 2.3 years)	JSW > 0, KL ≥ 2	255 subjects from 3 cohorts, 402 knees analysed, mean ages = 72.2 ± 5.8, 63.3 ± 10.9, 70.7 ± 9.0, males = 39, 32 and 29 %, mean BMI = 30.4 ± 6.2, 27.9 ± 5.2, 29.4 ± 5.1, number of OA knees = 368, mean minimal joint space = 4.1 ± 1.6, 4.0 ± 1.8, 3.5 ± 2.1 mm	- MTP alignment evaluated by IMD (satisfactory if ≤ 1 mm)	-Standing extended AP - Manual measurement of minimal medial JSW	- Baseline and follow-up MTP alignment satisfactory in 60 knees out of 402 - Mean joint space loss = 0.67 ± 0.70 mm in knees with serial satisfactory MTP alignment vs 0.32 ± 1.32 mm in others (p= 0.004 for mean and 0.006 for SD)

Table 14: Responsiveness: Analysis of x-rays (1)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Vignon Arthritis Rheum 2003	2 –year prospective cohort	ACR criteria, age > 50, knee pain > 6 months, at least 1 definite osteophyte, narrowing of the medial or lateral compartment	- 32 patients (58 knees), baseline mean age = 68.8 ± 8.8, 25 % males - Min baseline JSW = 3.55 ± 1.14 (AP views) and 2.92 ± 1.3 (schuss) mm - Mean baseline JSW = 4.2 ± 1.19 (AP views) and 3.47 ± 1.31 (schuss) mm - Mean baseline joint area = 72.2 ± 23 (AP) and 57.9 ± 22.4 (schuss) mm^2	Minimum JSW vs mean JSW vs joint area	- Standing extended AP and schuss - Fluoroscopy for both -Computerized measurement of minimal and mean JSW, and joint area - Medial (52 knees) or lateral (6 knees)	- Schuss:2 years decrease: Min JSW 0.24 ± 0.5 mm , Mean JSW 0.25 ± 0.55 mm, joint area 3.8 ± 9.0 mm2 (*P* = 0.007, 0;009 and 0.02; SRM = 0.48, 0.45 and 0.42, respectively) - Extended AP 2 years decrease: Min JSW = 0.17 ±0.75 mm, Mean JSW = = 0.14 mm ±0.78, Joint area = 2.5 ± 13.3 mm2 (NS, NS and NS, SRM = 0.23, 0.17 and 0.18, respectively) -
Raynaud Ann Rheum Dis 2009	RCT (naproxen vs Licofelone	Medial primary OA, 40-80 yrs, pain for at least 50 % of the 2-month duration before baseline, KL 2 ou 3, JSW ≥ 2 mm, WOMAC pain ≥ 40, indication of NSAID	301 patients, mean age = 60.4 ± 8.6 and 60.3 ± 8.1, 29.3 and 35.1% males, mean BMI = 32.7 ± 6.4 and 31.2 ± 5.5	Minimal vs mean medial JSW	Schuss with fluoroscopy Computerized measurement of minimal and mean medial JSW	- Lincofelone: change in min JSW = 0.29 ± 0.49, SRM = 0.59 (lincofelone) and change in mean JSW = 0.35 ± 0.55, SRM = 0.64 - NSAID: change in min JSW = 0.38 ± 0.54, SRM = 0.7, and change in mean JSW = 0.39 ± 0.59 mm, SRM = 0.66

Responsiveness: Analysis of x-rays (2)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Reginster Lancet 2001	3-year RCT (glucosamine vs placebo)	- Main inclusion: ACR criteria, medial OA, age > 50 yrs, primary OA - Main exclusion: secondary OA, knee trauma, BMI > 30	212 patients, mean age = 65.6 ± 7.7 yrs, 24 % males, mean BMI = 27.4 ± 2.7, mean WOMAC pain = 36.6 ± 21, mean WOMAC function = 41.5 ± 21.6, mean mean and min medial JSW = 5.32 ± 1.33 and 3.89 ± 1.28 mm	Minimum (manual measure) vs mean (computerized measure)JSW	Extended AP, with fluoroscopy,	Placebo: mean minimal joint space loss = 0.4 ± 0.92, SRM = 0.43; mean mean joint space loss = 0.31 ± 0.84, SRM = 0.37 Glucosaine: mean minimal joint space loss = 0.07 ± 0.76, SRM = 0.09; mean mean joint space loss = 0.06 ± 0.81, SRM = 0.07
Uebelhart Osteoarthritis Cartilage 2004	1-year RCT (chondroitine vs placebo)	Age > 40, KL 1-3, JSW ≥ 25 % normal	120 patients, mean age = 63.7 ± 8.1 and 63.2 ± 9.1yrs, 20.3 and 17.9 % males, mean min medial JSW = 3.54 ± 1.39 and 3.65 ± 1.46 mm, mean mean JSW = 4.03 ± 1.47 and 4.2 ± 1.51 mm, mean joint area = 63.3 ± 24.4 and 68 ± 27.2 mm2	Minimum vs mean JSW vs joint area	Extended AP, with fluoroscopy, computerized analysis	- Placebo: change in min JSW = 0.32 ± 1.11, SRM = 0.29; change in mean JSW = 0.29 ± 1.09, SRM = 0.27; change in joint area = 4.55 ± 18.1, SRM = 0.25 - CS: change in min JSW = 0.04 ± 0.83, SRM = 0.048; change in mean JSW = 0.006 ± 0.85, SRM = 0.007; change in joint area = 0.19 ± 15.1, SRM = 0.013
Michel Arthritis Rheum 2005	2-year RCT(chondroitine vs placebo)	40-85 yrs, pain on at least 25 days during the last 30, KL 1-3	300 patients, mean age = 63.1 ± 10.7 and 62.5 ± 9.1yrs, 52 and 49 % males, mean BMI = 28.1 ± 5.5 and 27.2 ± 5.2	Minimum vs mean JSW	Semi-flexed PA, no fluoroscopy, computerized analysis	- Placebo: change in min JSW = 0.07 ± 0.56, SRM = 0.125 ; change in mean JSW = 0.14 ± 0.61, SRM = 0.23 - CS: change in min JSW = increase of +0.045 ± 0.48, SRM = - 0.09; change in mean JSW = 0 ± 0.53 mm, SRM = 0
Uebelhart Osteoarthritis Cartilage 1998	1-year RCT (chondroitine vs placebo)	Symptomatic knee OA, ≥ 25 % normal	26 patients, mean age = 60 ± 13 and 57 ± 11yrs, 38.7 and 43.5 % males, mean min medial JSW = 3.4 ± 1 and 4 ± 1 mm, mean mean JSW = 4.4 ± 1.1 and 5.1 ± 1 mm, mean joint area = 108	Minimum vs mean JSW vs joint area	Extended AP, without fluoroscopy, computarized analysis	- Placebo: change in min JSW = 0.4 (SD not provided); change in mean JSW = 0.5 (SD not provided); change in joint area = 12 mm2 (SD not provided)

			± 32 and 129 ± 28 mm2			- CS: change in min JSW = increase of 0.1, change in mean JSW = 0. mm, (SRM = 0); change in joint area = increase of 1 mm2

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PREDICTION OF "FAST" AND "SLOW" LOSERS

Table 15: Is it possible to predict the progression of metric measurement of joint space in knee OA? Biomarkers (1)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Sharif, Br J Rheumatol 1995	5-year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any other rheumatic disease.	81 patients	Baseline serum cartilage oligomeric matrix protein (COMP) (ELISA)	- Extended AP views - JSW (minimal? Midpoint?) of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	-66 patients available for progression: 23 progressors (13 due to surgery) and 40 non progressors: baseline COMP not related to progression - 57 patients available for progression and for 0-1 year change in COMP: 20 progressors and 37 non progressors: 0-1 year change in COMP related to progression: non progressors, mean decrease of 0.07 ± 4.99 μg/ml, progressors, mean increase of 6.42 ± 6.64 μg/ml, p < 0.001. - 0-1 year change remains higher in progressors after allowing for confounding variables (difference = 5.04, 95%CI = 2.61-7.46, p < 0.001) - Sensibility and specificity of 1 year increase in COMP to predict progression (cut-off = 3.17 0.07 ± 4.99 μg/ml) = 70 % (95%CI = 50-90%) and 78% (95%CI = 63-93%)
Sharif, Arthritis Rheum 1995	5-year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any	- 94 patients at baseline, 75 evaluated at 5 years - Baseline (n = 94): mean age = 64.2 ± 11.6, 30.9 % males,	Baseline serum hyaluronic acid and keratane sulphate (ELISA for both)	- Extended AP views + lateral. - JSW measured at the midpoint of each femorotibial	- Progression in 26 (34.7%) patients (11 joint replacement, 12 joint space loss ≥ 2 mm, 3 both) - Baseline serum hyaluronic acid level associated with age and JSW, and significantly higher in patients with vs without progression (*P* = 0.007).

		other rheumatic disease.	mean weight/height ratio = 0.44 ± 0.09 - mean JSW = 3.0 ± 3.0, 66 and 41% with medial and lateral compartment diseases		compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- Baseline keratane sulphate not related to disease progression. - Others: see specific sections - In multiple logistic regression, weight/height ratio, number of affected joints, baseline hyaluronic acid, but not baseline JSW, correlated with progression.
Sharif, Ann Rheum Dis 2000	8 year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any other rheumatic disease.	- 90 patients - Baseline: mean age = 65.2 ± 9.9, 39 % males, mean BMI = 27.7 ± 5.0 - Baseline KL: KL1 24.4%, KL2: 26.7%, KL3 30%, KL4: 18.9%	- All patients: baseline CRP and serum hyaluronic acid levels (ELISA) - 40 patients: CRP and serum hyaluronic acid level 3 years prior to baseline	- Extended AP views - JSW measured at the midpoint of medial femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- Progression in 38 (42.2%) patients - Baseline hyaluronic acid related to progression, trend toward a relationship between serum hyaluronic acid 3 years prior to baseline and progression - Sensitivity and specificity of – 3 years hyaluronic acid for progression (cut-off = 117.3 ng/ml) = 46 and 87%, sensitivity and specificity of baseline hyaluronic acid for progression (cut-off = 150.0 ng/ml) = 38 and 89% - CRP: see specific section

Is it possible to predict the progression of metric measurement of joint space in knee OA? Biomarkers (2)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Sharif Arthritis Rheum 2004	5-year longitudinal cohort	Knee pain > 3 months and radiographic evidence of OA Exclusion if KL4, other forms of joint disease and conditions preventing repeated attendance	- 135 patients, 115 with full data available - Baseline: mean age = 63.6 ± 9.7, 45.2 % males, mean BMI = 29.6 ± 5.2, baseline KL: KL0: 25%, KL1 12%, KL2: 7%, KL3 67%, KL4: 3%, minimal joint space = 3.2 ± 1.9 mm	Baseline and every 6 months serum cartilage oligomeric matrix protein (COMP) (ELISA)	- Baseliine and 5 yrs extended AP viewsl. - Minimal JSW of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- 37 progressors (22 surgery and joint space loss, 15 joint space loss alone) - Mean age and gender not related to progression - Mean baseline serum COMP increased in progressors vs non progressors (14.12 ± 3.39 vs 12.62 ± 3.25 U/l, *P* = 0.036) - 5-year AUC of serum COMP increased in progressors vs non progressors (12.52 ± 2.71 vs 10.82 ± 2.71 U:l, *P* <0.003)
Sharif Rheumatology 2007	5-year longitudinal cohort	Knee pain > 3 months and radiographic evidence of OA Exclusion if KL4, other forms of joint disease and conditions preventing repeated attendance	- 135 patients, 84 with full data available - Baseline: mean age = 62.4 ± 10.0, 46.4 % males, mean BMI = 30.0 ± 5.4 - Baseline KL: KL0: 13%, KL1 5%, KL2: 4%, KL3 77%, KL4: 19%, minimal joint space = 3.5 ± 1.9 mm	- Baseline and 2, 3 and 5 year serum N-propeptide of type IIA collagen (PIIANP) (ELISA) and urinary crosslinked C-telopeptide (CTX-II) (ELISA)	- Baseliine and 5 yrs extended AP viewsl. - Minimal JSW of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- 84 patients with complete data, 24 progressors (15 loss of JSW and 9 loss of JSW + surgery) - Mean baseline age, BMI, minimal JSW, gender, similar in both groups - Trend toward higher baseline serum PIIANP and urinary CTX-II in progressors - 5-years mean levels of PIIANP and CTX-II higher in progressors. Each SD increase of 5-year mean PIIANP associated with a relative risk of progression of 1.75 (95%CI = 1.02-3.01). Each SD increase of 5-year mean CTX-II associated with a relative risk of progression of 2.02 (95%CI = 1.20-3.41)
Sugiyama Ann Rheum Dis 2003	4-year longitudinal cohort	- Women aged 40-59 with early knee OA, ≥ 2 episodes of knee pain, lasting ≥ 2	- 110 women - Mean age = 50.2 ± 6.0, mean BMI = 24.7 ±	- Synovial procollagene II C propeptide	- Semiflexed PA with fluoroscopy - Minimal femorotibial	- Mean 4-year minimal JSW loss = 0.53 ± 0.43 - Significant correlation between joint space loss and baseline synovial PIICP (r = 0.440, 95% CI = 0.282-0.575, *P* <0.001)

		weeks, during the last year - Median osteophytes graded between 0 and 1, JSN graded as 0, no sclerosis, bony attrition or chondrocalcinosis in the tibiofemoral joint , no patellofemoral OA	3.3, mean minimal JSW = 3.4 ± 0.3 mm	(PIICP) - Baseline age, BMI, JSW, synovial volume	JSW	- Patients with baseline synovial PIICP ≥ 3.8 ng/ml had a rate of joint space loss twice as those with PIICP < 3.8 (1.04 ± 0.62 vs 0.50 ± 0.40, *P* = 0.001) - Others: see specific sections

Is it possible to predict the progression of metric measurement of joint space in knee OA? Biomarkers (3)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Vilm Osteoarthritis Cartilage 2005	Placebo arm of a 3-year RCT	Symptomatic primary knee OA, ACR criteria, KL = 1-3	- 48 patients - Baseline: mean age = 62.8, 29 % males, mean BMI = 28.4 ± 1.7 - Baseline KL: KL1 17%, KL2: 46%, KL3 37%	Serum cartilage oligomeric matrix protein (COMP) (ELISA)	- Extended AP - Signal knee = the worst on the basis of complaints and physical examination - Progression = decrease in JSW > 0.5 mm for either knee	- No correlation between baseline serum COMP and 3-year change in mean JSW - When summed for both knees, correlation between baseline serum COMP and 3-year change in mean JSW ($P < 0.01$) - 10 progressors and 38 non progressors. Baseline serum COMP higher in progressors (4.92 ± 1.05 vs 3.96 ± 0.94 μg/ml, p < 0.05)
Bruyere J Rheumatol 2003	3-year RCT (glucosamine vs placebo)	Knee OA (ACR criteria) Exclusion: other rheumatic diseases that could be responsible of secondary OA, severe artiicular inflammation, knee trauma, BMI > 30, intraarticular or sysremic corticosteroids < 3 months	- 212 patients - Baseline: mean age = 66.0 ± 7.3, 24 % males, mean BMI = 27.4 ± 2.9, mean minimal medial joint space = 3.89 ± 1.31 mm, mean mean medial joint space = 5.3 ± 1.31 mm	Serum keratan sulphate, hyaluronic acid (HA), osteocalcin, cartilage oligomeric matrix protein (COMP), urinary pyridinoline and deoxypyridinoline	- Extended AP with fluoroscopy - Minimal and mean medial joint space - - Progressors = decrease in joint space > 0.5 mm	- Baseline biomarkers not correlated with the percentage change observed in minimal and mean JSW - 1-year changes in osteocalcin and HA correlated with 3-year changes in mean JSW (r = -0.24, $P = 0.04$, and r = 0.27, $P = 0.02$) as well as minimal JSW (r = -0.31, $P = 0.01$, and r = 0.24, $P = 0.04$) - Stepwise analysis: 1-year change in HA is the only measure correlated with 3-year change in mean JSW ($P = 0.02$) while 1-year change in osteocalcin remained correlated with changes in minimal

						JSW (*P* = 0.004) - Relative risk to have a decrease in joint space > 0.5 mm = 3.8 (95%CI = 1.001-14.561) in patients in the first vs fourth quartiles of 1-year HA change - Relative risk to have a decrease in joint space > 0.5 mm = 0.632 (95%CI = 0.272-1.469) in patients in the first vs fourth quartiles of 1-year osteocalcin change
Deberg Osteoarthritis Cartilage 2005	Placebo arm of a 3-year RCT (same as Bruyere)	Primary clinical and radiological OA (ACR criteria) Exclusion: see Bruyere	- 75 patients - Baseline: mean age = 65.8 ± 7.3, 20 % males, mean BMI = 27.2 ± 2.8, mean mean medial joint space = 5.3 ± 1.32 mm	Urine type II collagene propeptide Coll 2-1 and Coll-1 NO2, pyridinoline, deoxypyridinoline	- Extended AP with fluoroscopy - Mean medial joint space - Progressors = decrease in joint space > 0.5 mm -No results for minimal JSW	- 3-year decrease in mean JSW = 0.31 ± 1.10 - No correlation between 3-year change in mean JSW and baseline biomarkers - Negative correlation between 3-year change in mean JSW and 0-1 year changes in Coll 2-1 (r = -0.31, *P* = 0.03) and Coll 261 NO2 (r = -0.31, *P* = 0.03). - 50 % progressors (6/12) in the fourth quartile of 0-1 year change in Coll 1-2 vs 27.3% (3/11) in the first quartile; 57.8 % progressors (7/13) in the fourth quartile of 1-year change in Coll 1-2 NO2 vs 18.2% (2/11) in the first quartile;

Is it possible to predict the progression of metric measurement of joint space in knee OA? Biomarkers (4)

First author	Study design	Inclusion & exclusion (main)	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Garnero Arthritis Rheum 2002	Two 1-year RCT (tenidap vs diacerein)	Knee OA (ACR criteria), medial knee pain, pain ≥ 30 days in the last 2 months, , failure of prior treatment justifying arthroscopic lavage, minimal medial JSW ≥ 2 mm, medial compartment chondropathy at arthroscopy	- 75 patients - Baseline: mean age = 63 ± 8, 32 % males, mean BMI = 29.5 ± 4.5, mean medial joint space = 3.98 ± 1.46 mm	Serum N-propeptide of type IIA procollagen (PIIANP), urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II)	- Extended AP view with fluoroscopy - Minimal medial JSW - Progression = 1-year decrease in medial JSW ≥ 0.5 mm	- Trend toward a relation between baseline PIIANP and urinary CTX-II and 1-year change in joint space (r = 0.29, *P* = 0.059, and r = - 0.27, *P* = 0.056). Uncoupling index (Z score CTX-II – Z score PIIANP) correlated with 1-year change in JSW (r = - 0.46, *P* = 0.0016) - Patients classified as having low or high baseline PIIANP and as having low or high urinary CTX-II using as cut-off the mean +/- 1 SD of what observed in controls - Patients with low baseline PIIANP had a higher 1-year joint space loss vs high baseline PIIANP - Patients with high baseline urinary CTX-II had a higher 1-year joint space loss vs low baseline CTX-II (non significant) - 16 progressors and 36 non progressors - Baseline serum PIIANP = 17.8 ± 5.7 mg/ml in progressors and 20.1 ± 5.4 in non progressors, *P* = 0.2 - Baseline urinary CTX-II = 819 ± 566 ng/mmole creatinine in progressors and 539 ± 259 in non progressors, *P* = 0.04, uncoupling index = 4.84 ± 2.50 in progressors, vs 2.45 ± 2.07 in non progressors (*P* = 0.0024) - Relative risk of progression in patients with baseline PIIANP ≤ mean-1SD of healthy controls and baseline CTX-II ≥ mean -1 SD of healthy controls = 2.9 (unsignificant) and 1.4 (95%CI = 0.4-5.0). Relative risk of progression in patients with baseline CTX-II ≥ mean -2 SD of healthy controls = 2.7 (significance?)
Garnero Osteoarthritis Cartilage 2007	2-year RCT comparing risedronate (5 mg/d, 15 mg/w, 35 mg/w, 50	- Knee OA (ACR criteria), pain > 1 month during the last 3 months, medial JSW between 2 and 4 mm + at least one of the following: crepitus, age > 50, morning	- 1885 patients - Baseline: mean age = 62.0 ± 8.56, 28 % males, mean	Urinary N-terminal crosslinking telopeptide of type I collagene (NTX-I) and	- Semiflexed PA with fluoroscopy - Minimal medial joint space	- 13 % with radiologic progression - Risedronate induced a dose dependent decrease in NTX-I and CTX-II - Logistic regression analysis: baseline and 0-6 months absolute and relative changes in CTX-II related to progression (*P* = 0.0003, 0.0049 and 0.0063) after adjustment for BMI,

	mg/w) and placebo	knee stiffness < 30 min - Main exclusion: secondary OA, non OA cause of knee pain, intraarticular steroids in the last 3 months, trauma, arthroscopy or hyaluronate in the last 6 months, index knee surgery	BMI = 29.9 ± 4.58, mean medial minimak joint space = 3.0 ± 0.60 mm	urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II)	- Index knee = the knee with the smallest JSW - Progression = 2-year change ≥ 0.6 mm	gender, pain, presence of hip OA, knee crepitus, treatment and baseline JSW - Low vs high levels of CTX-II (cut-off = 150 ng/mmole creatinine) at baseline and 6 months: mean decrease in JSW = 0.121 ± 0.51 (15% of progressors) in patients with high levels at baseline and 6 months (1152 patients), mean decrease in JSW = 0.088 ± 0.44 (11% of progressors) in patients with high levels at baseline and low levels at 6 months (372 patients), mean decrease in JSW = 0.108 ± 0.43 (13% of progressors) in patients with low levels at baseline and high levels at 6 months (120 patients), mean decrease in JSW = 0.041 ± 0.37 (6% of progressors) in patients with low levels at baseline and 6 months (241 patients). Relative risk for progression (high/high as reference) = 0.57 (95% CI = 0.39-0.85) for high/low levels, 0.77 (95% CI = 0.43-1.36) for low/high levels, 0.36 (95% CI = 0.21-0.63) for low/low levels,

Is it possible to predict the progression of metric measurement of joint space in knee OA? Biomarkers (5)

First author	Study design	Inclusion & exclusion (main)	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Reijman Arthritis Rheum 2004	Population-based cohort study with 6.6 years mean follow-up	- Subjects included in the population-based cohort, selected on the availability of baseline and follow-up x-rays as well as availability of baseline urine sample - Subjects had to be mobile enough to visit the research centre at baseline and follow-up	- 1,235 subjects including 237 with knee OA on x-rays (KL ≥ 2 in 1 or both knees) - Baseline: mean age = 66.6 ± 6.8, 41.6 % males, mean BMI = 26.3 ± 3.6	Urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II)	- Extended AP - Minimal JSW of medial and lateral compartments - Definitions of progression with cut-off of 1.0, 1.5 and 2.0 decrease in JSW in at least 1 compartment	- Progression defined as joint loss ≥ 1 mm: association of baseline CTX-II by quartile and progression (233 patients), first quartile used as reference: OR second quartile = 0.9 (95%CI = 0.6-1.5), OR third quartile = 1.1 (95%CI = 0.7-1.7), OR fourth quartile = 1.1 (95%CI = 0.7-1.7) - Progression defined as joint loss ≥ 1.5 mm (73 patients): first quartile used as reference: OR second quartile = 1.3 (95%CI = 0.6-2.9), OR third quartile = 1.5 (95%CI = 0.6-3.3), OR fourth quartile = 1.8 (95%CI = 0.8-4.1) - Progression defined as joint loss ≥ 2 mm (26 patients): first quartile used as

						reference: OR second quartile = 4.1 (95%CI = 0.8-20.5), OR third quartile = 4.5 (95%CI = 0.9-23), OR fourth quartile = 6.0 (95%CI = 1.2-30.8)
Gensburger, Arthritis Rheum 2009	4-year longitudinal population-based cohort	- Patients with radiographic knee OA recruited in a longitudinal cohort evaluating the determinants of bone loss in women	125 women with radiographic OA (81 with medial knee OA) (OARSI JSW + OARSI osteophyte score ≥ 2) at baseline	- Serum osteocalcin, PINP,CTX-I, urinary CTX-II and glucosyl-galactosyl-pyridinoline	- Semi-flexed PA view with fluoroscopy - Minimal medial and lateral JSW assessed by computer	No correlation between biomarkers and joint space loss, in patients with knee OA and in patients with medial knee OA
Pavelka, Osteoarthritis cartilage 2004	2-year prospective cohort	ACR criteria, symptomatic with reported pain during the last month, disease duration > 3 years	89 patients, baseline mean age = 56.7 ± 7.2, 33.7 % males, mean BMI = 28.6 ± 4.6, mean JSW = 4.95 ± 1.46 mm	Serum MMP-9 and 13, tissue inhibitor of metalloproteases (TIMP), cartilage oligomeric matrix protein (COMP), pentosidine, hyaluronic acid, YKL40	Extended PA, manual measurement of minimal medial JSW	- Correlation between baseline serum hyaluronic acid and 2-year JSN (r = 0.56, *P* <0.005) - Correlation between baseline pentosidine levels and 2-year JSN (r = 0.34, *P* = 0.005) - No other correlations

Table 16: Is it possible to predict the progression of metric measurement of joint space in knee OA? Inflammation

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Sharif, Ann Rheum Dis 2000	5—8-year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any other rheumatic disease.	- 90 patients - Baseline: mean age = 65.2 ± 9.9, 39 % males, mean BMI = 27.7 ± 5.0 - Baseline KL: KL1 24.4%, KL2: 26.7%, KL3 30%, KL4: 18.9%	- All patients: baseline CRP and serum hyaluronic acid levels (ELISA) - 40 patients: CRP and serum hyaluronic acid level 3 years prior to baseline	- Extended AP views + lateral. - JSW measured at the midpoint of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- Progression in 38 (42.2%) patients - Baseline CRP not related to progression, but CRP 3 years prior to baseline related to progression - Sensitivity and specificity of – 3 years CRP for progression (cut-off = 9.65 mg/l) = 38 and 85% - Hyaluronic acid: see biomarkers

Table 17: Is it possible to predict the progression of metric measurement of joint space in knee OA? Baseline knee x-rays (1)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Botha-Scheepers, Osteoarthritis Cartilage 2008	Prospective longitudinal cohort (GARP), 2-year follow-up	- Same as above + exclusion of patients without symptomatic knee OA (pain or stiffness on most days the previous month + osteophytes) in at least 1 knee at baseline	- 83 patients, median age= 59.6 (IQR: 55.3-66.6), 19.3% males, median BMI = 26.4 (IQR: 24.9-29.8) - 109 knees including 48.6% with a medial OARSI +JSN grade of 0	- MTP alignment evaluated by IMD, baseline JSN OARSI and osteophytes grades	- Fixed-flexion PA with no fluoroscopy - Computerized-assisted measure of min right and left medial JSW - Progression = JSL > SDD (0.4 mm)	- Progression: 28.4 % of knees and 37.5% of knees with serial satisfactory MTP alignment (see definition above) - Predictors of progression in 48 knees with satisfactory serial alignment (adjusted ORs): * Baseline JSN OARSI grade 1 vs 0: OR = 14.7 (95%CI = 2.6-82.4), grade 2-3 vs 0 OR = 11.0 (95%CI = 1.3-90.7) * Baseline osteophyte score, par increase in grade, OR = 3.9 (95%CI = 1.1-13.3) (femoral) and 2.4 (95%CI = 0.6-9.2) tibial - Predictors of progression in all 109 knees: no association between baseline JSN and osteophytes grades and progression,
Sawitzke Arthritis Rheum 2008	24-months RCT (subpopulation from the GAIT trial)	- ≥ 40 years, knee pain ≥ 6 months, most days of the previous month, KL 2 or 3 - Knees with baseline medial JSW < 2 mm, predominant lateral OA, history of significant knee trauma or surgery excluded from the analysis	357 patients, 581 knees, mean age = 56.9 ± 9.8, 36.4% males, 53.2 % with BMI > 30, KL2 = 76.9%, KL3 = 23.1%, mean baseline min medial JSW = 4.0 ± 0.96 mm	- KL,, baseline metric minimal JSW, others (see specific section)	- Non fluoroscopy semi-flexed PA view - Computerized measure of min medial JSW - Progressors = joint space loss>0.48 mm	- Joint space loss greater in knees with KL 3 than KL 2 - Placebo group, 1 knee per patient: unajusted mean joint space loss = 0.273 and 0.523 mm in KL grade II and III knees - All treatment groups showed less joint space loss and less progressors than placebo in patients with KL 2 (non significant) - All treatment groups showed more joint space loss and more progressors than placebo in patients with KL 3 (non significant) - Baseline JSW not predictor of JSL
Bruyere, Osteoarthritis Cartilage 2003	3-year RCT (glucosamine sulphate vs placebo	- Inclusion: ACR criteria, medial OA, age > 50 yrs,primary OA - Exclusion: secondary OA, knee	Analysis of completers (71 placebo and 68 glucosamine)	Baseline metric JSW, others (see specific section)	- Extended AP with fluoroscopy - Computerized measurement of	- Placebo: baseline JSW related to 3-year joint loss in univariate (r = -0.34, *P* = 0.003, the higher the baseline JSW, the higher the 3-year JSL), but not in multivariate analyses - Glucosamine: baseline JSW related to 3-year JSL (r = - 0.28, *P* = 0.019, the higher baseline JSW, the higher JSL) (multivariate

		trauma, BMI > 30			mean medial JSW	analysis not provided)
Nevitt, Arthritis Rheum 2007	Weight-related disease cohort (Health ABC), median follow-up = 37 months	Patients 70-79 yrs with knee OA symptoms (pain aching or stiffness on most days for at least 1 month during the last year or moderate or worse pain in the last 30 days during activity - KL 4 and OARSI JSN 3 excluded	80 patients, 153 knees, mean age = 73.5 ± 3.1, 36.4% males, mean BMI = 27.8 ± 4.3, 48.8 % with KL ≥ 2 (25% bilateral, 23.8 % unilateral), baseline min JSW = 3.66 ± 1.25 mm	Baseline JSN grade	PA 20-30° flexed, no fluoroscopy, computerized and manual measurement of minimal medial JSW	- Grade 0 JSN (111 knees): JSL = 0.14 ± 0.53 mm - Grade ≥1 JSN (42 knees): JSL = 0.50 ± 0.67 mm - Grade 1 JSN (23 knees): JSL = 0.36 ± 0.76 mm - Grade 2 JSN (19 knees): JSL = 0.63 ± 0.66 mm - p < 0.001 for trend across the 3 categories, NS for grade 2 vs 1
Neumann, Osteoarthritis cartilage 2009	Health-ABC cohort, follow-up = 36 months	Random selection of subjects with baseline and 36-months radiograph	118 subjects (217 knees), mean age = 74.3 ± 2.8, 51% women	Baseline KL	PA 20-30° flexed, no fluoroscopy, computerized measure of minimal medial JSW	KL0: 3-year JSL = 0.22 ± 0.52 (SRM = 0.43) (93 subjects) KL1: 3-year JSL = 0.25 ± 0.69 (SRM = 0.35) (38 subjects) KL2: 3-year JSL = 0.51 ± 0.59 (SRM = 0.86) (13 subjects) KL3: 3-year JSL = 0.32 ± 0.75 (SRM = 0.43) (55 subjects) KL4: 3-year JSL = 0.09 ± 0.30 (SRM = 0.29) (18 subjects)

Is it possible to predict the progression of metric measurement of joint space in knee OA? Baseline knee x-rays (2)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Sharif, Arthritis Rheum 1995	5-year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any other rheumatic disease.	- 94 patients at baseline, 75 evaluated at 5 years - Baseline: age = 64.2 ± 11.6, 30.9 % males, mean JSW = 3.0 ± 3.0, 66 and 41% with medial and lateral OA	Baseline metric JSW, biomarkers (see specific section), others (see specific section)	- Extended AP views + lateral. - JSW measured at the midpoint of each femorotibial compartment	- Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement - Progression in 26 (34.7%) patients (11 joint replacement, 12 joint space loss ≥ 2 mm, 3 both) - Baseline joint space predictive of disease progression (no progression mean = 4.0 ± 2.0, progression, mean = 2.0 ± 2.0, p < 0.001), but no more relation in multivariate analysis
Sharif Rheumatology 2007	5-year longitudinal cohort	Knee pain > 3 months and radiographic evidence of OA Exclusion if KL4, other forms of joint disease and conditions preventing repeated attendance	- 135 patients, 84 with full data available - Baseline: mean age = 62.4 ± 10.0, 46.4 % males, mean BMI = 30.0 ± 5.4 - Baseline mean minimal joint space = 3.5 ± 1.9 mm	Baseliine metric miinimal JSW, biomarkers and others (see specific sections)	- Baseline and 5 yrs extended AP viewsl. - Minimal JSW of each femorotibial compartment	- Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement - 84 patients with complete data, 24 progressors (15 loss of JSW and 9 loss of JSW + surgery) - Mean baseline minimal JSW similar in both groups
Sugiyama Ann Rheum Dis	4-year longitudinal cohort	- Women aged 40-59 with early knee OA, ≥ 2 episodes of knee pain, lasting ≥ 2 weeks, during the last year, median osteophytes	- 110 women - Mean age = 50.2 ± 6.0, mean BMI = 24.7 ±	Baseline metric minimal JSW, biomarkers	- Semiflexed PA with fluoroscopy - Minimal femorotibial	- Mean 4-year minimal JSW loss = 0.53 ± 0.43 - No correlation between joint space loss

2003		graded between 0 and 1, JSN graded 0, no sclerosis, bony attrition, CCA, patellofemoral OA	3.3, mean minimal JSW = 3.4 ± 0.3 mm	and others (see specific sections)	JSW	and baseline JSW
Garnero Arthritis Rheum 2002	Two 1-year RCT (tenidap vs piroxicam, diacerein vs	Knee OA (ACR criteria), medial knee pain, pain ≥ 30 days in the last 2 months, , failure of prior treatment justifying arthroscopic lavage, minimal medial JSW ≥ 2 mm, medial compartment chondropathy at arthroscopy	- 75 patients - Baseline: mean age = 63 ± 8, 32 % males, mean BMI = 29.5 ± 4.5, mean pain (10 mm VAS) = 51.8 ± 17.5, mean Lequesne's index (0-24) = 8.8 ± 2.96, mean medial joint space = 3.98 ± 1.46 mm	Baseline metric JSW, biomarkers and others (see specific sections)	- Extended AP view with fluoroscopy - Minimal medial JSW - Progression = 1-year decrease in medial JSW ≥ 0.5 mm	- 16 progressors and 36 non progressors - No significant difference between progressors and non progressors in baseline minimal medial JSW
Michel Arthritis Rheum 2005	2-year RCT comparing chondroitine sulphate and placebo	- Main inclusion: 40-85 years, ACR criteria, pain on at least 25 out of the last 30 days, KL 1-3 - Main exclusion: KL 4, secondary OA, traumatic knee lesions, severe comorbidity, intraarticular medications < 1 month	- 300 patients, mean age = 63.1 ± 10.7 (plac) and 62.5 ± 9.1 yrs (CS), 52 (plac) and 49 (CS) % males, mean BMI = 28.1 ± 5.5 (plac), 27.2 ± 5.2 (CS), mean WOMAC pain = 27 ± 18 (plac), 25 ± 16 (CS), mean WOMAC function = 25 ± 18 (plac), 21 ± 16 (CS), mean minimum and mean JSW = 2.35 ± 0.14 and 3.0 ± 0.15 (plac), 2.41 ± 0.14 and 3.04 ± 0.14 mm (CS).	Baseline metricmean JSW (and pain, si "others" section)	- Partial flexion (20° PA view) without fluoroscopy - Minimal and mean JSW in the more affected compartment of the target knee	- - No influence of baseline mean JSW on radiographic progression, either in the placebo or the chondroitine sulphate groups

Is it possible to predict the progression of metric measurement of joint space in knee OA? Baseline knee x-rays (3)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Miyazaki Ann Rheum Dis 2002	6-year prospective cohort	- Inclusion : patients with primary knee medial OA, > 50 years, pain at some daily activity - Main exclusion: other musculoskeletal disorders, history of knee trauma, RA, gout, pseudogout, infectious diseases	- 74 patients, mean age = 69.5 ± 7.5 yrs, 21.6 % males, mean BMI = 24.5 ± 3.3, mean pain (0-30, worse to best) = 24.3 ± 4.7, mean and min medial JSW = 3.3 ± 1.1, KL 1: 27%, 2: 29.7%, 3: 31.1, 4: 12.2%	Baseline metric JSW, others (see specific section	Semiflexed AP with no fluoroscopy (x-ray beam determined using lateral x-rays) - Minimal medial JSW	- Significant correlation between 6-year JSL (1.4 ± 1.2) and baseline JSW (r = - 0.25, *P* = 0.03)
Gensburger, Arthritis Rheum 2009	4-year longitudinal population-based cohort	- Patients with radiographic knee OA recruited in a longitudinal cohort evaluating the determinants of bone loss in women	606 women including 125 with radiographic OA (81 with medial knee OA) (OARSI JSW + OARSI osteophyte score ≥ 2) at baseline	Baseline metric JSW, biologic markers (see specific section), others (see specific section)	- Semi-flexed PA view with fluoroscopy - Minimal medial and lateral JSW assessed by computer	- In the whole OA population, the only variable predictive of joint space loss was the baseline minimal JSW (r = 0.31 and 0.35 for the medial right and left medial compartment, p < 0.0001 (women with the most important baseline JSW will experience the most severe joint space loss). - In the medial knee OA population, there was no variable predictive of joint space loss
Mazzuca J Rheumatol 2005	174 patients from a 30-months RCT (Doxy)	ACR criteria, obese women, 45-64 years, unilateral OA (KL 2-3 on one knee, 0-1 on the other knee	174 women, mean age = 55.6 ± 5.7, mean BMI = 36.0 ± 5.9, mean minimal joint space = 3.6 ± 1.2 mm, KL2 = 64%, KL3 = 36%	Baseline TC-MDP Bone scintigraphy, KL and WOMAC pain	Semi-flexed AP with fluoroscopy Manual measurement of minimal medial JSW	- Baseline KL = 3: sensitivity and specificity for prediction of 16 months progressors = 71 and 57%, for prediction of 30-months progressors = 65 and 64% - Baseline KL = 3 + baseline WOMAC pain > 11 (median): sensitivity and specificity for prediction of 16 and 30 months progressors =

						65%, 79%, and 52%, 83%, respectively - Scintigraphy and WOMAC pain: see specific section
Pavelka, Clin Exp Rheumatol 2000	5-year RCT	Patients > 40 years, primary OA, knee pain, radiological evidence of JSN and/or osteophytes and/or sclerosis	139 patients, mean age = 59.1 ± 8.0, 24% males, KL 0: 2.2%, KL1: 12.9%, KL2: 14.4%, KL3: 48.2%, KL4: 22.3%	Baseline KL	Extended AP without fluoroscopy, manual measurement of minimal JSW	- Whole population: 5-year JSN = 0.39 ± 0.95 mm (SRM = 0.41) - KL0 or 1: 5-year JSN = 0.22 ± 0.74 mm (SRM = 0.30) - KL2: 5-year JSN = 0.33 ± 0.85 mm (SRM = 0.39) - KL3: 5-year JSN = 0.49 ± 0.89 mm (SRM = 0.55) - KL4: 5-year JSN = 0.38 ± 1.26 mm (SRM = 0.30)
Buckland-Wright Ann Rheum Dis 1995	18-months RCT (diclofenac vs placebo)	Patients with evidence of osteophytes, sclerosis, and <50% decrease in JSW	33 completers (66 knees), mean age = 65.5 ± 10.2, 27.3% males	Baseline min medial JSW greater or less than 2.3 mm	Semiflexed view with fluoroscopy, macroradiographs (x5), computerized measure of min medial JSW	- 51 knees with baseline JSW > 2.3 mm, 15 with JSW < 2.3 mm - Changes in JSW, knees with JSW > 2.3: placebo 3.39 ± 0.74 to 3.27 ± 0.81, NS; NSAID 3.49 ± 0.88 to 3.43 ± 0.95, *P* < 0.04 - Changes in JSW, knees with JSW < 2.3: placebo 0.92 ± 0.61 to 0.55 ± 1.09, NS; NSAID 1.92 ± 0.82 to 1.26 ± 1.09, *P* < 0.02)

Is it possible to predict the progression of metric measurement of joint space in knee OA? Baseline knee x-rays (4)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Jubb Int J Clin Pract 2003	1-year RCT (intraarticular injections of hyaluronate vs placebo)	-Inclusion: primary knee OA (ACR critera), radiographic involvement of the medial femorotibial compartment KL 2-3 - Main exclusion: clinically important valgus or varus deformity	408 included, 273 evaluated in the primary analysis, mean age = 65.6 ± 8.7 (placebo) and 64.0 ± 9.1 yrs (hyaluronate), 35.8 % (placebo) and 28.7 % (hyaluronate) males, mean BMI = 30.1 ± 5.1 (placebo), 29.3 ± 4.7 (hyaluronate), mean medial JSW = 4.5 ± 1.6 (placebo), 4.9 ± 1.5 (hyaluronate).	Baseline JSW ≥ or < 4.6 mm (median of the population)	- AP weight-bearing of the index knee - Medial JSW using computer	- Interaction between baseline JSW and treatment (P = 0.01) - Baseline JSW ≥ 4.6: joint space loss = 0.55 ± 1.04 (placebo) and 0.13 ± 1.05 (hyaluronate), P = 0.02 - Baseline JSW < 4.6: joint space loss = -0.20 (increase) ± 1.12 (placebo) and 0.06 ± 1.00 (hyaluronate), P = 0.16

Table 18: Is it possible to predict the progression of metric measurement of joint space in knee OA? Malalignment

Miyazaki Ann Rheum Dis 2002	6-year prospective cohort	- Inclusion : patients with primary knee medial OA, > 50 years, pain at some daily activity - Main exclusion: other musculoskeletal disorders, history of knee trauma, RA, gout, pseudogout, infectious diseases	- 74 patients, mean age = 69.5 ± 7.5 yrs, 21.6 % males, mean BMI = 24.5 ± 3.3, mean pain (0-30, worse to best) = 24.3 ± 4.7, mean and min medial JSW = 3.3 ± 1.1, KL 1: 27%, 2: 29.7%, 3: 31.1, 4: 12.2%	Age, sex, baseline BMI, pain, mechanical axis, adduction moment, JSW	Semiflexed AP with no fluoroscopy (x-ray beam determined using lateral x-rays) - Minimal medial JSW	- Significant correlation between 6-year JSL (1.4 ± 1.2) and baseline pain (r = - 0.37, p = 0.001), mechanical axis (r = 0.41, p < 0.001), adduction moment (r = 0.62, p < 0.0001), baseline JSW (r = - 0.25, P = 0.03 - No correlation between 6-year JSL and age, sex, baseline BMI - NB: multiple regression analysis using radiographic progression as dependent variable, BUT defining progression as grade increase (OARSI JSW scale) and not metric measurement: variables related to progression = age (OR = 1.22 for 1 year increase) and adduction moment (OR = 6.46 for 1 % increase)
Sharma, JAMA 2001	18-months prospective cohort (MAK)	KL ≥ 2 in at least one knee and at least some difficulty with knee-requiring activity	230 subjects, mean age = 64.0 ± 11.1, 75.2 % women, mean BMI = 30.3 ± 5.86. KL0: 1 dominant knee, KL1: 14 dominant knees, KL2: 108 right knees, KL3: 71 right knees, KL4: 36 right knees; alignment: 117 varus, 97 valgus, 16 neutral	Varus and valgus malalignment, assessed AP radiographs of the lower extremity	Semiflexed PA views with fluoroscopy. Measurement of the narrowest interbone distance using callipers with electronic readout	- Greater varus alignment correlated with greater subsequent 18-months change in medial joint space (r = 0.52, 95%CI = 0.4-0.62) - Greater valgus alignment correlated with greater subsequent 18-months change in lateral joint space (r = 0.35, 95%CI = 0.21-0.47) - Relationships persist after adjustement for age, sex, BMI, laxity

Table 19: Is it possible to predict the progression of metric measurement of joint space in knee OA? Others (1)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Sharif, Arthritis Rheum 1995	5-year longitudinal cohort	Knee OA diagnosed on use-related knee pain and radiographic features of OA, and the absence of any other rheumatic disease.	- 94 patients at baseline, 75 evaluated at 5 years - Baseline (n = 94): mean age = 64.2 ± 11.6, 30.9 % males, mean weight/height ratio = 0.44 ± 0.09, mean disease duration = 16.1 ± 12.9 - mean JSW = 3.0 ± 3.0, 66 and 41% with medial and lateral compartment diseases	- Baseline age, gender, disease duration, previous surgery, number of other joint sites involved, weigh/height ratio, JSW - Baseline serum hyaluronic acid and keratane sulphate	- Extended AP views + lateral. - JSW measured at the midpoint of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- Progression in 26 (34.7%) patients (11 joint replacement, 12 joint space loss ≥ 2 mm, 3 both) - Age, gender, disease duration, previous surgery, number of other joint sites involved, not predictive of progression. - Baseline weight/height ratio predictive of progression (no progression 0.42 ± 0.08, progression 0.49 ± 0.08, P = 0.0048) - Serum hyaluronic acid and keratane sulphate: see biomarkers. - In multiple logistic regression, weight/height ratio, number of affected joints, baseline hyaluronic acid, but not baseline JSW, correlated with progression.
Sharif Rheumatology 2007	5-year longitudinal cohort	Knee pain > 3 months and radiographic evidence of OA Exclusion if KL4, other forms of joint disease and conditions preventing repeated attendance	- 135 patients, 84 with full data available - Baseline: mean age = 62.4 ± 10.0, 46.4 % males, mean BMI = 30.0 ± 5.4 - Baseline KL: KL0: 13%, KL1 5%, KL2: 4%, KL3 77%, KL4: 19%, minimal joint space = 3.5 ± 1.9 mm	- Baseliine BMI, age, minimal JSW - Baseline and 2, 3 and 5 yrs serum PIIANP and urinary CTX-II	- Baseline and 5 yrs extended AP viewsl. - Minimal JSW of each femorotibial compartment - Progression = decrease of JSW ≥ 2 mm in any compartment or total knee replacement	- 84 patients with complete data, 24 progressors (15 loss of JSW and 9 loss of JSW + surgery) - Mean baseline age, BMI, minimal JSW, gender, similar in both groups - Serum PIIANP and urinary CTX-II: see biomarkers
Sugiyama Ann Rheum Dis	4-year longitudinal cohort	- Women aged 40-59 with early knee OA, ≥ 2 episodes of knee pain,	- 110 women - Mean age = 50.2 ± 6.0, mean BMI = 24.7 ± 3.3,	Age, BMI, baseline minimal JSW, synovial	- Semiflexed PA with fluoroscopy - Minimal femorotibial	- Mean 4-year minimal JSW loss = 0.53 ± 0.43 - Significant correlation between joint space loss and baseline BMI (r

2003		lasting ≥ 2 weeks, during the last year, median osteophytes graded between 0 and 1, JSN graded as 0, no sclerosis, bony attrition or chondrocalcinosis, no patellofemoral OA	mean minimal JSW = 3.4 ± 0.3 mm	volume, synovial procollagene II C propeptide (PIICP)	JSW	= 0.260, 95% CI = 0.0084-0.419, P <0.005) - No correlation between joint space loss and age, baseline synovial volume and baseline JSW - Synovial PICP: see biomarkers

Is it possible to predict the progression of metric measurement of joint space in knee OA? Others (2)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Garnero Arthritis Rheum 2002	Two 1-year RCT (tenidap vs piroxicam, diacerein vs	Knee OA (ACR criteria), medial knee pain, pain ≥ 30 days in the last 2 months, , failure of prior treatment justifying arthroscopic lavage, minimal medial JSW ≥ 2 mm, medial compartment chondropathy at arthroscopy	- 75 patients - Baseline: mean age = 63 ± 8, 32 % males, mean BMI = 29.5 ± 4.5, mean disease duration = 58 ± 62 months, mean pain (10 mm VAS) = 51.8 ± 17.5, mean Lequesne's index (0-24) = 8.8 ± 2.96, mean medial joint space = 3.98 ± 1.46 mm	Age, BMI, disease duration, pain (VAS), Lequesne's index, baseline minimal medial JSW, chondropathy score on arthroscopy, biomarkers (PIIANP and CTX-II)	- Extended AP view with fluoroscopy - Minimal medial JSW - Progression = 1-year decrease in medial JSW ≥ 0.5 mm	- 16 progressors and 36 non progressors - No significant difference between progressors and non progressors in age, BMI, disease duration, pain (VAS), Lequesne's index, baseline minimal medial JSW, chondropathy score on arthroscopy - CTX-II and PIIANP: see biomarkers
Michel Arthritis Rheum 2005	2-year RCT comparing chondroitine sulphate and placebo	- Main inclusion: 40-85 years, ACR criteria, pain on at least 25 out of the last 30 days, KL 1-3 - Main exclusion: KL 4, secondary OA, traumatic	- 300 patients, mean age = 63.1 ± 10.7 (plac) and 62.5 ± 9.1 yrs (CS), 52 (plac) and 49 (CS) % males, mean BMI = 28.1 ± 5.5 (plac), 27.2 ± 5.2 (CS), mean WOMAC pain = 27	Baseline pain and mean JSW	- Partial flexion (20° PA view) without fluoroscopy - Minimal and mean JSW in the more affected compartment	- No influence of baseline pain on radiographic progression, either in the placebo or the chondroitine sulphate groups - No influence of baseline mean JSW on radiographic progression, either in the placebo or the chondroitine sulphate groups

		knee lesions, severe comorbidity, intraarticular medications < 1 month	± 18 (plac), 25 ± 16 (CS), mean WOMAC function = 25 ± 18 (plac), 21 ± 16 (CS), mean minimum and mean JSW = 2.35 ± 0.14 and 3.0 ± 0.15 (plac), 2.41 ± 0.14 and 3.04 ± 0.14 mm (CS).		of the target knee	
Miyazaki Ann Rheum Dis 2002	6-year prospective cohort	- Inclusion : patients with primary knee medial OA, > 50 years, pain at some daily activity - Main exclusion: other musculoskeletal disorders, history of knee trauma, RA, gout, pseudogout, infectious diseases	- 74 patients, mean age = 69.5 ± 7.5 yrs, 21.6 % males, mean BMI = 24.5 ± 3.3, mean pain (0-30, worse to best) = 24.3 ± 4.7, mean and min medial JSW = 3.3 ± 1.1, KL 1: 27%, 2: 29.7%, 3: 31.1, 4: 12.2%	Age, sex, baseline BMI, pain, mechanical axis, adduction moment, JSW	Semiflexed AP with no fluoroscopy (x-ray beam determined using lateral x-rays) - Minimal medial JSW	- Significant correlation between 6-year JSL (1.4 ± 1.2) and baseline pain (r = - 0.37, *P* = 0.001), mechanical axis (r = 0.41, *P* <0.001), adduction moment (r = 0.62, *P* <0.0001), baseline JSW (r = - 0.25, *P* = 0.03 - No correlation between 6-year JSL and age, sex, baseline BMI - NB: multiple regression analysis using radiographic progression as dependent variable, BUT defining progression as grade increase (OARSI JSW scale) and not metric measurement: variables related to progression = age (OR = 1.22 for 1 year increase) and adduction moment (OR = 6.46 for 1 % increase)

Is it possible to predict the progression of metric measurement of joint space in knee OA? Others (3)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Reijman, Ann Rheum Dis 2007	Population-based cohort Mean follow-up = 6.6 years	Inclusion of subjects with baseline KL1, 2 or 3, mobile enough to visit the research centre	532 participants, 865 knees, mean age = 68.6 ± 7, 31.6% males, mean BMI = 27.4 ± 3.9	Baseline BMI	- Standing extended AP - Manual measurement of minimal medial & lateral JSW (0.5 mm magnifying glass) - Progression = decrease in minimal JSW ≥ 1 or ≥ 1.5 mm	- 21.8 (1 mm) and 8.1 (1.5) % progressors - Progressors defined with 1 mm cut-off: 18.2 % when baseline BMI ≤ 25; 20.8 % when BMI between 25 and 25.7 (OR = 1.2, 95%CI = 0.6-2.4); 24.5 % when baseline BMI > 27.5 (OR vs = ≥ 25 = 1.4, 95%CI = 0.8-2.6) - Progressors defined with 1.5 mm cut-off: 3.6 % when baseline BMI ≤ 25; 7.5 % when BMI between 25 and 25.7 (OR = 2.3, 95%CI = 0.7-7.7); 11.2 % when baseline BMI > 27.5 (OR vs ≤ 25 = 3.2, 95%CI =

						1.1-9.7) - Analysis with only baseline KL 2 or 3: ORs remained similar but did not reach statistical significance (no other data)
Sawitzke Arthritis Rheum 2008	24-months RCT (subpopulation from the GAIT trial)	- ≥ 40 years, knee pain ≥ 6 months, most days of the previous month, KL 2 or 3 - Knees with baseline medial JSW < 2 mm, predominant lateral OA, history of significant knee trauma or surgery excluded from the analysis	357 patients, 581 knees, mean age = 56.9 ± 9.8, 36.4% males, 53.2 % with BMI > 30, KL2 = 76.9%, KL3 = 23.1%, mean baseline min medial JSW = 4.0 ± 0.96 mm	- KL, minimal JSW - Gender, age, baseline pain score, disease duration, categorical BMI (< 25, 25-30, > 30)	- Non fluoroscopy semi-flexed PA view - Measurement of minimum medial JSW, using computerized technique - Progressors = joint space loss > 0.48 mm	- KL: see specific section - No other predictor of joint space loss
Gensburger, Arthritis Rheum 2009	4-year longitudinal population-based cohort	- Patients with radiographic knee OA recruited in a longitudinal cohort evaluating the determinants of bone loss in women	606 women including 125 with radiographic OA (81 with medial knee OA) (OARSI JSW + OARSI osteophyte score ≥ 2) at baseline	Age, BMI, total WOMAC, lumbar spine and hip BMD, baseline JSW, biologic markers	- Semi-flexed PA view with fluoroscopy - Minimal medial and lateral JSW assessed by computer	- In the whole OA population, the only variable predictive of joint space loss was the baseline minimal JSW (r = 0.31 and 0.35 for the medial right and left medial compartment, *P* <0.0001 - In the medial knee OA population, there was no variable predictive of joint space loss - Biologic markers: see specific section
Botha-Scheepers, Osteoarthritis Cartilage 2008	Prospective longitudinal cohort (GARP), 2-year follow-up	- Same as above + exclusion of patients without symptomatic knee OA (pain or stiffness on most days the previous month + osteophytes) in at least 1 knee at baseline	- 83 patients, median age= 59.6 (IQR: 55.3-66.6), 19.3 % males, median BMI = 26.4 (IQR: 24.9-29.8) - 109 knees including 48.6% with a medial OARSI +JSN grade of 0	- MTP alignment evaluated by IMD - age (< or ≥ 60), sex, BMI (< 30 or ≥ 30), hand OA, nb of OA affected joint groups	- Fixed-flexion PA with no fluoroscopy - Computerized-assisted semi-automatic measurement of minimal right and left medial JSW - Progression = JSL > SDD (0.4 mm)	- Predictors of progression in 48 knees with satisfactory serial alignment (adjusted ORs) * OR for baseline age ≥ vs < 60 = 3.0 (95%CI = 0.9-10.4) * OR for women vs men = 4.7 (95%CI = 1.4-15.4) * OR for baseline BMI ≥ vs < 30 = 2.9 (95%CI = 0.4-21.0) * OR for presence vs absence of hand OA = 2.1 (95%CI = 0.4-11.1) * OR for OA joint sites, per increase in site = 3.1 (95%CI = 1.2-8.3) - Predictors of progression in all 109 knees: weaker associations for all variables tested than in knees with serial satisfactory MTP alignments. No significant association between any of the evaluated variables and progression

Is it possible to predict the progression of metric measurement of joint space in knee OA? Others (4)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Bruyere, Osteoarthritis Cartilage 2003	3-year RCT (glucosamine sulphate vs placebo	- Inclusion: ACR criteria, medial OA, age > 50 yrs,primary OA - Exclusion: secondary OA, knee trauma, BMI > 30	Analysis of completers (71 placebo and 68 glucosamine)	Age, BMI, baseline WOMAC pain, function and stiffness, baseline JSW	- Extended AP with fluoroscopy - Computerized measurement of mean medial JSW	- Age, BMI, baseline WOMAC pain, function and stiffness not related to the 3-year JSL in the placebo & the glucosamine groups - Placebo: baseline JSW significantly related to 3-year joint loss in univariate, but not in multivariate analyses - Glucosamine: baseline JSW related to 3-year JSL (multivariate analysis not provided)
Dieppe, Ann Rheum Dis 1993	5-year prospective cohort	Knee pain with radiographic OA (definite osteophytes and/or narrowing of joint space)	- 94 included (mean age = 64.2± 11.6, 44.6% males, mean BMI = 26.2 ± 5.1 - 60 patients evaluated at 5 years (	Baseline TC-MDP Bone scintigraphy	- Extended AP, no fluoroscopy - Manual measure of medial & lateral JSW (midpoint)	- Data very difficult to extract - Loss of JSW ≥ 2 mm in 0 out of 55 knees with no scan abnormality - Loss of JSW ≥ 2 mm in 14 out of 65 knees with scan abnormality
Mazzuca J Rheumatol 2004	86 patients from a 30-months RCT (Doxy)	ACR criteria, obese women, 45-64 years, unilateral OA (KL 2-3 on one knee, 0-1 on the other knee	86 women, mean age = 55.2 ± 6.8, mean BMI = 36.5 ± 6.6, mean minimal joint space = 3.7 ± 1.4 mm, KL2 = 56%, KL3 = 44%	Baseline TC-MDP Bone scintigraphy	Semi-flexed AP with fluoroscopy Manual measurement of minimal medial JSW	- Medial tibial uptake related to 16 and 30 months JSN (r = 0.28 and 0.3, p < 0.05), but no more statistical correlation after controlling for age, BMI and KL - 30-months JSN more rapid in patients with Tc-MDP uptake in the medial tibia in the lower tertile = 0.10 ± 0.11 vs 0.46 ± 0.18 in the middle and upper tertiles (*P* = 0.045), but no more statistical correlation after controlling for KL
Mazzuca J Rheumatol 2005	174 patients from a 30-months RCT (Doxy)	ACR criteria, obese women, 45-64 years, unilateral OA (KL 2-3 on one knee, 0-1 on the other knee	174 women, mean age = 55.6 ± 5.7, mean BMI = 36.0 ± 5.9, mean minimal joint space = 3.6 ± 1.2 mm, KL2 = 64%, KL3 = 36%	Baseline TC-MDP Bone scintigraphy, KL and WOMAC pain	Semi-flexed AP with fluoroscopy Manual measurement of minimal medial JSW	- Adjusted Tc-MDP uptake in the medial tibia related to 16 (b mm/unit = 0.18, 95%CI = 0.036-0.323) and 30 months (b mm/unit = 0.221, 95%CI = 0.003-0.439) JSN - Uptake in the middle and upper tertiles of the distribution predicted a JSN > 0.5 mm in patients of the placebo group with a 65% sensitivity and a 36% specificity (16 months), 74% sensitivity and 40% specificity (30 months) - Baseline WOMAC pain > 11/25 (median): sensitivity and specificity for prediction of 16 and 30 months progressors = 77%, 59%, and

						65%, 62%, respectively - Baseline KL, see specific section, Baseline KL = 3 + baseline WOMAC pain > 11: sensitivity and specificity for prediction of 16 and 30 months progressors = 65%, 79%, and 52%, 83%, respectively

Is it possible to predict the progression of metric measurement of joint space in knee OA? Others (5)

First author	Study design	Inclusion & exclusion	Number and characteristics of the patients	Evaluated predictive factors	X-rays	Results
Kahan, Arthritis Rheum 2009	2-year RCT (Chondroitine sulfate vs placebo)	Age 45-80, primary medial knee OA, ACR criteria, pain ≥ 30/100 (VAS), min JSW ≥ 1 mm	622 patients, mean age = 61.8 and 62.9, 33 and 30% males, mean BMI between 28.3 and 29.3, mean minimal joint space = 3.81 and 3.73 mm	BMI = unknown	Lyon schuss with fluoroscopy Computerized measurement of medial minimal JSW	"Among the initial patient characteristics, only the BMI significantly interacted with treatment, with the (structural) effect of treatment being more important in patients with higher BMI (*P* = 0.03)"
Mazzuca, Arthritis Rheum 2001	Data from 3 longitudinal cohorts (mean follow-ups = 2.6, 3.0 and 2.3 years	JSW > 0, KL ≥ 2	255 subjects from 3 cohorts, 402 knees analysed (368 with OA), mean ages = 72.2 ± 5.8, 63.3 ± 10.9, 70.7 ± 9.0, % males = 39, 32 and 29 %, mean BMI = 30.4 ± 6.2, 27.9 ± 5.2, 29.4 ± 5.1, mean minimal joint space = 4.1 ± 1.6, 4.0 ± 1.8, 3.5 ± 2.1 mm	- MTP alignment evaluated by IMD (satisfactory if ≤ 1 mm) - Age, sex, BMI	-Standing extended AP - Manual measurement of minimal medial JSW	- Baseline and follow-up MTP alignment satisfactory in 60/402 knees - MTP alignment: see specific section - All knees: no correlation between baseline BMI and JSN (all cohorts) (r = 0.06, *P* = 0.51). Knees with satisfactory MTP alignment, r = 0.13 (*P* = 0.1) - All knees: no correlation between age and JSN. Knees with satisfactory MTP alignment: no correlation between age and JSN in 2 cohorts, correlation in 1 (r = O.39, *P* = 0.02) - All knees, no correlation between sex and JSN in 2 cohorts, correlation in 1 (men 0.92± 1.92, women 0.09 ± 1.22, *P* = 0.0007). Knees with satisfactory alignment: no relation between sex and JSN
Dayal, Arthritis Rheum 2005	18-months prospective study (MAK cohort)	KL ≥ 2 in at least one knee and at least some difficulty with knee-requiring activity	230 subjects, mean age = 64 ± 11, 75 % women, mean BMI = 30 ± 6. KL = 0-1: 15 right knees, KL = 2: 108 right knees, KL = 3: 71 right knees, KL = 4: 36 right knees	Knee anteroposterior laxity	Standing semi-flexed PA view with fluoroscopy, measurement of minimum medial JSW	- No relationship between joint space loss and knee AP laxity

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HIP

Table 20: Hip OA: correlations between symptoms and joint space measurement in the general population and in patients with hip pain

Reference	Design	Number of patients	Age, yrs, mean (SD) and % males	Type of JSW	Results
Reijman Ann Rheum Dis 2004	Community-based cohort, cross-sectional	3595	66.0 ± 6.9 yrs, 41.8%	JSW continuous: minimal joint space	Hip pain associated with minimal joint space - Minimal JS ≤ 2.5 mm: OR = 2.4 (1.7-3.4) - Minimal JS ≤2.0mm: OR = 4.5 (2.9-7.0) - Minimal JS ≤1.5mm: OR = 6.6 (3.6-12.2) Similar results for stiffness and disability (see the text)
Jacobsen Osteoarthritis Cartilage 2004“	Community-based, cross-sectional	3208	Men : 62.5 (NA) Women : 65.0 (NA) 37.8%	JSW continuous: mean minimum joint space	A minimum joint space ≥ 2 mm was significantly associated to self-reported pain in or around the hip joint during the previous 12 months
Lane Arthritis Rheum 2004	Cohort of women with fractures, sectional 8-year follow-up	745	71.8 (5.2), 0%	JSW binary: decline in minimum joint space > or ≤0.5 mm	- The 8-year decrease in joint space was higher in subjects with vs without hip pain (0.5 vs 0.35 mm, *P* = 0.034) - Decrease ≥ 0.5 mm: 53.7% of painful hips vs 30.7%, OR = 1.9 (1.4-2.6), *P* <0.001
Birell Rheumatology 2000	Cross-sectional	195 Median age = 63, 33.3%	Median age = 63, 33.3%	JSW binary : Minimal joint space Cut off : <2.5 mm and 1.5mm	Pain duration < 3 months, 28% with ≤ 2.5 mm and 7% with minimal joint space ≤ 1.5 mm; pain duration = 3-12 months, 25% with ≤ 2.5 mm and 13% with minimal joint space ≤ 1.5 mm; pain duration > 12 months, 43% with ≤ 2.5 mm and 26% with minimal joint space ≤ 1.5 mm, *P* = 0.02

Bierma-Zienstra J Rheumatol 2002	Descriptive, cross sectional	220	66 (9.6), 27%	Minimal joint space ≤2.5 mm and ≤1.5 mm	- Minimal JS ≤ 2.5 mm correlated with pain duration ≥ 3 months (OR 2.34 (1.26,4.32)* and with morning stiffness (OR 2.0 (1.15, 3.62)* - Minimal JS ≤ 1.5 mm correlated with morning stiffness (OR 2.6 (1.12, 6.06))*
Gossec, Osteoarthritis Cartilage 2009	Community-based cohort, cross sectional	735	67.2 (9.5), 34.3%	Categorical minimal joint space, cut-offs of 1.5, 2.5, and 3.0 mm	Categorical JSW not related to pain, minimal joint space < 2.5 mm associated with functional impairment, categorized in quartiles (OR = 1.67, 95%CI = 1.0-2.78 compared to joint space > 3 mm)

Table 21: Hip OA: correlations between symptoms and joint space measurement in hip OA patients

Reference	Design	Number of patients	Age, yrs, mean (SD) and % males	Type of JSW	Results
Amaro Int J Sport 2007	Descriptive, cross sectional	41	68.4 (9.4), 41%	JSW continuous: minimal joint space	Prior to joint replacement, Lequesne's index correlated with JSW, r = -0.57* for operated hip and r= -0.70* for non operated hip
Dougados Ann Rheum Dis 1996	RCT, cross sectional	458	63 (7), 40.4%	JSW continuous	12 months changes in JSW correlated with baseline Lequesne's index>10 (OR 2.66 (1.46,

					4.83)) *P* <0.0001 Baseline clinical parameters explained only 0.4% of the variability of the baseline JSW (*P* = 0.44)
Gossec, Osteoarthritis Cartilage 2009	Same RCT as above cross-sectional	507	63.0 (7.0), 40.4%	Categorical minimal joint space, cut-offs of 1.5, 2.5, and 3.0 mm	Categorical JSW not related to pain or functional impairment

*P <0.05

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Table 22: Hip OA: longitudinal relationship between symptoms and joint space measurement

Reference	Design	Number of patients	Age, yrs, mean (SD) and % males	Type of JSW	Results
Dougados Ann Rheum Dis 1996	RCT, cross sectional	458	63 (7), 40.4%	JSW continuous	- 12 months changes in JSW correlated with baseline Lequesne's index>10 (OR 2.66 (1.46, 4.83)) p<0.0001 - The level of clinical parameters (pain, disability, patients' overall assessment) and the amount of symptomatic treatment during the 1-year follow-up explained 20% of the 1-year changes in joint space (*P* < 0.0001)
Lane Arthritis Rheum 2004	Cohort of women with fractures, sectional 8-year follow-up	745	71.8 (5.2), 0%	JSW binary: decline in minimum joint space > or ≤0.5 mm	- The 8-year decrease in joint space was higher in subjects with vs without hip pain (0.5 vs 0.35 mm, *P* = 0.034) - Decrease ≥ 0.5 mm: 53.7% of painful hips vs 30.7%, OR = 1.9 (1.4-2.6), p< 0.001
Conrozier Br J Rheumatol 1998	Retrospective study of OA hips from a case registry of patients who had undergone total hip replacement for OA, mean radiological follow-up of 81.2 ± 59.9 months	61 patients, 69 hips	Men: 62.0 (10.4) Women: 61.8 (10.4)) 44.2%	JSW continuous: mean mean joint space	The mean joint space at entry was not related to further annual joint space loss
Reijman, BMJ 2005	Prospective cohort, mean follow-up of 6.6 years	1904 subjects with hip OA at baseline, defined as KL ≥1, including 411 with baseline hip pain	66.2 (7.0) 47.2	Minimal joint space Progression, defined as joint space loss ≥ 1.0 mm or total hip replacement (a	- Multivariate analysis including clinical variables: a disability index score ≥ 0.5 (OR = 1.9, 95%CI = 1.4-2.6) and the presence of hip pain (OR = 2.6, 95%CI = 1.9-3.7) were

				radiological progression was observed in 13.1% of the subjects, among whom 35.8% had joint replacement)	predictors of progression. - Model including clinical and radiological variables, the presence of hip pain (OR = 2.4, 95%CI = 1.7-3.5) and a baseline minimal joint space ≤ 2.5 mm (OR = 1.9, 95%CI = 1.2-2.9) were predictors of progression

*P <0.05

Table 23: Hip OA: joint space measurement as a predictor of further joint space loss

Reference	Design	Number of patients	Age, yrs, mean (SD) and % males	Type of JSW	Results
Conrozier Br J Rheumatol 1998	Retrospective study of OA hips from a case registry of patients who had undergone total hip replacement for OA, mean radiological follow-up of 81.2 ± 59.9 months	61 patients, 69 hips	Men: 62.0 (10.4) Women: 61.8 (10.4)) 44.2%	JSW continuous: mean mean joint space	The mean joint space at entry was not related to further annual joint space loss
Reijman, BMJ 2005	Prospective cohort, mean follow-up of 6.6 years	1904 subjects with hip OA at baseline, defined as KL ≥1, including 411 with baseline hip pain	66.2 (7.0) 47.2	Minimal joint space Progression, defined as joint space loss ≥ 1.0 mm or total hip replacement (a radiological progression was observed in 13.1% of the subjects, among whom 35.8% had joint replacement)	On multivariate analysis, a baseline minimal joint space ≤ 2.5 mm was a predictor of progression (OR = 1.9, 95%CI = 1.2-2.9). However, in the analysis restricted to the 411 subjects with hip pain at baseline, joint space was no more predictor of progression (but the KL grade ≥ 2 was, with an OR of 24.3)
Dougados Ann Rheum Dis 1996	3-year RCT	458	63 (7), 40.4%	JSW continuous	Baseline joint space < 2.0 mm was an independent predictor of a further 0-1 year radiological progression, defined as a 1-year joint space loss of at least 0.6 mm (OR = 2.11, 95%CI = 1.30-3.44)

Table 24: Hip OA: joint space measurement as a predictor of joint replacement

Reference	Design	Number of patients	Age, yrs, mean (SD) and % males	Type of JSW	Results
Reijman	Community-based cohort (mean follow-up = 6.6 ± 0.5 yrs	3561	67.1 (7.98)	JSW continuous: mean joint space	Baseline minimal joint space ≤ 2.5 mm predicts further joint replacement - OR right hip = 18.6 (10.7-32.3) - OR left hip = 22.6, 95%CI = 11.8-43.0
Birrell Br J General Practice 2003	Cohorts of patients with a new episode of hip pain recruited by GPs , median duration follow-up = 36 months	195	63 (11), 32% males	Minimal joint space	- Minimal joint space predictive of further joint replacement - In a 0-6 composite score for prediction of joint replacement, the weight of minimal joint space measurement is 2 (joint space > 2.5 = 0, , joint space 1.5-2.5 = 1, joint space < 1.5 = 2)
Lievense, Arthritis Rheum 2007	Subjects aged > 50 years with hip pain, followed-up for a mean 2.7 ± 0.25 years (193 subjects) then 5.8 ± 0.3 years (163 subjects),	224	65.6 (9.6), 26.9%	Minimal joint space	Baseline joint space < 2.5 mm was predictor of further joint replacement on univariate (OR for further 3 years joint replacement = 6.6, p < 0.01; OR for further 6 years joint replacement = 7.1, p < 0.01), but not on multivariate analysis (in which KL ≥ 2 was predictor)
Dougados, J Rheumatol 1999	3-year RCT	506		JSW continuous: Minimal joint space	- Baseline minimal JSW < 2 mm associated with a total hip replacement during the 3 following years (relative risk = 1.85, 95%CI = 1.18-2.90) - First year change in minimal joint space associated with total hip replacement during the

					2 following years, relative risk of being operated = 2.89; *P* <0.01 (no worsening vs worsening < 25%), 2.09, *P* = 0.07 (worsening < 25% vs worsening between 25 and 50%), and 5.3, p < 0.0001 (worsening between 25 and 50% vs over 50%)
Maillefert Rheumatology 2002	3-year RCT, 2 years follow-up after end of the trial	422 (first analysis)		Minimal joint space	0-1 year changes in JSW predictive of further joint replacement: a decrease in JSW of at least 0,2 mm or at least 15% predicted joint replacement during the next 4 years with sensibility of 75 and 68% (-0,2mm) and 74 and 78% (-15%) respectively Similar results for 0-2 years changes in JSW

[Click here to return to your place in the text, p 43 (Predictive Validity/Conventional Radiography/Hip).]

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HAND OA TABLES: CONCURRENT VALIDITY

Table 25: Hand OA: concurrent validity

Correlations between x-rays and hand symptoms (1)

(Authors are listed in alphabetic order)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL of DIP, PIP, MCP and wrist as a single joint - Nocturnal joint pain, morning stiffness, joint swelling	Acheson, Ann Rheum Dis 1970	Cross-sectional, population-based study	1127 subjects, 42.4% males	- Males: no difference in number of OA joints in subjects with or without morning stiffness, nocturnal joint pain and joint swelling - Females: no difference in number of OA joints in subjects with or without nocturnal joint pain. Increased number of OA joints in women with vs without morning stiffness (7.11 vs 4.56, $p < 0.01$) and with vs without joint swelling (9.10 vs 3.91, $p < 0.005$)
- KL, scoring of DIP, PIP, MCP, CMC, intracarpal and radiocarpal; OA grade = the most severely affected joint - symptoms (pain and stiffness), clinical signs (nodular swelling or periarticular enlargement of DIP and PIP, palpable enlargement or instability in the IP1 and 1st MCP, palpable enlargement or squaring of 1st CMC	Bagge, Ann Rheum Dis 1991	Cross-sectional, 2 population-based cohorts	160 subjects from 2 population-based cohorts, aged 79 and 85, 38.1% males	Significant correlation between joint complaints and radiographic OA: KL1: 8% with joint complaints, KL2 12 %, KL3-4 29% Significant correlation between signs at examination and radiographic OA - DIP: clinical signs in 0, 17, 24 and 74% of patients with KL0, KL1, KL2, and KL3-4, respectively ($P < 0.001$) - PIP: clinical signs in 16, 16, 36 and 33% of patients with KL0, KL1, KL2 and KL 3-4, respectively ($P < 0.01$) - IP1: clinical signs in 0, 7, 12, and 60 % of patients with KL0, KL1, KL2 and KL 3-4, respectively ($P < 0.01$)

				- MCP1: clinical signs in 19, 33, 38 and 75 % of patients with KL0, KL1, KL2 and KL 3-4, respectively ($P < 0.001$) - CMC1: clinical signs in 0, 2, 17, and 31% of patients with KL0, KL1, KL2 and KL 3-4, respectively ($P < 0.001$)
- KL grade of DIP, PIP and CMC joints. Definition of patients with grade 2, 3 and 4 OA not provided - Grip strength, pinch strength, functional impairment (Dreiser's index)	Bagis, Clin Rheumatol 2003	Cross sectional, case-control (data from controls not used in this report since controls were defined using clinical criteria)	100 post-menopausal women with hand OA (ACR criteria), mean age = 61.47 ± 8.21 yrs.	- Significant difference in Grip strength and Pinch strength between patients with grade 4 OA (n = 15) vs grade 2 and grade 3 OA: - Right grip strength = 13.5 ± 4.2, 19.8 ± 6.4 and 21.7 ± 4.9 in grade 4, 3 and 2 OA, respectively; $P < 0.05$ grade 4 vs grade 2 and grade 3 - Left grip strength = 12.6 ± 4.3, 21.7 ± 5.6, 19.0 ± 5.7 in grade 4, 3 and 2 OA, respectively, $P < 0.05$ grade 4 vs grade 2 and grade 3 - Right pinch strength = 3.9 ± 1.2, 6.56 ± 2.2, 6.6 ± 1.7 in grade 4, 3 and 2 OA, respectively, $P < 0.05$ grade 4 vs grade 2 and grade 3 - Left pinch strength = 4.2 ± 1.7, 6.4 ± 2.0, 6.3 ± 1.9 in grade 4, 3 and 2 OA, respectively, $P < 0.05$ grade 4 vs grade 2 and grade 3 - Functional limitation : Dreiser's index = 6.6 ± 5.6, 4.7 ± 4.8, 1.2 ± 1.4 in grade 4, 3 and 2 OA, respectively, $P < 0.05$ grade 4 vs 2 and vs 3 and grade 3 vs 2

Hand OA: Correlations between x-rays and hand symptoms (2)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL grading of all joints of both hands. Radiographic score = sum of score of all DIP, PIP, MCP, 1st	Baron et al, J Rheumatol	Cross-sectional	32 subjects aged > 60 (mean age = 76.8, 18.7% males),	Mean radiographic score (52.7 ± 15.5) correlated with the Clinical OA index (r = 0.53, $P = 0.001$) and with total range of motion score (r = 0.44, $P = 0.008$)

CMC, number of OA joints = number of joints with KL ≥ 2. - Clinical OA index (sum of the tenderness or pain on motion, osteophytes and crepitus (0-3) of all joints); sum of ROM scores of all finger joints; upper extremity HAQ score; hand function index (sum of Z-scores of time to achieve 15 tasks + 10); hand strength index	1987		including 29 with x-rays	Radiographic score not correlated with the hand function index nor with hand strength Number of joints with OA correlated with upper extremity HAQ score
- OARSI - Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of DIP, PIP, 1st CMC (not MCP and TS), maximal score = 60 for osteophytes and for JSN - Pain and function (AUSCAN)	Botha-Scheepers, Ann rheum Dis 2009	2-years prospective cohort	192 subjects (172 completers) from the GARP longitudinal cohort study (sib pairs with OA at multiple sites), mean age = 59.7 years, 21.5% women, 75% with hand OA (ACR criteria)	- At baseline, pain correlated with osteophyte (r = 0.27*) and JSN (r = 0.26*) scores - At baseline, function correlated with osteophyte (r = 0.30*) and JSN (r = 0.20*) scores - Baseline pain higher in patients with vs without JSN progression over 2 years (7.6 ± 4.9 vs 5.8 ± 4.5*, mean difference adjusted for age gender and family effect = 1.8 points, 95% CI = 0.2-3.4). No difference seen for osteophyte score - Changes in self-reported pain and function scores not associated with progression (= increase of at least 1 in the total score) of osteophyte and JSN scores
- KL grading of 32 joints of hands and wrists. Maximum score derived from the grades assigned to the 32 joints (no more detail). Radiological hand OA = subjects with maximum score > 1 - Current hand pain (mild to very severe pain during the last month)	Carman, Seminars Arthritis Rheum 1989	Cross-sectional, population-based study	1411 subjects aged 50 to 74	- Prevalence of current pain: 46% in subjects with hand OA, 30% in subjects with no hand OA ($P < 0.001$). After adjustment for sex, relative risk of hand pain for those with radiological OA = 1.91 (95%CI = 1.52-2.41) - The prevalence of pain increased significantly with increasing levels of maximum grade of radiological OA ($P < 0.0001$): grade 0 24%, grade 1 31%, grade 2 43%, grade 3 46%, grade 4 60%
- Osteophytes grades (0-3) using an atlas (Burnett). - DIP joints examined as separate	Cicuttini, Ann Rheum Dis 1998	Cross-sectional, population-based study	Female twins, mean = 56.4 ± 6.8 years), 89% post-	- Modest agreement between the presence of Heberden's nodes and the presence of osteophytes: K = 0.36 (95%CI = 0.33-0.39). - When grade 1 osteophytes and grade 1 Heberden's nodes were considered as

units - Heberden's nodes (0-3)			menopausal. 6590 DIP evaluated	no osteophytes and no Heberden's, K = 0.27, 95%CI = 0.24-0.30) - 13.2% of DIP had Heberden's nodes, 16.2% had osteophytes, 6.6% had both

Hand OA: Correlations between x-rays and hand symptoms (3)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- Modified KL (grade 3 takes only into account the presence of joint space narrowing) - DIP, PIP, MCP, 1st CMC, TS joints - DIP, PIP, MCP, and CMC/TS joint groups defined as OA if at least 1 joint of the group had KL ≥ 2 Hand OA = KL ≥ 2 in 2 of 3 groups of hand joints (DIP, PIP, CMC/TS) - Pain (home interview) and disability (HAQ)	Dahaghin, Ann Rheum Dis 2005	Cross-sectional, population-based study	3906 participants aged ≥ 55 (mean age = 66.6 ± 7.3, 58.3% females)	- Modest association between OA and hand pain, the strongest being with involvement of the base of the thumb. Association of hand OA with hand pain: OR = 1.9 (95%CI = 1.5-2.4). Association of hand pain with radiographic OA (right hand), univariate analysis. DIP OR = 1.5 (95%CI 1.2-1.8), DIP OR = 1.8 (95%CI 1.4-2.3), MCP OR = 1.6 (95%CI 1.1-2.3), CMC1/TS OR = 2.0 (95%CI 1.6-2.4); multivariate analysis: DIP OR = 1.1 (95%CI 0.9-1.4), DIP OR = 1.4 (95%CI 1.1-1.9), MCP OR = 1.2 (95%CI 0.8-1.7), CMC1/TS OR = 1.7 (95%CI 1.4-2.2) - Weak association between OA and hand disability (HAQ), the strongest being with involvement of the MCP and the base of the thumb. Association of hand OA with hand disability: OR = 1.5 (95%CI 1.1-2.1). Association of hand disability with radiographic OA, univariate analysis. DIP OR = 1.3 (95%CI 0.9-1.8), DIP OR = 1.1 (95%CI 0.8-1.7), MCP OR = 2.0 (95%CI 1.3-3.0), CMC1/TS OR = 1.3 (95%CI 1.0-1.9); multivariate analysis: DIP OR = 1.2 (95%CI 0.8-1.7), DIP OR = 0.9 (95%CI 0.6-1.4), MCP OR = 1.8 (95%CI 1.2-2.9), CMC1/TS OR = 1.2 (95%CI 0.8-1.7)
- Modified KL (grade 3 takes only into account the presence of joint space narrowing) - DIP, PIP, MCP, 1st CMC, TS joints	Dahaghin, Ann Rheum Dis 2005	Cross-sectional, population-based study	3906 participants aged ≥ 55 (mean age = 66.6 ± 7.3, 58.3% females)	- Dose-response relation with hand pain and the number of joints affected by OA, with generalized hand OA (all 4 joint groups affected) and with the severity of OA (KL 4) Association of hand OA with hand pain: OR = 1.9 (95%CI = 1.5-2.4). With the cut-off point of KL ≥ 3, OR mostly the same (1.8, 95%CI = 1.3-2.5). With the cut-off point of KL ≥ 4, stronger association (OR = 3.6, 95%CI = 2.2-5.8). OA of all

- DIP, PIP, MCP, and CMC/TS joint groups defined as OA if at least 1 joint of the group had KL ≥ 2 Hand OA = KL ≥ 2 in 2 of 3 groups of hand joints (DIP, PIP, CMC/TS) - Pain (home interview) and disability (HAQ)				four joint groups: OR for hand pain = 2.7 (95%CI = 1.4-5.2) - Dose-response relation with hand disability which increased with the number of joints affected by OA, with generalized hand OA (all 4 joint groups affected), but not with the severity of OA Association of hand OA with hand disability: OR = 1.5 (95%CI = 1.1-2.1). With the cut-off point of KL ≥ 3, OR mostly the same (1.6, 95%CI = 1.1-2.5). With the cut-off point of KL ≥ 4, OR mostly the same (OR = 1.6, 95%CI = 0.9-2.9). OA of all four joint groups: OR for hand pain = 2.7 (95%CI = 1.3-6.0)
- KL - DIP, PIP and MCP, . Radiographic sum score - Pain intensity graded (0-3, 1 = mild, 2-3 = at least moderate) for all joints, then sum score	Ding, Rheumatology 2007	Cross-sectional	543 women, 295 dentists and 248 teachers, aged 45-63 years	- Pain sum score correlated with the number of joints with KL ≥ 2 (r = 0.28, *P* = 0.0005) and to radiological sum score (r = 0.26, *P* = 0.0005). - Adjusted (age and occupation) prevalence ratio of pain = 1.70 (95%CI = 1.44-2.01) in KL 2 OA, and 5.17 (95%CI = 4.34-6.16) in KL 3-4 OA, vs no OA - Intensity of pain associated with OA score: prevalence ratio of mild pain = 1.93 (95%CI = 1.54-2.41) for KL2 OA and 4.92 (3.77-6.43) for KL 3-4 OA; prevalence ratio of at least moderate pain = 2.21 (95%CI = 1.58-3.10) for KL2 OA and 11.73 (8.95-15.38) for KL 3-4 OA

Hand OA: Correlations between x-rays and hand symptoms (4)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL of DIP, PIP, MCP and CMC - Sum of KL grades (range = 0-60 for each hand) - Grip and pinch strength	Dominick, Arthritis Rheum 2005	Cross-sectional	700 subjects with KL ≥ 2 in at least 1 DIP joint, mean age = 68.7 ± 8.8 years, 20% males	- Summed KL associated with a lower right hand grip strength and pinch strength (nonstandardized parameter estimates = -0.67 and -0.16, p < 0.001 and < 0.001) (similar results for left hand) in bivariate as well as in multivariate analysis controlling for demographic and clinical variables (*P* < 0.05). - PIP OA (nonstandardized parameter estimate = -6.67, *P* = 0.003), CMC OA (nonstandardized parameter estimate = -9.06, *P* < 0.001), OA in each ray (nonstandardized parameter estimate from -5.37 to -11.08, p < 0.001 for rays 1-4, *P* = 0.02 for ray 5) associated with a lower right hand grip strength. Same

				results for left hand grip strength except that OA in MCP joint was related (b = -6.52, *P* = 0.004) and OA in the 5th ray was not - MCP OA (nonstandardized parameter estimate = -1.78, *P* = 0.003), CMC OA (nonstandardized parameter estimate = -1.03, p = 0.049), OA in each ray (nonstandardized parameter estimate from -1.45 to -2.05, p from 0.023 to 0.001) associated with a lower right pinch strength. Same results for left hand grip strength except that OA in CMC joints, and in rays 3, 4 and 5 were not related - Multivariate analysis including joint groups: OA in the CMC joints related to lower right hand grip strength (nonstandardized parameter estimate = -3.02, *P* = 0.026), but not to left hand grip strength (b = -1.92, p = 0.154). OA in the MCP related to a lower grip pinch (nonstandardized parameter estimate = -1.40, *P* = 0.02), but not to left hand grip pinch (b = -1.23, *P* = 0.08). - Multivariate analysis including joint rays: OA in ray 1 associated with a right hand lower grip strength *P* < 0.05). No individual ray associated with left hand grip strength neither to right and left hand lower grip pinch
- KL - Evaluated joints: probably DIP, PIP, MCP, CMC, but not stated precisely. - Patients categorized as KL2 (n = 18), KL3 (n = 12), or KL4 (n = 10), probably according to the worst joint KL, but not stated precisely - Pain, function and stifness (AUSCAN), grip strength, morning stiffness, joint tenderness	El-Sherif, Osteoarthritis Cartilage 2008	Cross-sectional	40 post-menopausal women with hand OA (ACR criteria), mean age = 58.35 ± 10.12 years	- AUSCAN Pain score (r = 0.459, *P* = 0.003), AUSCAN Function score (r = 0.394, *P* = 0.012), right grip strength (r = -0.322, *P* = 0.043, 36 patients right-handed and 1 ambidextrous) related to KL score. AUSCAN Stiffness score, left grip strength, morning stiffness, tenderness, not correlated with KL - AUSCAN Pain scores (0-4) = 1.17 ± 0.52 in patients with KL2, 1.60 ± 0.76 in KL3, 1.91 ± 0.58 in KL4, *P* = 0.013 KL2 vs 4, NS for KL3 vs 2 and vs 4 - AUSCAN Function scores (0-4) = 1.36 ± 0.53 in patients with KL2, 1.86 ± 0.68 in KL3, 1.97 ± 0.70 in KL4, *P* = 0.026 KL2 vs 4, NS for KL3 vs 2 and vs 4

Hand OA: Correlations between x-rays and hand symptoms (5)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL of DIP, PIP, MCP, 1st CMC - OA = KL ≥ 2 in any joint, symmetrical DIP OA = KL ≥ in at least two DIP joints symmetrically - Finger pain and restriction in the flexion of the fingers	Haara, Ann Rheum Dis 2003	Cross-sectional, population-based study	3595 subjects (3130 subjects screened positive for history, symptoms or findings suggestive of musculoskeletal disease + 1090, including 627 screened positive, belonging to a random sample	- Moderately increased prevalence of restriction in the flexion of fingers 2 to 4 (OR = 1.59; 95% CI = 1.08-2.34) and in the opposing movement of the thumb (OR = 1.42, 95%CI = 1.00-2.03) in OA of any finger, but not in symmetrical DIP OA - Finger pain associated with OA of any finger (OR = 1.38, 95%CI = 1.14-1.67) and symmetrical DIP OA (OR = 1.68, 95%CI = 1.34-2.10)
- KL of DIP, PIP, MCP, 1st CMC - OA = KL ≥ 2 in any joint - Pain and disability	Haara, J Bone Joint Surg Am 2004	Cross-sectional, and longitudinal (over a period of up to 17 years) population-based study	3595 subjects (3130 subjects screened positive for history, symptoms or findings suggestive of musculoskeletal disease + 1090, including 627 screened positive, belonging to a random sample	- Strong association between 1st CMC OA and the physical status of the carpometacarpal joint of the ipsilateral thumb, including restriction of movement, pain with movement, swelling and tenderness. Subjects with any of these findings had a threefold risk of having radiographic signs of OA in the right hand (OR = 3.29, 95%CI = 2.03-5.33) and a twofold risk in the left hand (OR = 2.16, 95%CI = 1.34-3.51) - No association between 1st CMC OA and baseline overall disability (ordinary daily activities) (adjusted OR = 0.80, 95% CI = 0.63-1.01) - No association between 1st CMC OA and follow-up work disability (adjusted RR = 0.91, 95% CI = 0.61-1.38 for any 1st CMC OA; 1.47, 95%CI = 0.65-3.31 for 1st CMC grade 3 or 4 OA)
- KL scoring of DIP, PIP and CMC	Hart, Ann	Cross-sectional,	541 women aged	- DIP: 185 women with KL ≥ 2, including 76 (41%) with symptoms (questionnaire

joints. - Radiographic joint score = the highest score for the joint group (bilaterally) - Bony swelling, tenderness and pain on movement	Rheum Dis 1991	subjects from general practice register, a cancer screening study and patients previously attending hospital for non-joint related symptoms	between 45 and 65 (mean age = 54)	including pain, stiffness and swelling of a joint lasting more than one month) All patients: sensitivity and specificity of bony swelling, tenderness and pain on movement for KL ≥ 2 = 49 and 90%, 7 and 97%, 1 and 99%, respectively; patients with symptoms: 82 and 49%, 17 and 83%, 3 and 94%, respectively. - PIP: 62 women with KL ≥ 2, including 20 (32%) with symptoms All patients: sensitivity and specificity of bony swelling, tenderness and pain on movement for KL ≥ 2 = 40 and 87%, 8 and 99, 5 and 99%, respectively; patients with symptoms: 75 and 49%, 20 and 93%, 10 and 95%, respectively. - CMC: 133 women with KL ≥ 2 including 49 (37%) with symptoms All patients: sensitivity and specificity of bony swelling, tenderness and pain on movement for KL ≥ 2 = 19 and 98%, 26 and 92%, 22 and 96%, respectively; patients with symptoms: 41 and 100%, 49 and 43%, 57 and 61%, respectively

Hand OA: Correlations between x-rays and hand symptoms (6)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL scoring of DIP, PIP and CMC - Symptoms (had ever experienced pain or stiffness) - Bony swelling (IP) and palpable squaring (1st CMC)	Hart, Ann Rheum Dis 1994	Cross-sectional, population-based study	967 women aged 45-65	- Overall prevalence of symptoms (had ever experienced pain or stiffness) in interphalangeal joints (IP of thumb excluded) = 15.2% in KL 0-1 joints, 48.7% in KL 2, 80.9% in KL3-4 ($P < 0.01$). - Prevalence of symptoms of the 1st CMC joint (painful or have been painful in the past) = 10.6% in KL0-1 joints, 34.2% in KL2, 65.1% in KL3-4, $p < 0.01$ - High clinical grades tended to be associated with more severe radiographic abnormalities
- Assessment of DIP and first carpometacarpal joint - OARSI osteophyte and joint	Jones, Osteoarthritis Cartilage 2001	Population-based study, cross-sectional	522 subjects, 33.7% males, mean age = 53.2 ± 14.0 (males)	- AUSCAN pain score associated with DIP (r = 0.32, $P < 0.001$) and CMC (r = 0.35,$P < 0.001$) scores. After adjustments for age, sex, Heberden's node score and other row score, r = 0.17 ($P < 0.003$) for DIP and 0.14 ($P < 0.024$) for CMC

space narrowing for each joint, then all DIP scores summed to obtain a 0-48 total score, and all first carpometacarpal scores summed to obtain a 0-12 total score - Pain, function, grip strength			and 57.0 ± 15.0 (females). ACR criteria for hand OA: 36% (males) and 56% (females)	- AUSCAN function score associated with DIP (r = 0.52, *P* < 0.001) and CMC (r = 0.48, *P* < 0.001) scores. After adjustments for age, sex, Heberden's node score and other row score, r = 0.15 (p < 0.012) for DIP and 0.19 (*P* < 0.001) for CMC. After adjustments for all mentioned variables plus pain, r = 0.08 (*P* = 0.057) for DIP and r = 0.08 (*P* = 0.015) for CMC. - Grip strength associated with DIP (r = - 0.53, p < 0.001) and CMC (r = 0.48, *P* < 0.001) scores. After adjustments for age, sex, Heberden's node score and other row score, r = - 0.12 (*P* < 0.012) for DIP and - 0.09 (*P* < 0.01) for CMC. After adjustments for all mentioned variables plus pain, r = - 0.09 (*P* = 0.052) for DIP and r = - 0.05 (*P* = 0.15) for CMC.
- KL grading of DIP, PIP, MCP, 1st CMC and wrist, OA = KL ≥ 2 - Pain, ROM, hand function (Jebsen test: time spent on 7 maneuvers), grip strength	Labi, Arch Phys Med Rehabil 1982	Cross-sectional	67 subjects, mean age = 81.9 years, 35.8% males	- Pain and ROM not related to OA - Trend toward relation between the Jebsen test and the number of OA joints and severity of OA, but mean time not statistically different between those with and without hand OA (no other data) - After adjustment for sex, grip strength related to OA severity (average grade of all joints) and number of affected joints (*P* < 0.001). Right hand grip strength = 117.3 mm Hg in males hands OA vs 140.5 without OA, 74.4 in females hand OA vs 93.8 without OA. Left hand grip strength = 114.9 mm Hg in males hands OA vs 127.3 without OA, 71.5 in females hand OA vs 72.2 without OA

Hand OA: Correlations between x-rays and hand symptoms (7)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- KL of DIP, PIP, MCP, CMC, wrists - Prevalence of pain during the last week	Lawrence, Ann Rheum Dis 1966	Population-based study, cross-sectional	2292 subjects, 47.9% males	Prevalence of hand pain in the last week - DIP: males KL0-1 1.4%, KL2 8.1%, KL3-4 9.4% (*P* < 0.01) - DIP females: KL0-1 1.3%, KL2 6.2%, KL3-4 25% (*P* < 0.01) - PIP: males KL0-1 4.3%, KL2 22.7%, KL3-4 50.0% (*P* < 0.01) - PIP females: KL0-1 6.8%, KL2 14.1%, KL3-4 41.2% (*P* < 0.01) - MCP: males KL0-1 3.4%, KL2 9.0%, KL3-4 22.2% (*P* < 0.05) - MCP females: KL0-1 6.0%, KL2 13.9%, KL3-4 13.3% (NS) - CMC: males KL0-1 2.2%, KL2 3.8%, KL3-4 33.3% (*P* < 0.01) - CMC females: KL0-1 3.4%, KL2 20.2%, KL3-4 34.4% (*P* < 0.01) - Wrists: males KL0-1 4.3%, KL2 9.1%, KL3-4 42.9% (*P* < 0.01) - Wrists females: KL0-1 6.5%, KL2 4.2%, KL3-4 0% (*P* < 0.01) - Hands males: KL0-1: 2.6 %, KL2: 6.8%, KL3-4: 18.3% - Hands females: KL0-1: 4.3%, KL2: 21.1%, KL3-4: 27.3%
- KL DIP, PIP, MCP, 1st CMC, TS - Pain and disability (AUSCAN)	Marshall, Osteoarthritis Cartilage 2009	Cross-sectional, population-based study	592 participants, mean age = 64 ± 8.2, 38% males	- Mean pain = 5.4 (95%CI = 4.6-6.2) in subjects with no OA, 5.8 (95% CI = 4.9-6.7) in subjects with thumb OA only , 5.7 (95%CI = 4.7-6.8) in subjects with other fingers OA only, 6.5 (95%CI = 6.1-7.0) in subjects with combined fingers and thumb OA, *P* = 0.077 - Mean function = 8.3 (95%CI = 6.7-9.8) in subjects with no OA, 8.6 (95% CI = 6.9-10.3) in subjects with thumb OA only , 8.2 (95%CI = 6.3-10.1) in subjects with other fingers OA only, 10.5 (95%CI = 9.6-11.4) in subjects with combined

				fingers and thumb OA, *P* = 0.018 (but not significant when adjusted for age and adjusted for gender)
- Modification of Thomas's method. DIP, PIP, MCP, CMC, TS. Each joint scored for osteophytes (0-3), JSN (0-3), sclerosis (0-3), cysts (0-3), subchondral erosion (0-1), attrition (0-1), remodelling (0-1). Sum score for both hands - Light pinch, heavy pinch, tripod pinch, lateral grip, dexterity and power grip by timing of different standardized activities. Total time to completion calculated by adding together all the time functions	Pattrick, Ann Rheum Dis 1989	Cross-sectional	- 57 patients, mean age = 69, 7% males, with nodular generalized OA - 10 patients, mean age 70, 10% males, same characteristics + erosive OA - 52 controls (no hand symptom and normal examination), mean age = 71, 9.2% males	- Controls: total radiographic score related to time to complete for light and heavy pinch (r = 0.29 and 0.27,*P* < 0.02 and 0.03), and right thumb base score related to dexterity (r = 0.35, *P* < 0.006). - Nodular generalized OA, total radiographic score related to dexterity (r = 0.28, *P* < 0.02), but no other association. Nodular generalized OA and erosive OA groups, no difference in summed radiographic score between those with or without pain, trick, difficulty or inability.

Hand OA: Correlations between x-rays and hand symptoms (8)

X-ray scoring methods and evaluated symptoms	Reference	Design	Number of subjects, mean age ± SD and % males	Results
- Kallman total score (sum of the scores of individual joints) - Cochin disability index	Poiraudeau, Osteoarthritis Cartilage 2001	Cross-sectional	89 patients, 63.2 ± 8.9 years, 9% males, with hand OA (ACR criteria)	No relationship between the Kallman's index score and the Cochin disability index (Spearman r = 0.14)
- KL - Osteophytes, JSN, cysts, sclerosis grades 0-3 (modification in KL by the fusion of doubtful and	Sonne-Holm, Osteoarthritis Cartilage 2005	Population-based study, cross-sectional	3355 participants 38.6% males, 2747 with KL available (166 with KL ≥ 2),	- Correlation between self-reported pain of the thumb and KL grading, JSN, osteophytes, cysts and sclerosis of the first carpometacarpal joint (*P* < 0.001): 15.7, 24.4, 40.2 and 52.4% with pain in KL 0, 1, 2, 3 and 4, respectively, same patterns for individual features

minimal) - Self-reported pain			3355 individual features available	- Multivariate logistic regression analysis: sclerosis (OR = 1.543, 95%CI = 1.206-1.974) and cysts (OR = 1.229, 95%CI = 1.009-1.498) had independent effects on pain whereas JSN and osteophytes had not. The relationship persisted after including age, sex and BMI in the model - Multivariate logistic regression analysis including KL grading, age, sex and BMI: KL associated with pain (OR = 1.478, 95%CI = 1.325-1.649)
- Kallman score (total, thumbs, and PIP-DIP) - Disability (Cochin index)	Spacek, Osteoarthritis Cartilage 2004	Cross-sectional	- 116 patients fulfilling the ACR criteria, mean age = 62.1 ± 7.4, 7.8% males - 67 with symptoms predominant in thumb base, 49 in PIP and DID	- Disability not correlated with radiological scores - Correlation between disability and radiographic score: r = 0.199 in the whole population, 0.162 in the predominant thumb base pain and disability group, and 0.347 in the predominant DIP and PIP pain and disability - Correlation between disability and thumb base radiographic score: r = 0.009 in the predominant thumb base pain and disability group - Correlation between disability and DIP and PIP radiographic score: r = 0.342 in the predominant DIP and PIP pain and disability
- OARSI atlas for osteophytes and JSN, evaluation of DIP, PIP, thumb IP and 1st MCP - Heberden's and Bouchard's nodes	Thaper, Ann Rheum Dis 2005	Cross-sectional	498 subjects with finger nodes (232 patients and 257 siblings, parents or offspring), 17.1% males, mean age = 65.8 ± 9.2 (males and 65.7 ± 10.0 (females)	- OR of Heberden's node for underlying joint space narrowing = 1.72 (95%CI = 1.47-2.02) - OR of Heberden's node for underlying joint osteophytes = 5.15 (95%CI = 4.37-6.08) - OR of Bouchard's node for underlying joint space narrowing = 1.62 (95%CI = 1.37-1.91) - OR of Bouchard's node for underlying joint osteophytes = 2.98 (95%CI = 2.55-3.47)
- Modified KL (grade 2 included mild joint space narrowing) - DIP, PIP, MCP, base of the thumb joint - Pain	Zhang, Am J Epidemiol 2002	Cross-sectional, population-based study	1041 subjects aged > 70, 35.8% males	- Pain among joints with KL 2, 3 or 4 in men and women was 1.4 and 2.0, 2.7 and 3.4, 5.0 and 4.3 times higher than among joints with KL < 2.

OR: odds ratio, RR = relative risk

KL: Kellgren and Lawrence scoring system, JSN: joint space narrowing

DIP, PIP, MCP, CMC, TS: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, carpometacarpal, trapezoscaphoid

*: not provided in the article, asked directly to the authors

ROM: range of motion

[Click here to return to your place in the text, p 41 (Concurrent Validity/Conventional Radiography/Hand.]

[Click here to return to your place in the text, p 46.]

HAND OA TABLES: RELIABILITY

Table 26: Reliability hand: total hand scores (1)

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Scoring system	Author	Method	Patients	Reliability of measurement (1 time point): ICC	Reliability of change (2 time points): ICC
Verbruggen anatomical phase progression system	Maheu, Ann Rheum Dis 2007	Sum of the scores of all finger joints (DIP, PIP, MCP), normalized on a 0-100 scale	Baseline and hand x-rays of 105 patients, 2 readers (inter), 2 evaluations (intra)	- Inter reader: 0.996 (95%CI = 0.994-0.998) - Intrareader: = 0.999 (0.998-1.000) and 0.999 (0.998-1.000) for readers 1 and 2	- Inter reader: = 0.998 (95%CI = 0.997-0.999) - Intrareader: = 0.941 (0.922-0.958) and 0.988 (0.984-0.992) for readers 1 and 2
Kallman	Kallman, Arthritis Rheum 1989	Mean score of all joints (DIP, PIP, CMC1, TS) for osteophyte, JSN, sclerosis, cysts, deformity, collapse, overall global score not evaluated	50 subjects, 4 readers	- Osteophytes: inter = 0.71, intra = 0.77 - JSN: inter = 0.70, intra = 0.75 - Sclerosis: inter = 0.60, intra = 0.77 - Cysts: inter = 0.29, intra = 0.74 - Deformity: inter = 0.42, intra = 0.80 - Collapse: inter = 0.56, intra = 0.84	ND
Kallman	Maheu, Ann Rheum Dis 2007	Sum of the scores of all features of all hand joints except MCP (DIP, PIP, 1st CMC, TS), normalized on a 0-100 scale	Baseline and hand x-rays of 105 patients; 2 readers (inter), 2 evaluations (intra)	- Inter reader: = 0.706 (95%CI = 0.631-0.781) - Intrareader: = 0.962 (0.950-0.974) and 0.999 (0.998-1.000) for readers 1 and 2	- Inter reader: = 0.995 (95%CI = 0.993-0.997) - Intrareader: = 0.986 (0.982-0.990) and 0.959 (0.947-0.971) for readers 1 and 2
Modified Kallman	Lane, J Rheumatol 1993	Evaluation of DIP, PIP, 1st CMC, TS Only joints with a summary score of 2 evaluated	27 films Inter: 3 reader Intra : 1 reader, 2 evaluations separated by 1	- Inter for average narrowing and osteophytes in the 9 IP joints: ICC > 0.90 - Inter for average erosions and deformity:in the 9 IP joints: K > 0.70	ND

			month Kappa and ICC for raw data	(and < 0.90) - Inter for average sclerosis:in the 9 IP joints: K = 0.42 - Similar results for PIP and DIP separated - Inter CMC ranging from 0.49 (sclerosis) to 0.75 (osteophytes) - Inter TS = 0.66 (narrowing) and 0.56 (sclerosis) - Intra for DIP: 0.93 (narrowing), 0.86 (osteophytes), 0.60 (sclerosis), 0.65 (erosions), 0.61 (deformity) - Intra for PIP: 0.92 (narrowing), 0.86 (osteophytes), 0.82 (sclerosis), 0.85 (erosions), 0.55 (deformity)	
KL	Kallman, Arthritis Rheum 1989	Mean score of all joints (DIP, PIP, CMC1, TS)	50 subjects, 4 readers	-Interreader: 0.74 - Intrareader: 0.80	
KL (with modifications by Lane)	Maheu, Ann Rheum Dis 2007	Sum of the scores of all features of all hand joints (except TS), normalized on a 0-100 score	Baseline and hand x-rays of 105 patients; 2 readers (inter), 2 evaluations (intra)	- Inter reader: = 0.951 (95%CI = 0.936-0.966) - Intrareader: = 0.988 (0.984-0.992) and 0.991 (0.988-0.994) for readers 1 and 2	- Inter reader: = 0.998 (95%CI = 0.997-0.999) - Intrareader: = 0.990 (0.980-1.000) and 0.998 (0.997-0.999) for readers 1 and 2

Reliability hand: total hand scores (2)

Scoring system	Author	Method	Patients	Reliability of measurement (1 time point): ICC	Reliability of change (2 time points): ICC
OARSI	Botha-Scheepers, Arthritis Rheum 2007 and Ann Rheum dis 2009	Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of 1- DIP, PIP, MCP, 1st CMC, TS, maximal score = 96 for osteophytes and for JSN (2007); 2- DIP, PIP, 1st CMC maximal score = 60 for osteophytes and for JSN (2009)	20 radiographs 2 readers reaching a consensus, 2 evaluations	- Intrareader osteophyte score: ICC = 0.98 (both 0-96 and 0-60 scores) - Intrareader JSN score: ICC = 0.92 (both 0-96 and 0-60 scores)	ND
OARSI	Jones, Osteoarthritis Cartilage 2001	Sum of the 0-3 osteophytes scores and of the 0-3 JSN scores of DIP and 1st MCP	45 subjects, 90 hands	- Intrareader osteophyte score: ICC = 0.98 - Intrareader JSN score: ICC = 0.94	ND
Global score	Maheu, Ann Rheum Dis 2007	All hand joints sore 0 = no OA or 1 = OA, sum of all score, normalized on a 0-100 scale	Baseline and hand x-rays of 105 patients; 2 readers (inter), 2 evaluations (intra)	- Inter reader: = 0.859 (95%CI = 0.819-0.899) - Intrareader: = 0.922 (0.899-0.945) and 0.961 (0.949-0.973) for readers 1 and 2	- Inter reader: = 0.999 (95%CI = 0.998-1.000) - Intrareader: = 0.939 (0.921-0.957) and 0.956 (0.943-0.969) for readers 1 and 2
Ordinal summary score 0-2:	Lane, J Rheumatol 1993	Evaluation of DIP, PIP, 1st CMC, TS	27 films Inter: 3 readers Intra : 1 reader, 2 evaluations separated by 1 month Long-term: all films reread by the 3 readers at 6 months Kappa and ICC	- Interrater for average summary grade = 0.85 (DIP), 0.81 (PIP), 0.87 (the 9 IP) 0.72 (CMC) - Intrarater for average grade = 0.86 (DIP) and 0.81 (PIP) - Long-term intrarater for average grade ranged from 0.80 to 0.92 (all joints combined), 0.82 to 0.90 (DIP), 0.77 to 0.89 (PIP), 0.71 to 0.86 (CMC), 0.56	ND

			for raw data	to 0.84 (TS)	

Table 27: Reliability hand: joint scoring without summing to obtain a total score (1)

Scoring system	Author	Method	Patients	Reliability of measurement (1 time point)	Reliability of change (2 time points)
KL	Harris, Osteoarthritis Cartilage 1994	Evaluation of DIP, PIP and CMC	15 films (30 hands) 2 readers (inter), 2 evaluations (intra), reader 1 and reader 2), unweighted Kappa	- DIP: inter, K = 0.58, intra = 0.89 and 0.58 - PIP: inter, K = 0.72; intra, K = 0.86 and 0.80 - CMC: inter, K = 0.61; intra, K = 0.80 and 0.80	ND
KL	El-Sherif, Osteoarthritis Cartilage 2008	We do not know which joints were evaluated (probably DIP, PIP, MCP and CMC)	N = unknown, 2 readers (intra), 2 evaluations (inter), Kappa	- Inter: K = 0.65 - Intra: K = 0.79 (reader 1) and 0.82 (reader 2)	ND
KL	Haara, Ann Rheum Dis 2003	Evaluation of DIP, PIP, MCP, 1st CMC	N = unknown, 2 readers, Kappa	- Inter: K = 0.53 - Intra: K = 0.71	
KL	Dahaghin, Ann Rheum Dis 2005	Evaluation of DIP, PIP, MCP, 1st CMC, TS Careful: evaluates reliability of classifying joints as ≥ 2 or < 2 (OA vs no OA)	205 hands, 2 observers, reliability intra not evaluated, Kappa	- DIP inter: K = 0.6 - PIP inter: K = 0.61 - MCP inter: K = 0.63 - 1st CMC + TS inter: K = 0.74	ND
Framingham modified KL	Chaisson, J Rheumatol 1997	Evaluation of DIP, PIP, MCP, base of thumb (= 1st CMC and TS) Evaluates reliability of classifying joints as ≥ 2 or < 2 (OA vs no OA)	54 hands, 2 readers, 2 evaluations	- Inter: K = 0.65 - Intra: K = 0.79 (reader 1) and 0.82 (reader 2)	ND
Altman	McCarthy, Osteoarthritis	Evaluation of DIP, PIP, MCP, CMC, thumb	20 hands, 1 reader, 2 evaluations, Kappa	- Intra: K = 0.74 for the presence of an OA joint	ND

	Cartilage 1994	base, radio-ulnar joints Careful: evaluates reliability of classifying joints as ≥ 2 or < 2 (OA vs no OA)			
Balblanc	Balblanc, Osteoarthritis Cartilage 1995	- Only DIP and PIP evaluated - JSN, osteophytes, sclerosis, cysts and subluxation scored 0-3 for each joint. Sum score (0-15) for each joint	10 radiographs, 2 readers (inter), 2 evaluations (intra), reader 1 and reader 2), coefficient of correlation	- Sum score: inter, r = 0.74; intra, r = 0.78 and 0.79 - JSN: inter, r= 0.83; intra, r = 0.90 and 0.89 - Osteophytes: inter, r = 0.77; intra, r = 0.82 and 0.77 - Sclerosis: inter, r = 0.67; intra, r = 0.79 and 0.76 - Cysts: inter, r = 0.66; intra, r = 0.75 and 0.81 - Subluxation: inter, r = 0.73; intra, r = 0.68 and 0.67	ND

Reliability hand: joint scoring without summing to obtain a total score (2)

Scoring system	Author	Method	Patients	Reliability of measurement (1 time point)	Reliability of change (2 time points)
Kallman	Harris, Osteoarthtitis Cartilage 1994	Evaluation of DIP, PIP and CMC Osteophytes and JSN 0-3 according to Kallman	15 films (30 hands) 2 readers (inter), 2 evaluations (intra), reader 1 and reader 2), unweighted Kappa	- Osteophytes DIP: inter, K = 0.58, intra, K = 1.0 and 0.51 - Osteophytes PIP: inter, K = 0.72; intra, K = 0.86 and 0.80 - Osteophytes CMC: inter, K = 0.72; intra, K = 0.87 and 0.80 - JSN DIP: inter, K = 0.80; intra, K = 0.66 and 0.62 - JSN PIP: inter, K = 0.75; intra, K = 0.77 and 0.83	ND

				- JSN CMC: inter, K = 0.78; intra, K = 0.77 and 0.70	
Burnett	Cicuttini, Ann Rheum Dis 1998	Evaluation of osteophytes on DIP using an atlas (0-3 grades)	50 hands, number of readers and of evaluations unknown, Kappa	- Inter DIP osteophytes : K = 0.80 - Intra DIP osteophytes : K = 0.80	ND
Verbruggen	Verbruggen, Arthritis Rheum 1996	Evaluation of DIP and PIP, 2 readers, 2 readings	20 radiographs, weighted Kappa		- Pathologic phase score: intra: K = 0.623 (95% CI 0.329) and 0.726 (95% CI 0.399) (readers 1 and 2) - Pathologic phase score, inter: K = 0.726 (95% CI 0.388) - Anatomic score, intra: r = 0.934 and 0.666 (readers 1 and 2) - Anatomic score, inter: r = 0.744

[Return-to-text hyperlink located at the top of Table 26, p 239.]

HAND OA TABLES: RESPONSIVENESS

Responsiveness of x-rays in hand OA

Table 28: Change in total score (1)

Scoring system	Author, study design and length of follow-up	Scoring method	Number and characteristics of the patients	Results	Effect-size and SRM
Verbruggen anatomical PHASE progression system	Maheu, Ann Rheum Dis 2007, 1-year RCT	Sum of the scores of all finger joints (DIP, PIP, MCP), normalized on a 0-100 scale	105 patients (mean age = 60.9 ± 6.4 years, 5% males	Not provided	SRM (95% CI) = 0.18 (0.00 to 0.36) and 0.27 (0.07 to 0.45) for readers 1 and 2, respectively
Verbruggen anatomical PHASE progression system	Verbruggen, Rev Rhum 1995, 5-year cohort	Mean scores of DIP, PIP, and MCP, thumbs not evaluated	36 patients, mean age = 57 years	- Mean DIP scores = 14.43 ± 11.72 (baseline), 16.96 ± 14.02 (3 years), 18.40 ± 15.19 (5 years) - Mean PIP scores = 5.93 ± 7.09 (baseline), 7.76 ± 9.12 (3 years), 9.03 ± 10.12 (5 years) - Mean MCP scores = 2.21 ± 2.32 (baseline), 2.42 ± 2.54 (3 years), 4.64 ± 4.54 (5 years)	- * - DIP: ES = 0.22 (3 years), 0.34 (5 years) - PIP: ES = 0.26 (3 years), 0.44 (5 years) - MCP: ES = 0.09 (3 years), 1.04 (5 years)
Verbruggen anatomical PHASE progression system	Verbruggen, Clin Rheumatol 2002 Two 3-year RCTs (Chondroitin Sulfate vs placebo and chondroitin polysulfate vs placebo)	Mean scores of DIP, PIP, and MCP, thumbs not evaluated	- Placebo 1: n = 48, mean age = 55.9 yrs, 12.5% males - Placebo 2: n = 64, mean age = 56.1 yrs, 3.1% males	DIP placebo 1 + 2: mean baseline anatomical phase progression = 13.7, mean 3-year change = 2.6 PIP placebo 1 + 2: mean baseline anatomical phase progression = 6.9, mean 3-year change = 1.4 MCP placebo 1 + 2: mean baseline anatomical phase progression = 3.2, mean 3-year change = 0.4	Not provided
Verbruggen anatomical PHASE	Fioravanti, Rheumatol Int 2009, 1-year	Mean scores of DIP 2-5 and PIP 2-	10 patients with bilateral symptomatic	- DIP saline group: mean score = 4.57(baseline) and	Not provided

progression system	therapeutic trial (intraarticular injection in affected DIP and PIP of the most affected hand (infliximab) and the other hand (saline)	5	erosive hand OA, mean age = 60.7 ± 6.2, all females	4.84 (1 year) - PIP saline group: mean score = 2.6 (baseline) and 3.01 (1 year)	
Verbruggen anatomical LESION progression system	Verbruggen, Clin Rheumatol 2002 Two 3-year RCTs (same as line above)	Mean scores of DIP, PIP, and MCP, thumbs not evaluated	Same as line above	- DIP placebo 1 + 2: mean 3-year anatomical lesion progression = 3.5 - PIP placebo 1 + 2: mean 3-year anatomical lesion progression = 2.8 - MCP placebo 1 + 2: mean 3-year anatomical lesion progression = 0.5	Not provided

1) Change in total score (2)

Scoring system	Author, study design and length of follow-up	Scoring method	Number and characteristics of the patients	Results	Effect-size and SRM
Verbruggen anatomical LESION progression system	Verbruggen, Rev Rhum 1995, 5-year cohort	Mean scores of DIP, PIP, and MCP, thumbs not evaluated	36 patients, mean age = 57 years	- DIP: mean 3 and 5-year anatomical lesion progression = 2.83 ± 2.71 and 4.50 ± 4.35 (reader 1); 2.86 ± 1.96 and 5.03 ± 3.64 (reader 2) - PIP: mean 3 and 5-year anatomical lesion progression = 2.65 ± 3.19 and 4.31 ± 4.79 (reader 1); 2.13 ± 1.74 and 4.03 ± 3.16 (reader 2) - MCP: mean 3 and 5-year anatomical lesion progression = 0.43 ± 0.75 and 0.76 ± 1.39 (reader 1); 0.76 ± 1.39 and 1.04 ±	- 5-year SRMs = 1.03 and 1.38 (readers 1 and 2) for DIP, 0.90 and 1.28 (readers 1 and 2) for PIP, 0.55 and 0.64 (readers 1 and 2) for MCP - 3-year SRMs = 1.04 and 1.46 (readers 1 and 2) for DIP, 0.83 and 1.22 (readers 1 and 2) for PIP, 0.57 and 0.55 (readers 1 and 2)

				1.62 (reader 2)	for MCP
Kallman	Maheu, Ann Rheum Dis 2007, 1-year RCT	Sum of the scores of all features of all hand joints except MCP (DIP, PIP, 1st CMC, TS), normalized on a 0-100 scale	105 patients (mean age = 60.9 ± 6.4 years, 5% males, mean pain (VAS) = 55.7 ± 15.7.	Not provided	SRM (95% CI) = 0.26 (0.05 to 0.46) and 0.29 (0.00 to 0.51) for readers 1 and 2, respectively
Kallman	Olejarova, Joint Bone Spine 2000, cohort 2-year follow-up	Sum of the scores of all features of all hand joints (DIP, PIP, MCP,1st CMC), 0-300 total score	52 patients with hand OA, including 24 without erosions and 28 with at least 3 erosions, 45 with 2-year follow-up	- Erosive OA: Kallman score at inclusion = 91.81 ± 43.67, 2-year change = 5.0 - Non erosive OA: Kallman score at inclusion = 25.88 ± 12.81, 2-year change = 4.3	- Erosive OA: ES = 0.11 - Non erosive OA: ES = 0.34
KL (with modifications by Lane)	Maheu, Ann Rheum Dis 2007, 1-year RCT	Sum of the scores of all features of all hand joints (except TS), normalized on a 0-100 score	105 patients (mean age = 60.9 ± 6.4 years, 5% males, mean pain (VAS) = 55.7 ± 15.7.	Not provided	SRM (95% CI) = 0.17 (0.00 to 0.34) and 0.24 (0.05 to 0.42) for readers 1 and 2, respectively
KL	Kalichman, Am J Human Biol 2005, cohort, follow-up = 8 years	Evaluation of DIP, PIP and MCP joints of both hands. Thumb IP considered as DIP. KL grades. Sum of KL scores of each raw of joints, sum of KL scores of all 28 joints	263 subjects, (127 males, mean age at baseline = 45.3 ± 16.1 years; and 136 females, mean age at baseline = 49.7 ± 15.3 years)	- DIP score: 6.0 ± 5.6 to 8.0 ± 5.8 in men (change = 8.0 – 6.0 = 2.0), 8.0 ± 6.0 to 10.1 ± 7.0 in women - PIP score: 3.2 ± 2.8 to 4.4 ± 3.1 in men (change = 4.4 - 3.2 = 2.2), 4.2 ± 3.5 to 5.7 ± 3.8 in women - MCP score: 6.1 ± 2.7 to 7.9 ± 2.4 in men (change = 7.9 – 6.1 = 1.8), 6.9 ± 2.6 to 8.0 ± 2.4 in women - Total hands score: 15.3 ± 9.8 to 20.4 ± 9.7 in men (change = 20.4 – 15.3 = 5.1), 19.1 ± 10.8 to 24.3 ± 11.6 in women	- * - DIP score: ES = 0.36 in men, 0.35 in women - PIP score: ES = 0.43 in men and in women - MCP score: ES = 0.69 in men, 0.42 in women - Total hands score: ES = 0.52 in men, .0.48 in women

1) Change in total score (3)

Scoring system	Author, study design and length of follow-up	Scoring method	Number and characteristics of the patients	Results	Effect-size and SRM
OARSI	Botha-Scheepers, Rheumatology 2005, cohort, follow-up = 2 years	Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of DIP, PIP, MCP, 1st CMC, TS, maximal score = 96 for osteophytes and for JSN	20 patents from the GARP study including 75% with hand OA (ACR), mean age = 61.6 years, 10% males	- Baseline total JSN & osteophyte scores = 16 and 7 - Reading without knowledge of the chronology: 2-year changes in mean JSN and osteophyte scores = 0.00 ± 0.56 and = 0.25 ± 0.64 - Reading with knowledge of the chronology: 2-year changes in mean JSN and osteophyte scores = 0.20 ± 0.52 and = 0.15 ± 0.37 (NS vs without knowledge)	- Reading without knowledge of chronology: SRM = 0.00 (JSN), and SRM = 0.39 (osteophyte) - Reading with knowledge of chronology: SRM = 0.38 (JSN), and SRM = 0.41 (osteophyte)
OARSI	Botha-Scheepers, Ann rheum Dis 2009, cohort, follow-up = 2 years	Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of DIP, PIP, 1st CMC (not MCP and TS), maximal score = 60 for osteophytes and for JSN	172 subjects from the GARP study, mean age = 59.7 years, 21.5% males	- Osteophyte score: baseline 9.3 ± 7.9, 2-year follow-up 9.7 ± 8.5, 2-year change = 0.4 ± 1.2 (95%CI = 0.2-0.6) - JSN score: baseline 14.6 ± 10.5, 2-year follow-up 14.9 ± 10.9, 2-year change = 0.3 ± 1.0 (95%CI = 0.2-0.5)	- Osteophyte score: ES = 0.05, SRM = 0.35 - JSN narrowing score: ES = 0.03, SRM = 0.34
Global score	Maheu, Ann Rheum Dis 2007, 1-year RCT	All hand joints, score 0 = no OA or 1 = OA, sum of all scores, normalized on a 0-100 scale	105 patients (mean age = 60.9 ± 6.4 years, 5% males, mean pain (VAS) = 55.7 ± 15.7.	Not provided	SRM (95% CI) = 0.17 (0.00 to 0.37) and 0.27 (0.06 to 0.47) for readers 1 and 2, respectively

Balblanc	Balblanc et al, Osteoarthritis Cartilage 1995, 4-year cohort	PIP and DIP scored 0-3 for joint space, osteophytes, sclerosis, bone cysts and subluxation, leading to a total score/joint ranging from 0 to 15.	15 patients, mean age = 59 yrs, 6.7% males, clinically and radiographic hand OA.	- OA joints (n = 207) mean baseline score = 3.9 ± 3.15 - Mean OA joints mean follow-up score = 4.67 ± 3.74 - All joints baseline score = 2.58 ± 3.16 - All joints mean follow-up mean score = 3.33 ± 3.63	- * - ES = 0.24 (OA joints) and 0.24 (all joints)
Number of joints with erosions	Rovetta, Int J Tissue React 2002, 2-years RCT (naproxen vs naproxen + chondroitine sulphate)	Number of PIP and DIP joints with erosion	24 patients, mean age = 53.0 ± 6 yrs, 8.3% males with symptomatic hand OA and central erosions of at least 1 PIP or DIP	- Naproxen alone: mean number of DIP and PIP joints with erosion = 2.33 ± 0.65 (baseline) and 4.00 ± 0.43 (2-years), Mean change = 1.67 ± 0.78	Naproxen alone: Effect-size = 2.57, SRM = 2.14
Osteophyte number and area	Buckland-Wright, Eur J Nucl Med 1991, 1-year cohort	Microfocal radiography Measurement of the osteophytes number and area of all radiocarpal, ulneocarpal, intracarpal, CMCCP, PIP and DIP joints	32 patients, mean age = 61.4 ± 10 years, 9.4% males	- Osteophyte number = 26.9 ± 11.6 at baseline and 28.0 ± 11.5 after 1 year - Osteophyte area = 60.7 ± 43.6 mm^2 at baseline and 64.3 ± 42.9 mm^2 after 1 year	- * - Osteophyte number: Effect-size = 0.095 - Osteophyte area: Effect-size = 0.083

KL: Kellgren and Lawrence scoring system, JSN: joint space narrowing

DIP, PIP, MCP, CMC, TS: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, carpometacarpal, trapezoscaphoid

*: not provided, calculated using mean follow-up – mean baseline instead of mean change

Table 29: Percentage of progressors (1)

Scoring system	Author, study design and length of follow-up	Scoring method	Number and characteristics of the patients	Results
Kallman	Harris, Osteoarthritis Cartilage 1994, 10 years (8-15 yrs) follow-up cohort	Evaluation of DIP, PIP and CMC using osteophytes and joint space narrowing 0-3 grades according to Kallman. For each hand, the DIP, PIP, and CMC score = the highest score of the evaluated DIP, PIP and CMC joints	59 patients, mean age at follow-up = 69 years, 23.7 % males	Osteophytes: percentage of hands with progression of at least 1 grade = 39% (DIP), 39 % (PIP), 38 % (CMC) - Joint space narrowing: percentage of hands with progression of at least 1 grade = 39% (DIP), 42 % (PIP), 48 % (CMC)
KL	Cvijetic, Eur J Epidemiol 2004, population-based cohort, 10 years follow-up	Evaluation of each DIP, PIP, 1st CMC, and radiocarpal (RC) joints, highest radiographic grade recorded	286 subjects, 160 women, mean baseline age = 56.4 ± 8.4 years; 126 men, mean baseline age = 54.9 ± 9.4 years	- Percentage of participants with changes of at least 1 osteoarthritic grade - DIP: 54.5 % men and 59.9 % women - PIP: 33.7 % men and 34.9 % women - CMC: 49.9 % men and 41.2 women - RC: 8.1% men and 1.2 % women
KL	Harris, Osteoarthritis Cartilage 1994, 10 years (8-15 yrs) follow-up cohort	Evaluation of DIP, PIP and CMC using KL. For each hand, the DIP, PIP, and CMC score = the highest score of the evaluated DIP, PIP and CMC joints	59 patients, mean age at follow-up = 69 years, 23.7 % males	Percentage of hands with progression of at least 1 grade = 47% (DIP), 50 % (PIP), 47 % (CMC)
KL	Busby, Ann Hum Biol 1994, community-based cohort with x-rays taken at leat 5 years apart (mean follow-up = 9.2 yrs, range = 5.0-16.3)	DIP and PIP were graded with KL. For each subject, DIP and PIP grades = the grades of the most affected DIP and the most affected PIP joints DIP progression = increase in the DIP	386 males	- DIP time to progression of 50% of the population = 11.75 years in subjects aged < 40 years, 11.16 ± 1.25 in subjects aged 40-60, and 8.34 ± 0.51 in subjects aged > 60 - PIP time to progression of 50% of the population = 12.26 ± 0.98 years in subjects aged < 40 years, 12.13 ± 0.94 in subjects aged 40-60, and

		grade, PIP progression = increase in the PIP grade (after exclusion of grades 4)		10.01 ± 0.76 in subjects aged > 60 - Time to increase in the number of DIP OA joints in 50 % of the population = 15.0 ± 0.5 yrs in youngs, 9.4 ± 0.9 in olds - Time to increase in the number of PIP OA joints in 50 % of the population = 15.7 ± 1.5 yrs in middle-aged, 9.4 ± 0.9 in olds
KL	Plato, Am J Epidemiol 1979, longitudinal cohort, V1, V2, V3 and V4 = x-rays taken 3 (mean = 2.3), 7 (mean = 5.8), 11 (mean = 9.5) and 16 (mean = 13.4) years after baseline	Evaluation of DIP and PIP joints using KL. DH = highest score of the 4 DIP + thumb IP, PH = highest score among the 4 PIP + 1st MCP, IH = highest score among all joints	478 subjects who had hand radiographs at least twice	- DH. Patients with OA at baseline (KL ≥ 2): increase at V1 in 18.2%, at V2 in 31.6%, at V3 in 58.3%, at V4 in 72.4% (out of 22, 136, 60 and 29 patients, respectively) (patients with grade 4 at baseline excluded) - PH. Patients with OA at baseline (KL ≥ 2): increase in DH at V1 in 13.3%, at V2 in 21.1%, at V3 in 23.1%, at V4 in 21.4% (out of 15, 57, 26 and 14 patients, respectively) (patients with grade 4 at baseline excluded)

2) Percentage of progressors (2)

Scoring system	Author, study design and length of follow-up	Scoring method	Number and characteristics of the patients	Results
OARSI	Botha-Scheepers, Rheumatology 2005, cohort, follow-up = 2 years	Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of DIP, PIP, MCP, 1st CMC, TS. Progression = increase in at least one grade in osteophytes or JSN total scores of the different joint groups	20 patents from the GARP study including 75% with hand OA (ACR), mean age = 61.6 years, 10% males	- Reading without knowledge of the time sequence: progression in 5% patients for JSN and 15% for osteophytes - Reading with knowledge of the time sequence: progression in 15% patients for JSN and 15% for osteophytes
OARSI	Botha-Scheepers, Ann Rheum Dis 2009, cohort,	Sum of the 0-3 osteophyte scores and of the 0-3 JSN scores of DIP, PIP, 1st	172 subjects from the GARP longitudinal cohort	- Radiological progression in 21.5% of patients for osteophyte score and

	follow-up = 2 years	CMC (but not MCP and TS). Progression = osteophyte or JSN progression score of at least 1 over the 2 years	study, mean age = 59.7 years, 21.5% males	19.2% for JSN score
Burnett	Hassett, Ann Rheum Dis 2006, patients from the Chingford cohort, with baseline and 11-year follow-up x-rays	Evaluation of DIP and CMC joints for osteophytes (0-3 scale) and joint space narrowing (0-3 scale) using the Burnett atlas. Progression if patients developed an increased grade ≥ 1 or a new grade 1 or more in an unaffected joint.	704 women	- 222 patients with baseline hand OA assessed by osteophytes. After 11 years, 161 (72.5%) progressors - 308 patients with baseline hand OA assessed by JSN. After 11 years, 197 (64.0%) progressors
Other	McCarthy et al, Osteoarthritis Cartilage 1994, prospective cohort, mean follow-up = 67.3 months	Evaluation of DIP, PIP, MCP, 1st CMC, wrist joint and radio-ulnar joint Progression = definite increase in osteophytosis, joint space narrowing or increase in subchondral bone damage (sclerosis, cysts or erosion)	67 patients with KNEE OA, mean age = 62.7 ± 10.7 at entry, 38.8% males	- 349 joints with evidence of hand OA at entry (47 patients) - Progression on 87 joints (3.8%), including 23 with no OA at baseline (1.2%) and 64 with OA at baseline (18.3%)

KL: Kellgren and Lawrence scoring system, JSN: joint space narrowing

DIP, PIP, MCP, CMC, TS: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, carpometacarpal, trapezoscaphoid

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APPENDIX 6

MAGNETIC RESONANCE IMAGING

Conventional radiography (CR) has been the mainstay of assessing structural change in osteoarthritis (OA) clinical trials and is currently part of FDA recommendations on how to conduct trials to assess structural progression. The focus of such evaluations has been on the radiographic joint space as a surrogate for hyaline cartilage assessment. Modern imaging, especially magnetic resonance imaging, allows unparalleled visualisation of all the tissues involved in OA joint pathology, including cartilage, menisci, subchondral bone and soft tissue. MRI is ideally suited for imaging synovial joints as is it free of ionizing radiation, and its tomographic viewing perspective obviates morphological distortion, magnification and superimposition. More importantly, MRI has unlimited image contrast variability resulting in an unparalleled ability to discriminate articular tissues and therefore holds great potential as a tool for whole-organ imaging of the OA joint. The last 20 years has seen a rapid improvement in imaging technology and in the last decade this has translated into improved understanding of the importance of individual features, their relation to clinical outcome and disease pathogenesis and better data on the quantification of these pathologies.[1,2] The over-arching aim of the Assessment of Structural Change Working Group is to make recommendations on the state-of-the art in assessing structural change in OA for the purposes of optimising utilisation in OA clinical trials. As part of this initiative the following systematic review was undertaken.

4.1 Objective

The overarching aim was to perform a systematic literature review regarding the psychometric properties of MRI assessment in knee, hip or hand osteoarthritis (OA).

More specifically we:

1. Summarized the available evidence on the rate of MRI structural progression as it pertains to the validity (truth domain of OMERACT filter) and responsiveness (discrimination domain of OMERACT filter).[3,4] For this aim we extracted data from longitudinal studies (both observational studies and clinical trials).
2. Described the reliability and reproducibility of MRI-based measures of structural change. For this aim we extracted data from both longitudinal and cross-sectional studies.

The study assessed all synovial joint tissues (cartilage, meniscus, subchondral bone, synovium, etc) as it relates to MRI measurement pertaining to the above aims.

4.2 Methods

Literature Review Search Strategy

We conducted a standardized search strategy in Medline, CINAHL, Cochrane, and PsycINFO using the following search strategy.

1. Standard search strategy for osteoarthritis

*osteoarthritides/ OR *osteoarthrosis/ OR *Osteoarthroses/ OR *Arthritis, Degenerative/ OR *Arthritides, Degenerative/ OR *Degenerative Arthritides/ OR *Degenerative Arthritis/ OR *Osteoarthrosis Deformans/

OR

osteoarthritis.mp. or Osteoarthritis, Hip/ or Osteoarthritis, Knee/ or Osteoarthritis, Hand/

2. Standard search limits for searches

Language: English

Date range: 1950 – April 2009

Age groups: Humans, adults 19+ years

International studies can be included

Search Terms

1. MRI

*magnetic resonance imaging/ or *MRI

Additionally, we will examine the reference lists of all relevant studies, and hand-searched specialized journals in this field.

The Ovid and Cochrane search came up with 806 results.

The CINAHL & Psych Info search came up with 539 results.

There were 15 duplicates found between these 2 searches.

(806 + 539) – 15 duplicates = 1330 abstracts.

From the citations in the review articles, we also ended up reviewing a total of an additional 7 articles. Therefore, the total number of articles screened for relevance = 1337.

Screening for Relevance

We screened all citations identified through our search strategy and included English-language reports; published reports of original research, systematic reviews, conference proceedings, government reports, guidelines; studies examining the validity, reliability, sensitivity to change as SRMs, and clinical relevance.

We included studies with a focus on hip, knee or hand OA (whatever the criteria) with analysis of MRI (quantitative or semi-quantitative). We included both RCTs and observational studies (case control, cross sectional, and cohort studies).

We excluded studies not focused on OA or not presenting original data such as narrative, editorial, or clinical reviews, opinion papers, letters to the editor, and editorials; studies of conditions with questionable clinical relevance; studies using only cadavers or nonhuman subjects.

Individual citations were downloaded into bibliographic software that captured the following information: Abstract; Accession number / unique identifier; Affiliation / address; Article identifier / digital object identifier (DOI); Clinical trial number (if applicable); Index terms / thesaurus terms / keywords; Language; Comments, corrections, errata, retractions, and updates.

Two reviewers independently appraised the relevance of each citation found in the electronic search through a two-level screening process, with disagreements resolved by consensus. In the first-level screening, reviewers categorized citations as probably relevant, of unknown relevance, or irrelevant. For each citation rated as probably relevant or of unknown relevance, the entire paper was obtained and, in the second-level screening, these were deemed to be either relevant or irrelevant to the systematic review.

If the same group of authors published several articles on the same cohort, any articles that featured duplicate information were excluded.

Of the 1337 abstracts, 356 were deemed relevant to the purposes of this analysis. After further review of the full text article only 242 manuscripts were deemed relevant.

Critical appraisal

The aim of the systematic review was to provide a summary of the best evidence. However, as a result of issues related to the quality of research, findings of studies can sometimes be misleading or incorrect. To minimize these risks, the quality of the studies was critically appraised using Downs checklist.[5]

Data abstraction

We used a data abstraction tool constructed in EpiData and more than one reviewer undertook the data abstraction. The data collection forms were designed to target the objectives of the review, and were piloted prior to conducting the study.

The outcomes for psychometric properties on MRI were examined using the OMERACT filter.[3,4]

1. **Truth**: is the measure truthful, does it measure what it intends to measure? Is the result unbiased and relevant? This criterion captures the issues of face, content, construct and criterion validity.

- Does it agree (by independent and blind comparison) with a 'gold standard' (concurrent criterion validity)?

- Does it predict (by independent and blind comparison) a future 'gold standard' (predictive criterion validity)?

- Was an independent and blind comparison performed for determination of construct and criterion validity?

- Were the statistical methods adequately described and appropriately chosen?
  - If both measures are continuous are intraclass correlation coefficient (1.0 is perfect reliability agreement), 95% limits of agreement (the smaller the better), and mean difference (ie, paired t-test, and again the smaller the better) and mean vs difference or mean vs variance plot (to examine important trends) reported?
  - If both measures are categorical are the weighted and unweighted kappa (1.0 is perfect agreement), sensitivity, specificity, and likelihood ratio reported?

- If one measure is categorical and the other continuous is an ROC curve reported?
- If both measures are continuous but units are different are the units rescaled or standardized to allow reporting using the methods described above or are correlation and linear regression methods of analysis reported?

2. **Discrimination**: does the measure discriminate between situations that are of interest? The situations can be states at one time (for classification or prognosis) or states at different times (to measure change). This criterion captures the issues of reliability and sensitivity to change.

- Were all facets of reliability evaluated (between occasions, procedural, within observers, between observers, other sources of variability)?
- Was reliability tested independently and blind to previous results?

- Were the statistical methods adequately described and appropriately chosen?
  - If continuous measures, are the intraclass correlation coefficient, limits of agreement (smallest detectable difference), and mean difference (ie, paired t-test), coefficient of variation and mean vs difference or mean vs variance plot all reported?
  - If categorical measures, were percentage agreement (weighted and unweighted) and kappa statistic (weighted and unweighted) all reported?

- Was responsiveness tested independently and blind to previous results?

- Were the statistical methods adequately described and appropriately chosen?
  - Is the relative efficiency reported? This is the square of the ratio of two paired t statistics (or two paired z statistics). The square of the paired t statistic is also known as the coefficient of variation, so relative efficiency is also the ratio of the coefficients of variation.
  - Is the 'standardized response mean' (SRM) reported? This is the mean change in scores from time zero to time one divided by the standard deviation of these changes. A large SRM indicates good responsiveness.
  - Is the smallest detectable difference reported. This is a measurement error based definition of responsiveness and is the absolute value of the 95% confidence limits around the standard deviation of the difference scores from a test-retest reliability study?

4.3 Results

4.3.1 Concurrent Validity

[Click on the above hyperlink to return to your place in the text, p 42.]

The analysis included data from 142 manuscripts.

The mean Downs criteria score for these manuscripts was 72.6 (range 42-82).

What follows below are important excerpts from this data.

1) Relation to radiographic features

1.a. Relation of quantitative cartilage measures to radiographic abnormalities

- Significant difference in lateral and medial femorotibial cartilage thickness between those with and without radiographic OA. Significant cartilage thinning could be detected by MRI in patients with OA, even when the joint space was normal radiographically.[164,165]

- Univariate analysis revealed no relationship between grade of osteophytes and MRI cartilage volume, for every increase in grade of lateral tibiofemoral osteophytes the lateral tibial cartilage volume was significantly reduced by 255 mm^3, after adjustment. There was a reduction of 77 mm^3 in medial tibial cartilage volume for every increase in grade of medial tibiofemoral osteophytes, but this finding was only of borderline statistical significance.[165]

- Cartilage volume and thickness were less in patients with OA compared to normal controls (P <0.1).[166]

- KLG2 participants displayed, on average, thicker cartilage than healthy controls in the medial femorotibial compartment (particularly anterior subregion of the medial tibia (MT) and peripheral [external, internal] subregions of the medial femur), and in the lateral femur. KLG3 participants displayed significantly thinner cartilage than KLG0 participants in the medial weight-bearing femur (central subregion), in the external subregion of the MT, and in the internal subregion of the lateral tibia.[167]

- Mean cartilage signal intensity provided a clear separation of healthy from KL 1 (P = 0.0009). Quantification of cartilage homogeneity by entropy was able to clearly separate healthy from

OA subjects (P = 0.0003). Furthermore, entropy was also able to separate healthy from KL 1 subjects (P = 0.0004).[168]

1.b. Relation of other MRI measures to radiographic abnormalities

- Significant difference (P = 0.002) in the average T(1rho) within patellar and femoral cartilage between controls (45.04 +/- 2.59 ms) and osteoarthritis patients (53.06 +/- 4.60 ms). A significant correlation was found between T(1rho) and T(2); however, the difference of T(2) was not significant between controls and osteoarthritis patients.[168]

- Trend toward a lower dGEMRIC index with increasing Kellgren Lawrence (KL) radiographic severity grade; the spared compartments of knees with a KL grade 2 had a higher dGEMRIC index than those of knees with a KL grade 4 (mean 425 msec versus 371 msec; $P < 0.05$).[169]

- All cases, that demonstrated decrease of T1 values on dGEMRIC, showed abnormal arthroscopic or direct viewing findings. The diagnosis of damage in articular cartilage was possible in all 16 cases with radiographic K-L grade I on dGEMRIC, while the intensity changes were not found in 10 of 16 cases on PDWI.[170]

- No differences of T2 values were found across the stages of OA (P = 0.25), but the factor of BMI did have a significant effect (P <0.0001) on T2 value.[171]

- Average T(1rho) and T(2) values were significantly increased in OA patients compared with controls (52.04+/-2.97ms vs 45.53+/-3.28ms with P = 0.0002 for T(1rho), and 39.63+/-2.69ms vs 34.74+/-2.48ms with P = 0.001 for T(2)). Increased T(1rho) and T(2) values were correlated with increased severity in radiographic and MR grading of OA. T(1rho) has a larger range and higher effect size than T(2), 3.7 vs 3.0.[172] Statistically significant correlation between radiography and MR cartilage loss in the medial (r = 0.7142, P = 0.0001) and lateral compartments (r = 0.4004, P = 00136). Significant correlations also found between radiographic assessment of sclerosis and osteophytes and those found on MRI.[173]

- Patients in whom plain radiographs, MRI, and arthroscopy were compared, the plain radiographs and MRI significantly underestimated the extent of cartilage abnormalities.[174]

- Presence of synovial thickening was more likely with increasing KL grade, from 24.0% in those with KL grade 0 to 78.3% in those with grade 3/4 *(P* <0.001, chisquare).[175]

- Higher KL radiographic grade was correlated with a higher frequency of meniscal tears (r = 0.26, *P* <0.001).[176]

- KL score correlated significantly (*P* <.05) with the grade of cartilage lesions, and a substantially higher percentage of bone marrow and meniscal lesions with higher KL scores found on MR images.[177]

- Women with osteoarthritis had larger medial and lateral tibial plateau bone area (mean [SD]: 1850 [240] mm^2 and 1279 [220] mm^2, respectively) than healthy women (1670 [200] mm^2 and 1050 [130] mm^2) (*P* <0.001 for both differences). For each increase in grade of osteophyte, an increase in bone area was seen of 146 mm^2 in the medial compartment and 102 mm^2 in the lateral compartment.[178]

- Statistically significant correlations were observed between the medial tibial spur classification on x-ray, the medial meniscal displacement rate on MRI and the medial meniscal signal change classification on MRI.[179]

- Meniscal damage was mostly present in knees with OA and demonstrates a relation to KL grade.[180]

- Any bone attrition of the tibio-femoral joint, scored >1, was found in 228 MRIs (23.6%) and in 55 radiographs (5.7%). Moderate to strong correlation between MRIs and radiographs for bone attrition of the tibio-femoral joint (r = 0.50, *P* <0.001).[181]

- Surface curvature of articular cartilage for both the fine- and coarse-scale estimates were significantly higher in the OA population compared with the healthy population, with *P* <0.001 and *P* <0.001, respectively.[182]

- The prevalence of meniscal damage was significantly higher among subjects with radiographic evidence of tibiofemoral OA (KL grade 2 or higher) than among those without

such evidence (82% vs 25%, *P* <0.001), and the prevalence increased with a higher KL grade (*P* <0.001 for trend). Among persons with radiographic evidence of severe osteoarthritis (KL grade of 3 or 4 in their right knee), 95% had meniscal damage.[183]

2**) Relation to radiographic joint space width**

- Strong correlation between the degree of medial meniscal subluxation and the severity of medial joint space narrowing (r = 0.56, *P* = 0.0001).[184]

- Meniscal extrusion identified in all 32 patients with joint space narrowing (KL grades 1-4). Definite thinning or loss of articular cartilage was identified in only 15 of the 32 cases. In 17 patients with radiographic joint space narrowing (KL grades 1-3) and meniscalextrusion, no loss of articular cartilage was observed. A statistically significant correlation (*P* <0.001) was observed between KL grade and degree of meniscal extrusion and cartilage thinning on MRI.[185]

- For each increase in grade of joint space narrowing, tibial plateau bone area increased by 160 mm^2 in the medial compartment and 131 mm^2 in the lateral compartment (significance of regression coefficients all *P* <0.001).[178]

- Persons with symptomatic knee OA with ACL rupture had more severe radiologic OA (*P* <0.0001) and were more likely to have medial joint space narrowing (*P* <0.0001) than a control sample.[186]

- Compartments of the knee joint without joint space narrowing had a higher dGEMRIC index than those with any level of narrowing (mean 408 msec versus 365 msec; *P* = 0.001). In knees with 1 unnarrowed (spared) and 1 narrowed (diseased) compartment, the dGEMRIC index was greater in the spared versus the diseased compartment (mean 395 msec vs 369 msec; *P* = 0.001).[169]

- Grade of JSN as measured on skyline and lateral patellofemoral radiographs was inversely associated with patella cartilage volume. After adjusting for age, gender and body mass index, for every increase in grade of skyline JSN (0-3), the patella cartilage volume was reduced by 411 mm^3. For every increase in lateral patellofemoral JSN grade (0-3), the adjusted patella

cartilage volume was reduced by 125 mm^3. The relationship was stronger for patella cartilage volume and skyline JSN (r = -0.54, *P* <0.001) than for lateral patellofemoral JSN (r = -0.16, *P* = 0.015).[187]

- Grade one medial joint space narrowing was associated with substantial reductions in cartilage volume at both the medial and lateral tibial and patellar sites within the knee (adjusted mean difference 11-13%, all *P* <0.001).[188]

- Cartilage volume in the medial compartment and the narrowest JSW obtained by radiography at baseline in 31 knee OA patients (Figure 3, p 121), revealed that some level of correlation exists between these two measurements (r = 0.46, *P* <0.007).[189]

- Knee cartilage defects are inconsistently associated with joint space narrowing after adjustment for osteophytes but consistently with knee cartilage volume (beta: -0.27 to -0.70/ml; OR: 0.16-0.56/ml, all *P* <0.01 except for OR at lateral tibial cartilage site *P* = 0.06).[190]

- Moderate, but statistically significant, correlation between JSW and femoral and tibial cartilage volumes in the medial tibiofemoral joint, which was strengthened by adjusting for medial tibial bone size (r = 0.58-0.66, *P* = 0.001).[66]

- JSN seen on both medial and lateral radiographs of the tibiofemoral joint was inversely associated with the respective tibial cartilage volume. This inverse relationship was strengthened with adjustment for age, sex, body mass index (BMI), and bone size. After adjustment for these confounders, for every increase in JSN grade (0-3), the medial tibial cartilage volume was reduced by 257 mm^3 (95% CI 193-321) and the lateral tibial cartilage volume by 396 mm^3 (95% CI 283-509). The relationship between mean cartilage volume and radiologic grade of JSN was linear.[165]

3) Relation to histology

- Observed measurements of MRI volume of articular cartilage correlated with actual weight and volume displacement measurements with an accuracy of 82%-99% and linear correlation coefficients of 0.99 (*P* = 2.5e-15) and 0.99 (*P* = 4.4e-15).[191] The signal behavior of hyaline articular cartilage does not reflect the laminar histologic structure. Osteoarthrosis

and cartilage degeneration are visible on MR images as intracartilaginous signal changes, superficial erosions, diffuse cartilage thinning, and cartilage ulceration.[192]

- Comparison of data on cartilage thickness measurements with magnetic resonance imaging with corresponding histological sections in the middle of each sector revealed a very good magnetic resonance/anatomic correlation (r = 0.88).[193]

- Correlation between MRI Noyes grading scores and Mankin grading scores of natural lesions was moderately high (r = 0.7) and statistically significant (*P* = 0.001).[194]

4) Relation to arthroscopy

- Moderate correlation between imaged cartilage scores and the arthroscopy scores (Pearson correlation coefficient = 0.40).[174]

- Spearman rank linear correlation between arthroscopic and MR cartilage grading was highly significant (*P* <0.002) for each of the six articular regions evaluated. The MR and arthroscopic grades were the same in 93 (68%) of 137 joint surfaces, they were the same or differed by one grade in 123 surfaces (90%), and they were the same or differed by one or two grades in 129 surfaces (94%).[195]

- The overall sensitivity and specificity of MR in detecting chondral abnormalities were 60.5% (158/261) and 93.7% (89/95) respectively. MR imaging was more sensitive to the higher grade lesions: 31.8% (34/107) in grade 1; 72.4% (71/98) in grade 2; 93.5% (43/46) in grade 3; and 100% (10/10) in grade 4. The MR and arthroscopic grades were the same in 46.9% (167/356), and differed by no more than 1 grade in 90.2% (321/356) and 2 grades in 99.2% (353/356). The correlation between arthroscopic and MR grading scores was highly significant with a correlation coefficient of 0.705 (*P* <0.0001).[196]

- Statistically significant correlation between the SFA-arthroscopic score and the SFA-MR score (r = .83) and between the SFA-arthroscopic grade and the SFA-MR grade (weighted kappa = 0.84). The deepest cartilage lesions graded with arthroscopy and MR imaging showed correlation in the medial femoral condyle (weighted kappa = 0.83) and in the medial tibial plateau (weighted kappa = 0.84).[197]

- Magnetic resonance imaging was in agreement with arthroscopy in 81% showing more degenerations but less tears of menisci than arthroscopy. Using a global system for grading the total damage of the knee joint into none, mild, moderate, or severe changes, agreement between arthroscopy and MRI was found in 82%.[198]

5) Relation to CT

- MR frequently showed tricompartmental cartilage loss when radiography and CT showed only bicompartmental involvement in the medial and patellofemoral compartments. In the lateral compartment, MR showed a higher prevalence of cartilage loss (60%) than radiography (35%) and CT (25%) did. In the medial compartment, CT and MR showed osteophytes in 100% of the knees, whereas radiography showed osteophytes in only 60%. Notably, radiography often failed to show osteophytes in the posterior medial femoral condyle. On MR images, meniscal degeneration or tears were found in all 20 knees studied. Partial and complete tears of the anterior cruciate ligament were found in three and seven patients, respectively. MR is more sensitive than radiography and CT for assessing the extent and severity of osteoarthritic changes and frequently shows tricompartmental disease in patients in whom radiography and CT show only bicompartmental involvement. MR imaging is unique for evaluating meniscal and ligamentous disease related to OA.[173]

- Strong linear relationship (r = 0.998) between MRI imaging and CT arthrography. The mean absolute volume deviation between magnetic resonance imaging and computed tomography arthrography was 3.3%.[199]

6) Relation to symptoms

- Bone marrow lesions were found in 272 of 351 (77.5%) persons with painful knees compared with 15 of 50 (30%) persons with no knee pain (P <0.001). Large lesions were present almost exclusively in persons with knee pain (35.9% vs 2%; P <0.001). After adjustment for severity of radiographic disease, effusion, age, and sex, lesions and large lesions remained associated with the occurrence of knee pain (OR, 3.31 [95% CI, 1.54-7.41]). Using the same analytical approach, large lesions were also strongly associated with the presence of pain (OR, 5.78 [CI, 1.04-111.11]). Among persons with knee pain, bone marrow lesions were not associated with pain severity.[15]

- After adjusting for the severity of radiographic OA, there was a difference between those with and without knee pain in prevalence of moderate or larger effusions (P <0.001) and synovial thickening, independent of effusion (P <0.001). Among those with small (grade 1) or no knee (grade 0) effusion, those with knee pain had a prevalence of synovial thickening of 73.6% compared to 21.4% of those without knee pain (P <0.001, chi-square). There was a significant difference in VAS pain scores in those with synovial thickening compared to those without synovial thickening, after adjustment for radiographic severity, size of effusion, age, sex, and BMI. The mean pain score in those with synovial thickening after adjustment for radiographic severity and size of effusion was 47.2 mm (standard error 6.0), compared to 28.2 mm (SE 2.8) in those without synovial thickening (P = 0.006).[175]

- A medial or lateral meniscal tear was a very common finding in the asymptomatic subjects (prevalence, 76%) but was more common in the patients with symptomatic osteoarthritis (91%) (P <0.005). There was no significant difference with regard to the pain or WOMAC score between the patients with and those without a medial or lateral meniscal tear in the osteoarthritic group (P = 0.8 to 0.9 for all comparisons).[176] Significant differences between WOMAC scores were found for the grades of cartilage lesions (P <0.05) but not bone marrow edema pattern, and ligamentous and meniscal lesions.[177]

- Bone marrow lesions >1 cm were more frequent (OR,5.0; 95% CI 1.4-10.5) in the painful OAK group than all other groups. While the frequency of BME lesions was similar in the painless OAK and painful OAK groups, there were more lesions, >1 cm, in the painful OAK group. Full-thickness cartilage defects occurred frequently in painful OAK. Women with radiographic OA, full-thickness articular cartilage defects, and adjacent subchondral cortical bone defects were significantly more likely to have painful OAK than other groups (OR,3.2; 95% CI,1.3-7.6).[200]

- Peripatellar lesions (prepatellar or superficial infrapatellar) were present in 12.1% of the patients with knee pain and ROA, in 20.5% of the patients with ROA and no knee pain, and in 0% of subjects with neither ROA nor knee pain (P = 0.116). However, other periarticular lesions (including bursitis and iliotibial band syndrome) were present in 14.9% of patients with both ROA and knee pain, in only 3.9% of patients with ROA but no knee pain, and in 0% of the group with no knee pain and no ROA (P = 0.004).[201]

- More severe symptoms relating to knee OA (pain, stiffness, and function) are weakly inversely related to tibial cartilage volume. Patients with lower cartilage volume had more severe symptoms of knee OA than those with higher cartilage volume.[202] The increase in median pain from median quantile regression, adjusting for age and BMI, was significant for bone attrition (1.91, 95% CI, 0.68-3.13), bone marrow lesions (3.72, 95% CI, 1.76-5.68), meniscal tears (1.99, 95% CI, 0.60-3.38), and grade 2 or 3 synovitis/effusion vs grade 0 (9.82, 95% CI, 0.38-19.27). The relationship with pain severity was of borderline significance for osteophytes and cartilage morphology and was not significant for bone cysts or meniscal subluxation. When compared to the pain severity in knees with high scores for both bone attrition and bone marrow lesions (median pain severity 40 mm), knees with high attrition alone (30 mm) were not significantly different, but knees with high bone marrow lesion without high attrition scores (15 mm) were significantly less painful.[203]

- A large joint effusion was associated with pain (OR, 9.99; 99% CI, 1.28-149) and stiffness (OR, 4.67; 99% CI, 1.26-26.1). The presence of an osteophyte in the patellofemoral compartment (OR, 2.25; 99% CI, 1.06-4.77) was associated with pain. All other imaging findings, including focal or diffuse cartilaginous abnormalities, subchondral cysts, bone marrow edema, subluxation of the meniscus, meniscal tears, or Baker cysts, were not associated with symptoms.[204]

- Maximal BML size on the BLOKS scale had a positive linear relation with visual analogue scale (VAS) pain (*P* for linear trend = 0.04).[11]

- No correlation of baseline synovitis with baseline pain score (r = 0.09, *P* = 0.17).[205]

- No relation between baseline synovitis score and VAS pain score (r = 0.11, *P* = 0.60).[206]

- In the group of persons with radiographic evidence of OA (KL grade 2 or higher), the prevalence of a meniscal tear was 63% among those with knee pain, aching, or stiffness on most days and 60% among those without these symptoms (*P* = 0.75); the corresponding prevalences in the group without radiographic evidence of OA.

- (KL grade 2 or higher) were 32% and 23% (*P* = 0.02). A majority of the meniscal tears — 180 of 297 (61%)- were in subjects who had not had any pain, aching, or stiffness in the previous month.[183]

7) Relation to alignment

- Valgus-aligned knees tended to have lower dGEMRIC values laterally, and varus-aligned knees tended to have lower dGEMRIC values medially; as a continuous variable, alignment correlated with the lateral: medial dGEMRIC ratio (Pearson's R = 0.43, *P* = 0.02).[207]

- Limbs with varus alignment, especially if marked (≥7 degrees), had a remarkably high prevalence of medial lesions compared with limbs that were neutral or valgus (74.3% vs 16.4%; *P* = 0.001 for relation between alignment and medial lesions). Conversely, limbs that were neutral or valgus had a much higher prevalence of lateral lesions than limbs that were in the most varus group (29.5% vs. 8.6%; *P*= 0.002 for alignment and lateral lesions).[208]

- Medial tibial and femoral cartilage volumes increased as the angle decreased (ie, was less varus). Similarly, in the lateral compartment there was an inverse association at baseline between tibial and femoral cartilage volumes and the measured knee angle.[209]

- The main univariate determinants of varus alignment in decreasing order of influence were medial bone attrition, medial meniscal degeneration, medial meniscal subluxation, and medial tibiofemoral cartilage loss. Multivariable analysis revealed that medial bone attrition and medial tibiofemoral cartilage loss explained more of the variance in varus malalignment than other variables. The main univariate determinants of valgus malalignment in decreasing order of influence were lateral tibiofemoral cartilage loss, lateral osteophyte score, and lateral meniscal degeneration. (PMID).[210]

- Correlation between medial meniscal displacement rate on MRI and the femorotibial angle (r = .398).[179]

- Worsening in the status of each medial lesion (cartilage morphology, subarticular bone marrow lesions, meniscal tear, meniscal subluxation, and bone attrition was associated with greater varus malalignment[211].

- For every 1-degree increase in a valgus direction, there was an associated reduced risk of the presence of cartilage defects in the medial compartment of subjects with knee OA (P = 0.02). Moreover, for every 1-degree increase in a valgus direction, there was an associated increased risk of the presence of lateral cartilage defects in the OA group (P = 0.006).[212]

Summary of Data on Concurrent Validity

1. Inconsistent relation of cartilage volume and thickness to presence of radiographic OA.
2. Inconsistent relation of compositional measures to presence of radiographic OA.
3. Higher frequency of meniscal tears, synovitis, increased bone area, increased bone attrition/ curvature in persons with radiographic OA.
4. Radiographic change insensitive to early changes found on MRI.
5. Strong relation of meniscal subluxation and increased subchondral bone area to reduced radiographic joint space.
6. Inconsistent (but generally moderate) relation of reduced cartilage volume and thickness to reduced radiographic joint space.
7. Strong correlation of cartilage volume to measurement of histologic findings.
8. Moderate to strong relation of arthroscopic findings to cartilage and meniscal findings on MRI.
9. Strong relation of CT arthrography to MRI cartilage volume.
10. Inconsistent but generally strong relation of large bone marrow lesions to presence of pain.
11. Inconsistent but generally moderate relation of synovitis, effusion to presence of pain.
12. Weak relation of cartilage volume/ thickness to presence of pain.
13. No relation of meniscal tear to presence of pain.

4.3.2 Predictive Validity

[Click on hyperlink above to return to your place in the text, p 43 (Predictive Validity/MRI).]

[Click here to return to your place in the text, p 45.]

[Click here to return to your place in the text, p 47.]

The analysis included data from 61 manuscripts of which one pertains to the hip and the remainder to the knee. The mean Downs criteria score for these manuscripts was 62.8 (range 42-81).
What follows below are important excerpts from these data.

1) Prediction of joint replacement

- One study investigated the relation of change in quantitative cartilage volume to risk of knee replacement. For every 1% increase in the rate of tibial cartilage loss there was a 20% increase risk of undergoing a knee replacement at four years (95% CI 10% to 30%). Those in the highest tertile of tibial cartilage loss had 7.1 (1.4 to 36.5) higher odds of undergoing a knee replacement than those in the lowest tertile. Change in bone area also predicted risk of TKR OR 12 (95% CI 1-14).[213]

- Higher total cartilage defect scores (8-15) were associated with a 6.0-fold increased risk of joint replacement over 4 years compared with those with lower scores (2-7) (95% CI 1.6-22.3), independently of potential confounders.[214] A separate smaller study investigated the relation of bone marrow lesions (assessed semi-quantitatively) to need for TKR. Subjects who had a bone marrow lesion were 8.95 times as likely to progress rapidly to a TKA when compared to subjects with no BME (P = 0.016). There was no relation of TKR with meniscal tear or cartilage loss.[215]

2) Prediction of change in symptoms

- Weak associations between worsening of symptoms of OA and increased cartilage loss: pain (r(s) = 0.28, P = 0.002), stiffness (r(s) = 0.17, P = 0.07), and deterioration in function (r(s) = 0.21, P = 0.02).[202]

- Small study did not find a significant relation between changes in WOMAC scores with the amount of cartilage loss and the change in BME (P >0.05). (PMID 16222533).

- Multivariate analyses of knee pain 1 year following arthroscopic partial meniscectomy demonstrated that medial tibial cartilage damage accounting for 13% of the variability in pain scores.[216]

- The BOKS study examined the relationship between longitudinal fluctuations in synovitis with change in pain and cartilage in knee osteoarthritis. Change in summary synovitis score was correlated with the change in pain (r = 0.21, *P* = 0.0003). An increase of one unit in summary synovitis score resulted in a 3.15-mm increase in VAS pain score (0-100 scale). Effusion change was not associated with pain change. Of the three locations for synovitis, changes in the infrapatellar fat pad were most strongly related to pain change.[217]

- A nested case-control study examined if enlarging BMLs are associated with new knee pain. Case knee was defined as absence of knee pain at baseline but presence of knee pain both times at follow-up. Controls were selected randomly from among knees with absence of pain at baseline. Among case knees, 54 of 110 (49.1%) showed an increase in BML score within a compartment, whereas only 59 of 220 control knees (26.8%) showed an increase (*P* <0.001 by chi-square test). A BML score increase of at least two units was much more common in case knees than in control knees (27.5% versus 8.6%; adjusted odds ratio 3.2, 95% confidence interval 1.5-6.8).[217] Increases in WOMAC pain index and patient global scores over time are associated with change in cartilage volume of the medial tibial plateau and medial femoral condyle.[218]

- Weak association of cartilage volume loss with less knee pain. Medial cartilage volume loss and simultaneous pain change at 24 months (beta coefficient -0.45, *P* = 0.03) and SF-36 physical components (beta coefficient 0.22, *P* = 0.04).[219]

3**) Prediction of radiographic progression**

- No significant association between reduction in JSW and cartilage volume (R<0.13). Trend towards a significant association between change in medial tibiofemoral cartilage volume and joint replacement at 4 years (OR=9.0, P=0.07) but not change in medial tibiofemoral JSW (OR, 1.1; *P* = 0.92).[66]
- No correlation between the cartilage volume loss changes (either by using absolute or percentage values) and the JSW changes at 24 months (global cartilage volume, r = 0.11; medial compartment cartilage volume, r = 0.19).[219]

- Medial femoro-tibial joint space narrowing (JSN) after 1 year, assessed by radiography, was significantly correlated with a loss of medial tibial cartilage volume (r = 0.25, *P* = 0.046) and medial tibial cartilage thickness (r = 0.28, *P* = 0.025), over the same period.[220]

- Higher baseline composite cartilage scores and increases in composite cartilage scores during followup were moderately correlated with greater joint space loss (r = 0.33, *P* = 0.0002 and r = 0.26, *P* =0.01, respectively).[95]

- Loss in JSW (JSN) correlated with the loss of cartilage volume on the central weight-bearing area of the condyles and the plateaus as well as on the medial compartment.[218]

- Study examined the relation of magnetic resonance imaging (MRI) features at baseline with radiographically determined JSN in the medial compartment of the knee after 2 years in a group of patients with symptomatic OA. A significant association was observed for meniscal tears (RR 3.57; 95% CI,, 1.08-10.0) and meniscal subluxation (RR 2.73; 95% CI, 1.20-5.41), between KL <2 and meniscal subluxation (RR 11.3; 95% CI, 2.49-29.49) and KL > or = 2 and meniscus tears (RR 8.91; 95% CI, 1.13-22.84) and radiographic JSN 2 years later.[221]

4) Prediction of MRI progression

- Patients who had sustained meniscal tears showed a higher average rate of progression of cartilage loss (22%) than that seen in those who had intact menisci (14.9%) (*P* <or= 0.018). Anterior cruciate ligament (ACL) tears had a borderline significant influence (*P* < or = 0.06) on the progression of cartilage pathology. Lesions located in the central region of the medial compartment were more likely to progress to more advanced cartilage pathology (progression rate 28%; *P* < or = 0.003) than lesions in the anterior (19%; *P* < or = 0.564) and posterior (17%; *P* < or = 0.957) regions or lesions located in the lateral compartment (average progression rate 15%; *P* < or = 0.707). Lesions located in the anterior region of the lateral compartment showed less progression of cartilage degradation (6%; *P* < or = 0.001). No specific grade of lesion identified at baseline had a predilection for more rapid cartilage loss (*P* < or = 0.93).[222]

- There was a significant correlation between the degree of loss of tibial cartilage and the degree of loss of femoral cartilage, in both tibiofemoral joints (r = 0.81, *P* <0.001 at the medial

tibiofemoral joint; r = 0.71, *P* <0.001 at the lateral tibiofemoral joint).[223] A highly significant difference in global cartilage volume loss was observed between severe medial meniscal tear and absence of tear (mean [SD], -10.1 (2.1)% v -5.1 [2.4]%, *P* = 0.002). An even greater difference was found between the medial meniscal changes and medial compartment cartilage volume loss (-14.3 [3.0]% in the presence of severe tear v -6.3 [2.7]% in the absence of tear; *P* <0.0001). Similarly, a major difference was found between the presence of a medial meniscal extrusion and loss of medial compartment cartilage volume (-15.4 [4.1]% in the presence of extrusion v -4.5 [1.7]% with no extrusion; *P* <0.001).[224]

- Annual patellar cartilage loss was highest in those with defects compared with no defects (5.5% vs 3.2%, *P* = 0.01). Tibial cartilage loss was not associated with defects in the medial (4.6% vs 5.8%, *P* = 0.42) or lateral (4.7% vs 6.5%, P = 0.21) tibial cartilages,[214]

- Baseline cartilage defect score was negatively associated with the progression of cartilage defects in each compartment (all *P* <0.001).[225]

- Baseline cartilage defect scores at the medial tibia, lateral tibia, and patella had a dose-response association with the annual rate of change in knee cartilage volume at the corresponding site (beta = -1.3% to -1.2% per grade; *P* <0.05 for all comparisons). In addition, an increase in knee cartilage defect score (change of > or = 1) was associated with higher rates of knee cartilage volume loss at all sites (beta = -1.9% to -1.7% per year; *P* <0.01 for all comparisons). Furthermore, a decrease in the knee cartilage defect score (change of < or = -1) was associated with an increase in knee cartilage volume at all sites (beta = 1.0% to 2.7% per year; *P* < 0.05 for all comparisons).[226]

- Predictors of fast progressors were the presence of severe meniscal extrusion (*P* = 0.001), severe medial tear (*P* = 0.005), medial and/or lateral bone edema (*P* = 0.03), high body mass index (*P* <0.05, fast versus slow), weight (*P* <0.05, fast versus slow) and age (*P* <0.05 fast versus slow).[219]

- In the medial tibiofemoral joint, each measure of meniscal malposition was associated with an increased risk of cartilage loss. There was also a strong association between meniscal damage and cartilage loss.[227]

- A worsening in cartilage defect score was significantly associated with tibiofemoral osteophytes (OR, 6.22 and 6.04 per grade), tibial bone area (OR, 1.24 and 2.07 per square centimeter), and cartilage volume (OR, 2.91 and 1.71 per milliliter in the medial tibiofemoral and patellar compartments).[228]

- Knee compartments with a higher baseline BML score had greater cartilage loss. An increase in BMLs was strongly associated with further worsening of the cartilage score.[229]

- Despite cartilage loss occurring in over 50% of knees, synovitis was not associated with cartilage loss in either tibiofemoral or patellofemoral compartment.[205] Significant correlations were seen between the loss of cartilage volume and oedema size change in the medial condyle (-0.40, P = 0.0001) and the medial tibial plateau (-0.23, P = 0.03), and the changes in cyst size in the medial condyle (-0.29, P = 0.01). A multivariate analysis showed that the edema size change was strongly and independently associated with medial cartilage volume loss (-0.31, P = 0.0004).[230] Medial meniscal tear was associated with 103 mm^2 greater tibial plateau bone area within the medial (95% CI,, 6.2-200.3; P = 0.04) and a lateral meniscal tear with a 120 mm^2 greater area within the lateral compartment (95% CI, 45.5-195.2; P = 0.002).[231]

- Adjusting for age, body mass index, gender and baseline cartilage scores, complete ACL tear increased the risk for cartilage loss at the medial tibiofemoral compartment (OR: 1.8, 95% CI: 1.1-3.2). However, following adjustment for the presence of medial meniscal tears, no increased risk for cartilage loss was further seen (OR: 1.1, 95% CI: 0.6-1.8).[232]

- Medial meniscal damage predicted medial tibial cartilage volume loss and tibial and femoral denuded bone increase, while varus malalignment predicted medial tibial cartilage volume and thickness loss and tibial and femoral denuded bone increase. Lateral meniscal damage predicted every lateral outcome.[233]

- A positive correlation was found between the global severity of synovitis at baseline and the loss of cartilage volume at 60 days (P <0.03).[206]

Summary of Data on Predictive Validity

1. Quantitative cartilage volume change and presence of cartilage defects or bone marrow lesions are potential predictors of TKR. Existing data need to be corroborated.
2. Inconsistent but generally weak relation of cartilage loss to symptom change.
3. Moderate relation of BML change to incident symptoms and pain change.
4. Weak relation of change in synovitis to change in pain.
5. At best, weak relation between change in cartilage thickness and change in joint space.
6. Presence of meniscal damage, cartilage defects, and BMLs predicts MRI progression.

4.3.3 Reliability

[Click on the above link to return to your place in the text.]

The analysis included data from 89 manuscripts. Four contained data pertinent to the hip, one contained data relevant to the hand, and the remainder were focused upon the knee.

The data were divided using the following hierarchical structure into;

1) Intra-reader, inter-reader and test-retest reliability
2) Parameter (ICC, Kappa, CV)
3) Measurement method (quantitative, semi-quantitative, and compositional)
4) Tissue lesion (cartilage, synovium, bone, bone marrow lesions, meniscus, and ligament)
5) Plate/region for cartilage divisions

The mean Downs criteria score for these manuscripts was 70.7 (range 55-85).

Table 1. Results of random-effects pooling of ***intra-reader coefficients of variation*** (CV) from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled CV**	**95% Confidence Interval**
Quantitative				
Cartilage	32 (10)	60	0.03	-0.02, 0.07
Synovium	2 (1)	94	0.08	-0.06, 0.22
Compositional	6 (1)	60	0.05	-0.05, 0.15

Table 2. Results of random-effects pooling of ***inter-reader coefficients of variation*** (CV) from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates**	**Mean Sample**	**Pooled CV**	**95% Confidence Interval**

	(Studies)	Size		
Quantitative				
Cartilage	42 (13)	65	0.03	-0.01, 0.06
Synovium	1 (1)	94	0.05	-0.15, 0.25
Bone	9 (5)	119	0.02	-0.04, 0.08
Semi-Quantitative				
Cartilage	0 (0)	--	--	--
Synovium	0 (0)	--	--	--
Bone	0 (0)	--	--	--
Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	0 (0)	--	--	--
Ligament	0 (0)	--	--	--

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Table 3. Results of random-effects pooling of ***test-retest coefficients of variation*** (CV) from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	Number of Estimates (Studies)	Mean Sample Size	Pooled CV	95% Confidence Interval
Quantitative				
Cartilage	63 (16)	56	0.04	0.01, 0.07
Synovium	0 (0)	--	--	--
Bone	6 (1)	32	0.03	-0.11, 0.17

Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	0 (0)	--	--	--
Ligament	0 (0)	--	--	--
Compositional	4 (1)	22	0.17	-0.04, 0.38

[Click on Table 3, above, to return to your place in the text.]

Table 4. Results of random-effects pooling of ***intra-reader intra-class correlations*** (ICC) from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled ICC**	**95% Confidence Interval**
Quantitative				
Cartilage	23 (9)	108	0.92	0.88, 0.96
Synovium	2 (1)	30	0.87	0.61, 1.00
Bone	0 (0)	--	--	--
Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	1 (1)	291	0.93	0.82, 1.00
Ligament	0 (0)	--	--	--
Semi-Quantitative				
Cartilage	7 (4)	114	0.94	0.87, 1.00
Synovium	3 (2)	26	0.88	0.66, 1.00
Bone	0 (0)	--	--	--
Bone Marrow Lesion	2 (2)	178	0.93	0.83, 1.00
Meniscus	2 (1)	25	0.77	0.49, 1.00
Ligament	0 (0)	--	--	--
Compositional	0 (0)	--	--	--

Table 5. Results of random-effects pooling of ***inter-reader intra-class correlations*** (ICC) from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled ICC**	**95% Confidence Interval**
Quantitative				
Cartilage	10 (4)	196	0.90	0.86, 0.95
Synovium	0 (0)	--	--	--
Bone	0 (0)	--	--	--
Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	2 (1)	291	0.81	0.72, 0.89
Ligament	0 (0)	--	--	--
Semi-Quantitative				
Cartilage	9 (7)	88	0.85	0.77, 0.94
Synovium	5 (4)	46	0.87	0.74, 1.00
Bone	3 (2)	23	0.90	0.66, 1.00
Bone Marrow Lesion	2 (2)	22	0.84	0.54, 1.00
Meniscus	5 (3)	67	0.93	0.82, 1.00
Ligament	4 (2)	105	0.80	0.56, 1.00
Compositional	0 (0)	--	--	--

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Table 6. Results of random-effects pooling of ***intra-reader kappa*** values from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled Kappa**	**95% Confidence Interval**
Quantitative				
Cartilage	1 (1)	158	0.66	0.50, 0.82
Synovium	0 (0)	--	--	--
Bone	0 (0)	--	--	--
Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	0 (0)	--	--	--
Ligament	0 (0)	--	--	--
Semi-Quantitative				
Cartilage	0 (0)	--	--	--
Synovium	4 (2)	317	0.52	0.28, 0.77
Bone	0 (0)	--	--	--
Bone Marrow Lesion	1 (1)	256	0.66	0.54, 0.78
Meniscus	0 (0)	--	--	--
Ligament	0 (0)	--	--	--
Compositional	0 (0)	--	--	--

Table 7. Results of random-effects pooling of ***inter-reader kappa*** values from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	**Number of Estimates**	**Mean Sample Size**	**Pooled Kappa**	**95% Confidence Interval**

	(Studies)			
Quantitative				
Cartilage	0 (0)	--	--	--
Synovium	0 (0)	--	--	--
Bone	0 (0)	--	--	--
Bone Marrow Lesion	0 (0)	--	--	--
Meniscus	0 (0)	--	--	--
Ligament	0 (0)	--	--	--
Semi-Quantitative				
Cartilage	15 (4)	136	0.57	0.44, 0.71
Synovium	0 (0)	--	--	--
Bone	0 (0)	--	--	--
Bone Marrow Lesion	2 (2)	237	0.88	0.79, 0.97
Meniscus	3 (3)	418	0.73	0.63, 0.84
Ligament	3 (3)	209	0.80	0.69, 0.90
Compositional	0 (0)	--	--	--

Summary of Data on Reliability

1. Inter- and intra-reader coefficient of variation (CV) measures were confined to quantitative or compositional measures (Tables 1 and 2). The pooled CV for quantitative cartilage was 0.03 for both inter and intra-reader reliability.
2. Test-retest coefficient of variation (CV) measures were confined to quantitative or compositional measures (Table 3). The pooled CV for quantitative cartilage was 0.04 for both test retest.
3. The inter-reader and intra-reader intraclass correlations for quantitative, semi-quantitative and compositional measures were all excellent (range 0.8-0.94)(Tables 4 and 5).
4. The inter-reader and intra-reader kappa values for quantitative, semi-quantitative and compositional measures were all moderate to excellent (range 0.52-0.88)(Tables 6 and 7).

4.3.4 Responsiveness

The analysis included data from 42 manuscripts.

The data were divided using the following hierarchical structure into;

1) Measurement method (quantitative, semi-quantitative and compositional)
2) Tissue lesion (cartilage, synovium, bone, bone marrow lesions, meniscus and ligament)
3) Plate/region for cartilage divisions

The mean Downs criteria score for these manuscripts was 60.8 (range 38-79).

Table 1. Results of random-effects pooling of estimates from MRI studies stratified by measure (quantitative, semi-quantitative, and compositional) and tissue (cartilage, synovium, bone, bone marrow lesion, meniscus, and ligament)

Stratification	Number of Estimates (Studies)	Mean Sample Size	Pooled SRM	95% Confidence Interval
Quantitative Cartilage				
Medial Femoral	54 (12)	118	-0.39	-0.48, -0.30
Medial Tibial	55 (17)	134	-0.33	-0.39, -0.26
Medial Tibio-Femoral	31 (12)	92	-0.58	-0.75, -0.41
Lateral Femoral	32 (8)	151	-0.19	-0.27, -0.11
Lateral Tibial	44 (14)	152	-0.44	-0.51, -0.36
Lateral Tibio-Femoral	14 (5)	110	-0.56	-0.92, -0.20
Patella	13 (9)	131	-0.60	-0.83, -0.37
Global	5 (4)	48	-0.63	-2.23, 0.97
Quantitative Other				
Denuded area	19 (2)	114	-0.05	-0.15, 0.06
Synovium	0 (0)	--	--	--
Bone	14 (2)	167	-0.09	-0.23, 0.05
Bone Marrow Lesion	4 (1)	107	0.11	0.01, 0.20
Meniscus	2 (1)	264	-0.24	-0.33, -0.16
Semi-Quantitative Cartilage				
Medial Tibial	1 (1)	325	-0.07	-0.18, 0.04
Medial Tibial-Femoral	3 (3)	224	0.55	0.47, 0.64

Lateral Tibial	1 (1)	325	-0.05	-0.15, 0.06
Lateral Tibial-Femoral	3 (3)	224	0.37	0.18, 0.57
Patella	2 (2)	238	0.29	0.03, 0.56
Semi-Quantitative Other				
Synovium	3 (2)	68	0.52	0.28, 0.76
Osteophytes	4 (1)	150	0.36	0.28, 0.44
Bone Marrow Lesion	6 (2)	130	0.19	0.07, 0.30
Meniscus	2 (1)	264	0.27	0.14, 0.40
Compositional	3 (1)	18	-3.29	-3.88, -2.70

Table 2. Results of random-effects pooling of estimates from MRI studies evaluating quantitative cartilage stratified by year of publication and plate region.

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled SRM**	**95% Confidence Interval**
Quantitative Cartilage (2002-2006)				
Medial Femoral	3 (3)	126	-0.59	-1.21, 0.03
Medial Tibial	7 (7)	123	-0.58	-0.81, -0.35
Medial Tibial-Femoral	4 (3)	51	-0.92	-1.10, -0.75
Lateral Femoral	1 (1)	117	-0.01	-0.19, 0.17
Lateral Tibial	6 (6)	139	-0.55	-0.82, -0.29
Lateral Tibial-Femoral	0 (0)	--	--	--
Patella	5 (5)	141	-0.68	-1.04, -0.32
Global	2 (2)	24	-0.58	-1.15, -0.02
Quantitative Cartilage (2007-2009)				
Medial Femoral	51 (9)	117	-0.38	-0.47, -0.29
Medial Tibial	48 (10)	135	-0.29	-0.35, -0.23
Medial Tibial-Femoral	27 (9)	98	-0.54	-0.73, -0.35
Lateral Femoral	31 (7)	152	-0.19	-0.27, -0.11
Lateral Tibial	38 (8)	154	-0.42	-0.49, -0.34

Lateral Tibial-Femoral	14 (5)	110	-0.56	-0.92, -0.20
Patella	8 (4)	125	-0.55	-0.84, -0.27
Global	3 (2)	63	-0.68	-3.31, 1.95

Quantitative assessments of cartilage

Table 3. Results of random-effects model-based pooling of MRI studies (2007-2009) evaluating quantitative cartilage by plate region.

Stratification	**Number of Studies**	**Pooled SRM**	**95% Confidence Interval**
Medial Femoral	9	-0.48	-0.74, -0.23
Medial Tibial	10	-0.42	-0.62, -0.21
Medial Tibial-Femoral	9	**-0.84**	-1.35, -0.33
Lateral Femoral	7	-0.24	-0.54, 0.05
Lateral Tibial	8	-0.56	-0.79, -0.34
Lateral Tibial-Femoral	5	-1.01	-2.04, -0.02
Patella	4	-0.57	-0.97, -0.18
Global	2	-1.22	-4.43, 1.99

Table 4. Results of random-effects pooling of estimates from MRI studies evaluating quantitative cartilage stratified by duration of study and plate region for studies published between 2007 and 2009. Studies with multiple estimates had an estimate selected at random and a pooled analysis was performed.

Stratification	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled SRM**	**95% Confidence Interval**
Quantitative Cartilage				
1 year or less				
Medial Femoral	27 (5)	82	-0.50	-0.84, -0.16
Medial Tibial	18 (6)	93	-0.33	-0.53, -0.13

Medial Tibial-Femoral	16 (6)	83	-0.80	-1.28, -0.33
Lateral Femoral	7 (3)	137	-0.31	-0.98, 0.36
Lateral Tibial	8 (4)	130	-0.57	-0.89, -0.24
Lateral Tibial-Femoral	3 (2)	79	-1.03	-2.79, 0.73
Patella	7 (3)	129	-0.48	-0.92, -0.04
Global	2 (1)	18	0.39	-0.07, 0.85
1-2 years				
Medial Femoral	6 (3)	104	-0.52	-1.16, 0.11
Medial Tibial	6 (3)	104	-0.64	-1.14, -0.13
Medial Tibial-Femoral	5 (2)	53	-1.19	-2.88, 0.51
Lateral Femoral	6 (3)	104	-0.21	-0.51, 0.08
Lateral Tibial	6 (3)	104	-0.61	-1.14, -0.08
Lateral Tibial-Femoral	5 (2)	53	-1.28	-3.48, 0.93
Patella	1 (1)	99	-0.90	-1.10, -0.71
Global	1 (1)	154	-2.85	-3.01, -2.70
Greater than 2 years*				
Medial Femoral	18 (1)	174	-0.34	-0.49, -0.19
Medial Tibial	24 (1)	174	-0.29	-0.44, -0.14
Medial Tibial-Femoral	6 (1)	174	-0.40	-0.55, -0.25
Lateral Femoral	18 (1)	174	-0.20	-0.35, -0.05
Lateral Tibial	24 (1)	174	-0.38	-0.53, -0.23
Lateral Tibial-Femoral	6 (1)	174	-0.45	-0.60, -0.30
Patella	0 (0)	--	--	--
Global	0 (0)	--	--	--

*Represents results of one study by Felix Eckstein, et al. AC&R, 2008.

Semi-quantitative assessments of cartilage

Table 5

Stratification	**Number**	**Mean**	**Pooled**	**95% Confidence**

	of Estimates (Studies)	Sample Size	SRM	Interval
Medial Femoral	0 (0)	--	--	--
Medial Tibial	1 (1)	325	-0.07	-0.18, 0.04
Medial Tibial-Femoral	3 (3)	224	**0.55**	0.47, 0.64
Lateral Femoral	0 (0)	--	--	--
Lateral Tibial	1 (1)	325	-0.05	-0.15, 0.06
Lateral Tibial-Femoral	3 (3)	224	0.37	0.18, 0.57
Patella	2 (2)	238	0.29	0.03, 0.56

Assessment of other components

Table 6

Stratification	Number of Estimates (Studies)	Mean Sample Size	Pooled SRM	95% Confidence Interval
Quantitative Other				
Denuded area	19 (2)	114	-0.05	-0.15, 0.06
Synovium	0 (0)	--	--	--
Bone	14 (2)	167	-0.09	-0.23, 0.05
Bone Marrow Lesion	4 (1)	107	0.11	0.01, 0.20
Meniscus	2 (1)	264	-0.24	-0.33, -0.16
Ligament	0 (0)	--	--	--
Semi-Quantitative Other				
Denuded area	0 (0)	--	--	--
Synovium	3 (2)	68	0.52	0.28, 0.76
Bone	4 (1)	150	0.36	0.28, 0.44
Bone Marrow Lesion	6 (2)	130	0.19	0.07, 0.30
Meniscus	2 (1)	264	0.27	0.14, 0.40
Ligament	0 (0)	--	--	--

[Click here to return to your place in the text, p 38.]

Summary of Data on Responsiveness

1. The pooled SRM for quantitative measures of cartilage for medial tibiofemoral joint was -0.58 (95% CI, -0.75 to -0.41), for lateral tibofemoral joint was -0.56 (95% CI -0.92 to -0.20), and for the patella was -0.60 (95% CI, -2.23 to 0.97).
2. The pooled SRM for semi-quantitative measures of cartilage for medial tibiofemoral joint was 0.55 (95% CI, 0.47 to 0.64), for lateral tibiofemoral joint was 0.37 (95% CI, 0.18 to 0.57), and for the patella was 0.29 (95% CI, 0.03 to 0.56).
3. The pooled SRM for semi-quantitative measures of synovium was 0.52 (95% CI, 0.28 to 0.76), and for BMLs was 0.19 (95% CI, 0.07 to 0.30).

MRI Tables

Table 1: Summary table of studies reporting data on concurrent validity of MRI in OA

[Click on hyperlink above to return to your place in the text, p 42.]

[Click here to return to your place in the text, p 47.]

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Liga-ment	Study design	Score of method-ological quality
Chan WP; American Journal of Roentgenology; 1991; 1892040	20	20	0	58(Range:42-73)	11	No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	77
McAlindon TE; Annals of the Rheumatic Diseases; 1991; 1994861	.					No	No	Yes	Yes	Yes	Yes	No	Yes	No	Case control	77
Li KC; Magnetic Resonance Imaging; 1988; 3398728	10	10	0	(Range: 33-78)	9(90%)	No	No	Yes	Yes	No	No	No	No	No	Longi-tudinal Prospective	81
Fernandez-Madrid F; Magnetic Resonance Imaging; 1994; 7934656	92	52	40	Controls: 49(15), (Rang:22-78); OA patients: 55(14), (Range:25-86)	60	No	No	Yes	Yes	Yes	No	No	Yes	No	Cross-sectional	67
Karvonen RL; Journal of Rheumatology; 1994; 7966075	92	52	40	Reference: 49(15), (Range:22-78); All OA patients: 55(14), (Range:25-86); Bilateral OA: 53(13), (Range:25-73)	60	Yes	No	No	Yes	No	Yes	No	No	No	Case control	66
Peterfy CG; Radiology; 1994; 8029420	8	5	3	62(Range: 45-82)	4(50%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	79

Blackburn WD Jr; Journal of Rheumatology; 1994; 8035392	33	33	0	62.7(9.1), (Range: 44-79)	17	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	78
Broderick LS; American Journal of Roentgenology; 1994; 8273700	.					No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	75
Miller TT; Radiology; 1996; 8816552	384			47(Range: 14-88)		No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	74
Dupuy DE; Academic Radiology; 1996; 8959181	7			TKA patients:(Range:64-75); Asymptomatic: 35(Range:25-35)	3	Yes	No	No	Yes	No	No	No	No	No	Other	75
Kenny C; Clinical Orthopaedics & Related Research; 1997; 9186215	.					No	No	Yes	No	No	No	No	Yes	No	Case control	74
Breitenseher MJ; Acta Radiologica; 1997; 9332248	60	12	48	37(14.3), (Range: 15-68)	30(50%)	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	76
Ostergaard M; British Journal of Rheumatology; 1997; 9402860	46	14	47	70(Range: 24-85)		No	No	No	No	Yes	No	No	No	No	Cross-sectional	74
Trattnig S; Journal of Computer Assisted Tomography; 1998; 9448754	20	20	0	72.2(Range:62-82)	18	No	No	Yes	Yes	No	No	No	No	No	Other	78
Kawahara Y; Acta Radiologica; 1998; 9529440	72			58(Range:41-74)	46	No	No	Yes	Yes	No	No	No	No	No	Other	76
Drape JL; Radiology; 1998; 9646792	43	43	0	63(Range:53-78)	30	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	78

Eckstein F; Clinical Orthopaedics & Related Research; 1998; 9678042	8	0	8	50.6(Range:39-64)		Yes	No	No	Yes	No	No	No	No	No	Other	80
Uhl M; European Radiology; 1998; 9724423	22			(Range:50-72		No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	82
Boegard T; Acta Radiologica - Supplementum; 1998; 9759121	.					No	No	Yes	Yes	No	No	No	Yes	No	Longi-tudinal Prospective	75
Bachmann GF; European Radiology; 1999; 9933399	320			29.3(8.7), (Range:13-56)	122	No	No	Yes	Yes	No	No	No	Yes	No	Cross-sectional	75
Cicuttini F; Osteoarthritis & Cartilage; 1999; 10329301	28			Males: 40.4(Range:42-58); Females: 31.2(8.6);	11	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	77
Boegard T; Annals of the Rheumatic Diseases; 1999; 10343536	58			Women: 40.4(Range: 42-58); Men: 57(49.5), (Range:41-57)	29	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	76
Adams JG; Clinical Radiology; 1999; 10484216	.					No	No	Yes	Yes	No	No	No	Yes	No	Case control	70
Pham XV; Revue du Rhumatisme; 1999; 10526380	10	10	10	67.2(7.34), (Range:57-80)	6	No	No	Yes	No	No	No	No	No	Yes	Cross-sectional	65
Gale DR; Osteoarthritis & Cartilage; 1999; 10558850	.					No	No	No	No	No	No	No	Yes	No	Case control	67
Kladny B; International Orthopaedics; 1999; 10653290	.					Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	81
Zanetti M; Radiology; 2000; 10831707	16	16	0	67(Range:43-79)	15	Yes	No	No	Yes	No	Yes	Yes	No	No	Cross-sectional	76

Jones G; Arthritis & Rheumatism; 2000; 11083279	92	92	0	Boys: 12.8(2.7); Girls: 12.6(2.9)	43	Yes	No	No	Yes	No	Yes	No	No	No	Cross-sectional	63
McCauley TR; American Journal of Roentgenology; 2001; 11159074	193			40(Range:11-86)	83	No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	70
Wluka AE; Annals of the Rheumatic Diseases; 2001; 11247861	81	42	39	Cases: 58(6.1); Controls: 56(5.4)	81(100%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	59
Felson DT; Annals of Internal Medicine; 2001; 11281736	401	401	0	66.8		No	No	Yes	No	No	No	Yes	No	No	Cross-sectional	64
Hill CL; Journal of Rheumatology; 2001; 11409127	458	433	25	67	(34%)	No	No	Yes	No	Yes	No	No	No	No	Case control	64
Kawahara Y; Journal of Computer Assisted Tomography; 2001; 11584226	35			57(Range:33-70)	23	No	No	Yes	Yes	No	No	No	Yes	No	Cross-sectional	78
Arokoski JP; Annals of the Rheumatic Diseases; 2002; 11796401	57	27	30	Cases: 56.2(4.9), Range: (47-64); Controls:56.3(4.5), (Range:47-64)	0	Yes	No	No	No	No	No	No	No	No	Case control	71
Bergin D; Skeletal Radiology; 2002; 11807587	60	30	30	Cases: 50; Controls: 57		No	No	Yes	No	No	No	No	Yes	Yes	Case control	68
Beuf O; Arthritis & Rheumatism; 2002; 11840441	46	18	28	Mild OA: 68(9.1); Severe OA: 70(6.3)	17	Yes	No	No	No	No	No	No	No	No	Case control	76
Arokoski MH; Journal of Rheumatology; 2002; 12375331	57	27	30	Cases:56.2(4.9), (Range:47-64); Controls: 56.3(4.5), (Range:47-64)	0	Yes	No	No	Yes	No	No	No	No	No	Case control	70

Bhattacharyya T; Journal of Bone & Joint Surgery - American Volume; 2003; 125335	203	154	49	Cases: 65; Controls: 67		No	No	Yes	No	No	No	No	Yes	No	Case control	70
Link TM; Radiology; 2003; 12563128	50	50	0	63.7(11.5), (Range:43-81)	30	No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	77
Tiderius CJ; Magnetic Resonance in Medicine; 2003; 12594751	17			50(Range:35-70)	4	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	77
Cicuttini FM; Arthritis & Rheumatism; 2003; 12632421	252			60.2(10)	157962%)	Yes	No	No	Yes	No	Yes	No	No	No	Cross-sectional	73
Cicuttini FM; Clinical & Experimental Rheumatology; 2003; 12673893	81	42	39	ERT: 58(6.1); Controls: 56(5.4)	81(100%)	Yes	No	No	Yes	No	Yes	No	No	No	Case control	63
Sowers MF; Osteoarthritis & Cartilage; 2003; 12801478	120	60	60	no OAK, no Pain: 45(0.8); OAK, no Pain: 46(0.6); No OAK, Pain: 47(0.8); OAK and Pain: 47(0.7)	(100%)	No	No	Yes	Yes	No	No	Yes	No	No	Case control	67
McGibbon CA; Osteoarthritis & Cartilage; 2003; 12814611	.					No	No	Yes	Yes	No	No	No	No	No	Other	82
Cicuttini FM; Clinical & Experimental Rheumatology; 2003; 12846050	157	157	0	62(10)	(62%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	74
Felson DT; Annals of Internal Medicine; 2003; 12965941	256	256	0	Followed: 66.2(9.4); Not followed: 67.8(9.6)	(38.3%)	No	No	Yes	No	No	No	Yes	No	No	Longi-tudinal Prospective	65
Tarhan S; Clinical Rheumatology; 2003; 14505208	74	58	16	OA Patients: 57.4(8.5), (Range:45-75); Healthy controls: 59.1(5.8), (Range:46-77)	60	Yes	No	Yes	Yes	Yes	No	No	No	No	Case control	73

Hill CL; Arthritis & Rheumatism; 2003; 14558089	451	427		Knee pain/ROA/Male: 68.3; Knee pain/ROA/Female: 65; No knee pain/ROA/Male: 66.8; No knee pain/ROA/Female: 66.1		No	No	Yes	No	No	No	Yes	No	No	Cross-sectional	73
Kim YJ; Journal of Bone & Joint Surgery - American Volume; 2003; 14563809	43			30(Range:11-47); Median=31	40	No	Yes	No	Yes	No	No	No	No	No	Other	82
Lindsey CT; Osteoarthritis & Cartilage; 2004; 14723868	74	33	21	Controls: 34.2(12.5); OA1(KL1/2): 62.7(10.9); OA2(KL3/4): 66.6(11.6)	39	Yes	No	No	Yes	No	Yes	No	No	No	Case control	73
Jones G; Osteoarthritis & Cartilage; 2004; 14723876	372	186	186	45(Range:26-61)		Yes	No	No	Yes	No	Yes	No	No	No	Case control	71
Raynauld JP; Arthritis & Rheumatism; 2004; 14872490	32	32	0	62.9(8.2)	(74%)	Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	69
Wluka AE; Annals of the Rheumatic Diseases; 2004; 14962960	132	132	0	63.1(Range: 41-86)	71(54%)	Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	71
Cicuttini F; Rheumatology; 2004; 14963201	117	117	0	67(10.6)	(58%)	Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	63
Peterfy CG; Osteoarthritis & Cartilage; 2004; 14972335	19	19	0	61(8)	4	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Other	80
Graichen H; Arthritis & Rheumatism; 2004; 15022323	21	21	0	70.6(7.7), (Range:58-86)	17	Yes	No	No	Yes	No	Yes	No	No	No	Cross-sectional	77

Dashti M; Scandinavian Journal of Rheumatology; 2004; 15163109	174	117	57	61.6(9.5)	123(70.7%)	Yes	No	No	Yes	No	No	No	No	No	Case control	66
Arokoski JP; Journal of Clinical Densitometry; 2004; 15181262	57	27	30	Cases: 56.2(4.9), Range: (47-64); Controls:56.3(4.5), (Range:47-64)	0	No	Yes	No	No	No	No	No	No	No	Case control	66
Dunn TC; Radiology; 2004; 15215540	55	48	7	Healthy: 38(Range:22-71); Mild OA: 63(Range:46-81); Severe OA: 67(Range: 43-88)	30	No	Yes	No	Yes	No	No	No	No	No	Case control	75
Regatte RR; Academic Radiology; 2004; 15217591	14	6	8	Asymptomatic: 33.5(Range:22-45); Symptomatic: 45.5(Range:28-63)	2	No	Yes	No	Yes	No	No	No	No	No	Case control	75
Baysal O; Swiss Medical Weekly; 2004; 15243849	65	65	0	53.1(7), (Range:45-75)	65(100%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	80
Lerer DB; Skeletal Radiology; 2004; 15316679	205			46.5(Range:15-88); Median=46	113	No	No	Yes	Yes	No	No	No	Yes	No	Cross-sectional	74
Berthiaume MJ; Annals of the Rheumatic Diseases; 2005; 15374855	.					Yes	No	Yes	Yes	No	No	No	Yes	No	Longi-tudinal Prospective	64
King KB; Magnetic Resonance Imaging; 2004; 15527998	16	16	0	Males: Median=58.5, (11.3), (Range:43-76); Females: Median=70 (14.4), (Range:46-88)	8(50%)	Yes	Yes	No	Yes	No	No	No	No	No	Cross-sectional	78
Carbone LD; Arthritis & Rheumatism; 2004; 15529367	818			Non-users: 74.8(2.94); Antiresportive users: 74.8(2.9)	818(100%)	No	No	Yes	Yes	Yes	Yes	No	No	No	Cross-sectional	67
Cicuttini F; Journal of Rheumatology; 2004; 15570649	.					Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	81

Wluka AE; Annals of the Rheumatic Diseases; 2005; 15601742	149	68	81	Normal: 57(5.8); OA: 63(10.3)	1499100%)	No	No	No	No	No	Yes	No	No	No	Longi-tudinal Prospective	65
Ding C; Osteoarthritis & Cartilage; 2005; 15727885	372	162	210	No cartilage defects: 43.6(7.1); Any cartilage defect: 47(6.1)	(56.5%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	70
Hill CL; Arthritis & Rheumatism; 2005; 15751064	433	360	73	Cases males: 68.2; Cases females: 65; Control males: 66.8; Control females: 65.8	143	No	No	Yes	No	No	No	No	No	Yes	Case control	65
Kornaat PR; European Radiology; 2005; 15754163	205	205	0	Median=60; (Range:43-77)	163(80%)	No	No	Yes	Yes	No	No	Yes	Yes	No	Cross-sectional	75
Zhai G; Arthritis & Rheumatism; 2005; 15818695	151	23	128	Men: 64(8.1); Women: 62(7.7)	72	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	75
Cicuttini F; Osteoarthritis & Cartilage; 2005; 15922634	28	28	0	62.8(9.8)	(57%)	Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	68
Blankenbaker DG; Skeletal Radiology; 2005; 15940487	247	74	173	44	126	No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	75
Huh YM; Korean Journal of Radiology; 2005; 15968151	94	73	21	RA group: 49.2 (Range:37-76), Median=48; OA group: 57.8(Range:40-80), Median=58	73	No	No	Yes	No	Yes	No	No	No	No	Longit-udinal Retro-spective	71
von Eisenhart-Roth; Annals of the Rheumatic Diseases; 2006; 15975965	26	26	0	70.4(7.6), (Range:58-86)	20	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	79
Tan AL; Arthritis & Rheumatism; 2005; 16052535	58	40	18	Early OA: 56(Range:49-69); Chronic OA: 60(Range:51-68); Hand OA: 60(Range: 46-72);	44	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Cross-sectional	73

Lo GH; Arthritis & Rheumatism; 2005; 16145676	268	80	188	No BMLs: 64.8(8.5); Medial BMLs: 68.3(7); Lateral BMLs: 66.6(9.5)	(59%)	No	No	Yes	No	No	No	Yes	No	No	Cross-sectional	70
Li X; Magnetic Resonance in Medicine; 2005; 16155867	19	9	10	Cases: Median=52, (Range:18-72); Controls: Median=30, (Range:22-74)	8	No	Yes	No	Yes	No	No	No	No	No	Case control	74
Rhodes LA; Rheumatology; 2005; 16188949	35	35	0	Median=63; (Range:49-77)	23	No	No	Yes	No	Yes	No	No	No	No	Cross-sectional	76
Williams A; Arthritis & Rheumatism; 2005; 16255024	31	31	0	67(10.4), 9Range:45-86)	24(77%)	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	72
Loeuille D; Arthritis & Rheumatism; 2005; 16255041	39	39	0	56.4(12.71)	(56.4%)	No	No	Yes	No	Yes	No	No	No	No	Cross-sectional	72
Roos EM; Arthritis & Rheumatism; 2005; 16258919	30			45.8(3.3)	10(33.3%)	No	Yes	No	Yes	No	No	No	No	No	Random-ized controlled trial	42
Hunter DJ; Journal of Rheumatology; 2005; 16265702	132	162	0	33.5(9.7)	(44.2%)	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Cross-sectional	77
Nojiri T; Knee Surgery, Sports Traumatology, Arthroscopy; 2006; 16395564	28	9	21	40.3(Range:16-74)	17	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	76
Ozturk C; Rheumatology International; 2006; 16428993	7	4	3	Healthy controls: 23; OA cases: 56	4	No	Yes	No	Yes	No	No	No	No	No	Other	74
Sengupta M; Osteoarthritis & Cartilage; 2006; 16442316	217	217	0	67.3(9.1)	(30%)	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Cross-sectional	76
Hunter DJ; Arthritis & Rheumatism; 2006; 16508930	257	257	0	66.6(9.2), (Range:47-93)	(41.6%)	No	No	Yes	Yes	No	No	No	Yes	No	Long-itudinal Prospective	70

Hunter DJ; Arthritis & Rheumatism; 2006; 16646037	217	217	0	66.4(9.4)	(44%)	No	No	Yes	Yes	No	No	Yes	No	No	Longi-tudinal Prospective	66
Grainger AJ; European Radiology; 2007; 16685505	43	43	0	64(Range:48-75)	19	No	No	Yes	No	Yes	No	No	Yes	No	Cross-sectional	76
Cashman PM; IEEE Transactions on Nanobioscience; 2002; 16689221	27	10	17	OA patients: (Range: 45-73); Similar age controls: (Range: 50-65); Young healthy controls: (Range:21-32);	8(29.6%)	Yes	No	No	Yes	No	No	No	No	No	Other	75
Torres L; Osteoarthritis & Cartilage; 2006; 16713310	143	143	0	70(10)	(78%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Cross-sectional	75
Kornaat PR; Radiology; 2006; 16714463	205	97	103	60(Range:43-77)	163(80%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Cross-sectional	68
Bamac B; Saudi Medical Journal; 2006; 16758050	46	36	10	Cases: 41.9(Range: 20-67); Controls: 39.7(Range: 21-66)	25	No	No	No	No	No	No	No	Yes	No	Case control	72
Boks SS; American Journal of Sports Medicine; 2006; 16861575	134	136	132	40.8(Range:18.8-63.8)		No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	77
Koff MF; Osteoarthritis & Cartilage; 2007; 16949313	113	113	0	56(11), (Range:33-82)	84	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	75
Nakamura M; Magnetic Resonance Imaging; 2006; 17071336	63			51.8(Range:40-59)	42	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	77
Folkesson J; IEEE Transactions on Medical Imaging; 2007; 17243589	139			56(Range:22-79)	(59%)	Yes	No	No	Yes	No	No	No	No	No	Other	78

Li X; Osteoarthritis & Cartilage; 2007; 17307365	26	10	16	Healthy: 41.3(Range: 22-74); OA patients: 55.9(37-72)	11	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Case control	74
Iwasaki J; Clinical Rheumatology; 2007; 17322963	26	26	0	63.8(Rang:49-82)	18	No	No	No	No	No	No	No	No	No	Cross-sectional	78
Dam EB; Osteoarthritis & Cartilage; 2007; 17353132	139			Evaluation set: 55(Range: 21-78); Scan-rescan set: 61(Range:26-75)	(54.5%)	Yes	No	No	Yes	No	No	No	No	No	Other	72
Tiderius CJ; Magnetic Resonance in Medicine; 2007; 17390362	18	10	8	Controls: 28(Range: 20-47); Cases: 39(Range: 25-58)		No	Yes	No	Yes	No	No	No	No	No	Case control	74
Baranyay FJ; Seminars in Arthritis & Rheumatism; 2007; 17391738	297		297	58(5.5)	(63%)	Yes	No	No	Yes	No	No	Yes	No	No	Cross-sectional	58
Issa SN; Arthritis & Rheumatism; 2007; 17394225	146	146	0	70	109	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Cross-sectional	73
Hanna F; Menopause; 2007; 17413649	176	0	176	52.3(6.6), (Range:40-67)	176(100%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	64
Hunter DJ; Annals of the Rheumatic Diseases; 2008; 17472995	71			67.9(9.3)	(28.2%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Other	70
Hill CL; Annals of the Rheumatic Diseases; 2007; 17491096	270	270	0	66.7(9.2)	112	No	No	Yes	Yes	Yes	No	No	No	No	Longi-tudinal Prospective	65
Qazi AA; Osteoarthritis & Cartilage; 2007; 17493841	.					Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	75
Lammentausta E; Osteoarthritis & Cartilage; 2007; 17502160	14			55(18)	2	No	Yes	No	Yes	No	Yes	No	No	No	Other	82

Guymer E; Osteoarthritis & Cartilage; 2007; 17560134	176	0	176	52.3(6.6)	176(100%)	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Cross-sectional	70
Nishii T; Osteoarthritis & Cartilage; 2008; 17644363	33	23	10	Volunteers: 34(Range: 23-51); Patients: 40(Range: 22-69)	33(1005)	No	Yes	No	Yes	No	No	No	No	No	Case control	71
Janakiramanan N; Journal of Orthopaedic Research; 2008; 17763451	202	74	128	61(9)	(73%)	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	71
Lo GH; Osteoarthritis & Cartilage; 2008; 17825586	845	170		63.6(8.8)	(58%)	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	72
Davies-Tuck M; Osteoarthritis & Cartilage; 2008; 17869546	100	100	0	63.3(10.2)	61(61%)	Yes	No	No	Yes	No	No	No	No	No	Longi-tudinal Prospective	72
Qazi AA; Academic Radiology; 2007; 17889338	159			(Range:21-81)		No	No	Yes	Yes	No	No	No	No	No	Other	77
Folkesson J; Academic Radiology; 2007; 17889339	.			56(Range:22-79)	(59%)	No	No	No	No	No	No	No	No	No	Other	80
Englund M; Arthritis & Rheumatism; 2007; 18050201	310	102	208	Cases: 62.9(8.3); Controls: 61.2(8.3)	211(68%)	No	No	Yes	No	No	No	No	Yes	No	Case control	60
Kamei G; Magnetic Resonance Imaging; 2008; 18083319	37	27	0	Cartilage defect: 51.6(Range: 42-61); No cartilage defect: 54.5(Range:45-61)	20	No	No	Yes	Yes	No	No	No	Yes	No	Case control	73
Li W; Journal of Magnetic Resonance Imaging; 2008; 18183573	29	19	10	OA subjects: 61.7(Range: 40-86); Controls: 31(Range:18-40)	19	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	80
Amin S; Osteoarthritis & Cartilage; 2008; 18203629	265	265		67(9)	(43%)	No	No	Yes	Yes	No	No	No	Yes	Yes	Longi-tudinal Prospective	66

Taljanovic MS; Skeletal Radiology; 2008; 18274742	19	19	0	66	8	No	Yes	No	No	No	No	No	No	No	Case control	73
Oda H; Journal of Orthopaedic Science; 2008; 18274849	161			58.5(Range:11-85)	98	No	No	Yes	No	Yes	No	No	Yes	Yes	Cross-sectional	74
Hanna FS; Arthritis Research & Therapy; 2008; 18312679	176			52.3(6.6)	(100%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	71
Reichenbach S; Osteoarthritis & Cartilage; 2008; 18367415	964	217	747	63.3	(57%)	No	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	75
Petterson SC; Medicine & Science in Sports & Exercise; 2008; 18379202	123	123	0	64.9(8.5)	67	No	No	No	No	No	No	No	No	No	Case control	70
Bolbos RI; Osteoarthritis & Cartilage; 2008; 18387828	32	16	16	Cases: 47.2(11.54), (Range: 29-72); Controls: 36.3(10.54), (Range:27-56)	14	Yes	Yes	No	Yes	No	Yes	No	No	No	Case control	73
Quaia E; Skeletal Radiology; 2008; 18404267	35	35	0	42(17), (Range:22-67)	14	No	Yes	No	Yes	No	No	No	No	No	Other	80
Folkesson J; Magnetic Resonance in Medicine; 2008; 18506845	.		143	KL0: 48(Range:21-78); KL1: 62(Range:37-81); KL2: 67(Range:47-78); KL3&4: 68(Range:58-78)		No	No	No	Yes	No	No	No	No	No	Other	65
Mills PM; Osteoarthritis & Cartilage; 2008; 18515157	49	25	24	APMM: 46.8(5.3); Controls: 43.6(6.6)	18(36.7%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	66
Dore D; Osteoarthritis & Cartilage; 2008; 18515160	50	50		64.5(7.1)	23	Yes	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	73
Mutimer J; Journal of Hand Surgery; 2008; 18562375	20	20	0	47(Range:26-69)	9	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	79

Amin S; Journal of Rheumatology; 2008; 18597397	192	192		69(9)	0.	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	69
Li X; Journal of Magnetic Resonance Imaging; 2008; 18666183	38	13	25	Healthy: 28.5(Range:20-34); Knee OA or injury: 37.4 (Range:20-66)	10	Yes	No	No	Yes	No	No	Yes	No	No	Other	74
Pelletier JP; Osteoarthritis & Cartilage; 2008; 18672386	27	1		64.1(9.6)	14	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Other	76
Stahl R; European Radiology; 2009; 18709373	37	17	20	Mild OA: 54(9.98); Healthy control: 33.6(9.44)	19	No	Yes	Yes	Yes	No	No	No	No	No	Case control	70
Brem MH; Acta Radiologica; 2008; 18720084	23	23	0	55.5(10.3)	8	No	No	Yes	No	No	No	Yes	No	No	Other	74
Lancianese SL; Bone; 2008; 18755303	4			80(14)	3	No	No	No	No	No	Yes	No	No	No	Cross-sectional	78
Englund M; New England Journal of Medicine; 2008; 18784100	991	171		62.3(8.6), (Range:50.1-90.5)	565(57%)	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	72
Mamisch TC; Magnetic Resonance in Medicine; 2008; 18816842	.					No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	79
Rauscher I; Radiology; 2008; 18936315	60	37	23	Healthy controls: 34.1(10); Mild OA: 52.5(10); Severe OA: 61.6(11.6)	32	No	Yes	No	Yes	No	No	No	Yes	No	Case control	71
Li W; Journal of Magnetic Resonance Imaging; 2009; 19161210	31	17	14	OA patients: 61.8(Range:40-86); Healthy controls: 29.2(Range: 18-40)	21	No	Yes	No	Yes	No	No	No	No	No	Case control	74
Choi JW; Journal of Computer Assisted Tomography; 2009; 19188805	36			39.7(Range: 8-69)	21	No	No	Yes	Yes	No	No	No	Yes	No	Longi-tudinal Retro-spective	69

Chen YH; Journal of Computer Assisted Tomography; 2008; 19204464	96	25	71	OA patients: 56; Non-OA: 46		No	No	Yes	Yes	No	No	No	Yes	No	Case control	71

Table 2: Summary table of studies reporting data on predictive validity of MRI in knee OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Score of method-logical quality
Boegard TL; Osteoarthritis & Cartilage; 2001; 11467896 [1]	47			Women: Median=50, (Range:42-57); Men: Median=50, (Range:41-57)	25(53.2%)	No	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	63
Wluka AE; Arthritis & Rheumatism; 2002; 12209510 [2]	123	123	0	63.1(10.6)	71	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	61
Cicuttini FM; Journal of Rheumatology; 2002; 12233892 [3]	21	8	13	Case: 41.3(13.2); Controls: 49.2(17.8)	14(66.7%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Retropective	63
Biswal S; Arthritis & Rheumatism; 2002; 12428228 [4]	43	4	39	54.4(Range:17-65)	21	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Longitudinal Retropective	68
Cicuttini F; Journal of Rheumatology; 2002; 12465162 [5]	110	110	0	63.2(10.2)	66	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	69
Pessis E; Osteoarthritis & Cartilage; 2003; 12744942 [6]	20	20		63.9(9)	13	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Longitudinal Prospective	68
Felson DT; Annals of Internal Medicine; 2003; 12965941 [7]	256	156	0	Followed: 66.2(9.4); Not followed: 67.8(9.6)	(38.3%)	No	No	Yes	No	No	No	Yes	No	No	Longitudinal Prospective	65

Cicuttini FM; Arthritis & Rheumatism; 2004; 14730604 [8]	117	117		63.7(10.2)	(58.1%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	76
Wluka AE; Annals of the Rheumatic Diseases; 2004; 14962960 [9]	132	132	0	63.1(Range:41-86)	71(54%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	71
Cicuttini F; Rheumatology; 2004; 14963201 [10]	117	117	0	67(10.6)	(58%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	63
Cicuttini FM; Ann Rheum Dis; 2004; 15115714 [11]	123	123	0	Joint replacement: 64.1(9.3); No joint replacement: 63.1(10.3)	65(52.8%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	67
Dashti M; Scandinavian Journal of Rheumatology; 2004; 15163109 [12]	174	117	57	61.6(9.5)	123(70.7%)	Yes	No	No	Yes	No	No	No	No	No	Case control	66
Cicuttini FM; Journal of Rheumatology; 2004; 15229959 [13]	102	102	0	63.8(10.1)	(63%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	73
Berthiaume MJ; Annals of the Rheumatic Diseases; 2005; 15374855 [14]	.					Yes	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	64

Cicuttini F; Journal of Rheumatology; 2004; 15570649 [15]	.					Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	81
Cubukcu D; Clinical Rheumatology; 2005; 15599642 [16]	40	40		HA group: 52.6(7.16); Saline group: 57.6(2.77)	24(60%)	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Randomized controlled trial	52
Ozturk C; Rheumatol Int; 2006;15703953 [17]	47	47	0	HA-only group: 58(7.7); HA&Cortico group: 58.1(10.3)	39(97.5%)	No	No	Yes	Yes	No	No	Yes	No	No	Randomized controlled trial	42
Wang Y; Arthritis Res Ther; 2005; 15899054 [18]	126	126		63.6(10.1)	68	No	No	No	No	No	Yes	No	No	No	Longitudinal Prospective	63
Cicuttini F; Osteoarthritis & Cartilage; 2005; 15922634 [19]	28	28	0	62.8(9.8)	(57%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	68
Wluka AE; Rheumatology; 2005; 16030084 [20]	126	126	0	63.6(10.1)	68(54%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	58
Garnero P; Arthritis & Rheumatism; 2005; 16145678 [21]	377	377	0	62.5(8.1)	(76%)	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	66
Wang Y; Rheumatology; 2006; 16188947 [22]	124	124	0	Females: 57.1(5.8); Males: 52.5(13.2)	81(65.3%)	No	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	66

Phan CM; European Radiology; 2006; 16222533 [23]	40	34	6	57.7(15.6), (Range:28-81)	16	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Longitudinal Prospective	67
Hayes CW; Radiology; 2005; 16251398 [24]	117	117	115	No OA, No Pain: 44.6(10.7); OA, No Pain: 16.2(0.8); No OA, Pain: 47(0.7); OA&Pain: 47.1(0.8)	(100%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Longitudinal Prospective	63
Wang Y; Journal of Rheumatology; 2005; 16265703 [25]	40	0	40	52.3(13)	0	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	64
Ding C; Arthritis & Rheumatism; 2005; 16320339 [26]	325			45.2(6.5)	190	Yes	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	64
Bruyere O; Annals of the Rheumatic Diseases; 2006; 16396978 [27]	62	62	0	64.9(10.3)	49	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Longitudinal Prospective	70
Katz JN; Osteoarthritis & Cartilage; 2006; 16413210 [28]	83			61(11), (Range:45-89)	50(60%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Longitudinal Prospective	66
Raynauld JP; Arthritis Research & Therapy; 2006; 16507119 [29]	110	110	0	62.4(7.5)	(64%)	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Longitudinal Prospective	66

Hunter DJ; Arthritis & Rheumatism; 2006; 16508930 [30]	257	257	0	66.6(9.2), (Range:47-93)	(41.6%)	No	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	70
Ding C; Archives of Internal Medicine; 2006; 16567605 [31]	325			Decrease defects:45.4(6.4); Stable defects: 44.2(7.1); Increase defects: 46.1(5.9)	(58.1%)	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	58
Brandt KD; Rheumatology; 2006; 16606655 [32]	30	20	10	62	29	No	No	No	No	Yes	No	No	No	No	Other	55
Hunter DJ; Arthritis & Rheumatism; 2006; 16646037 [33]	217	217	0	66.4(9.4)	(44%)	No	No	Yes	Yes	No	No	Yes	No	No	Longitudinal Prospective	66
Wluka AE; Arthritis Research & Therapy; 2006; 16704746 [34]	105	105	0	All eligible: 62.5(10.7); MRI at FU: 63.8(10.6); Lost to FU: 61.6(11.3)	59(53%)	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	55
Hunter DJ; Osteoarthritis & Cartilage; 2007; 16857393 [35]	127	127		67(9.05)	(46.7%)	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	61
Bruyere O; Osteoarthritis & Cartilage; 2007; 16890461 [36]	62	62	0	64.9(10.3)	46	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Longitudinal Prospective	72

Amin S; Annals of the Rheumatic Diseases; 2007; 17158140 [37]	196	196	0	68(9)	0	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	60
Nevitt MC; Arthritis & Rheumatism; 2007; 17469126 [38]	80	39	0	73.5(3.1)	(63.6%)	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	70
Hill CL; Annals of the Rheumatic Diseases; 2007; 17491096 [39]	270	270	0	66.7(9.2)	112	No	No	Yes	Yes	Yes	No	No	No	No	Longitudinal Prospective	65
Pelletier JP; Arthritis Research & Therapy; 2007; 17672891 [40]	110	110	0	Q1 greatest loss global: 63.7(7.2); Q4 least loss gobal: 61.3(7.5); Q1 greatest loss_medial: 64.1(7.4); Q1 least loss_medial: 61.6(7.8)	(68.3%)	No	No	Yes	Yes	No	No	Yes	Yes	No	Longitudinal Prospective	56
Davies-Tuck ML; Osteoarthritis & Cartilage; 2008; 17698376 [41]	117	117	0	63.7(10.2)	68(58%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	60
Raynauld JP; Annals of the Rheumatic Diseases; 2008; 17728333 [42]	107	107	0	62.4(7.5)	(64%)	Yes	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Retropective	58
Felson DT; Arthritis & Rheumatism; 2007; 17763427 [43]	330	110	220	Cases: 62.9(8.3); Controls: 61.2(8.4)	211(63.9%)	No	No	Yes	No	No	Yes	Yes	No	No	Case control	65

Kornaat PR; European Radiology; 2007; 17823802 [44]	182	71		59(Range:43-76)	157(80%)	No	No	Yes	No	No	No	Yes	No	No	Longitudinal Prospective	72
Hunter DJ; Arthritis Research & Therapy; 2007; 17958892 [45]	160	80	80	67(9)	(46%)	No	No	Yes	Yes	No	No	No	No	No	Case control	64
Englund M; Arthritis & Rheumatism; 2007; 18050201 [46]	310	102	208	Cases: 62.9(8.3)	211(68.1%)	No	No	Yes	No	No	No	No	Yes	No	Case control	60
Davies-Tuck ML; Osteoarthritis & Cartilage; 2008; 18093847 [47]	74	0	74	Meniscal tear: 58.8(6); No meniscal tear: 55.5(4.3)	74(100%)	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Longitudinal Prospective	62
Hernandez-Molina G; Arthritis & Rheumatism; 2008; 18163483 [48]	258	258	0	66.6(9.2)	(42.6%)	No	No	Yes	Yes	No	No	Yes	No	Yes	Longitudinal Prospective	65
Teichtahl AJ; Osteoarthritis & Cartilage; 2009; 18194873 [49]	99	99	0	63 (10)	(60%)	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	62
Amin S; Osteoarthritis & Cartilage; 2008; 18203629 [50]	265	265		67(9)	(43%)	No	No	Yes	Yes	No	No	No	Yes	Yes	Longitudinal Prospective	66
Teichtahl AJ; Obesity; 2008; 18239654 [51]	297		297	58(5.5)	186	Yes	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	61

Blumenkrantz G; Osteoarthritis & Cartilage; 2008; 18337129 [52]	18	8	10	Cases: 55.7(7.3); Controls: 57.6(6.2)	18(100%)	No	Yes	Yes	Yes	No	No	No	No	No	Case control	66
Song IH; Annals of the Rheumatic Diseases; 2009; 18375537 [53]	41	41		65(6.7)	26	No	No	Yes	No	No	No	No	No	Yes	Randomized controlled trial	52
Scher C; Skeletal Radiology; 2008; 18463865 [54]	65	65	0	OA-only: 49.3(Range:28-75); OA&BME group: 53.5(35-82)		No	No	Yes	Yes	No	No	Yes	No	No	Longitudinal Retropective	65
Sharma L; Arthritis & Rheumatism; 2008; 18512777 [55]	153	153	0	66.4(11)		Yes	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	63
Owman H;; Arthritis & Rheumatism; 2008; 18512778 [56]	15	9	7	50(Range:35-70)		No	Yes	No	Yes	No	No	No	No	No	Longitudinal Prospective	64
Madan-Sharma R; Skeletal Radiology; 2008; 18566813 [57]	186	74	112	60.2(Range:43-76)	150	No	No	Yes	Yes	No	No	Yes	Yes	No	Longitudinal Prospective	65
Amin S; Journal of Rheumatology; 2008; 18597397 [58]	192	192		69(9)		No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	69
Pelletier JP; Osteoarthritis & Cartilage; 2008; 18672386 [59]	27	1		64.1(9.6)	14	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Other	76

Amin S; Arthritis & Rheumatism; 2009; 19116936 [60]	265	265	0	67(9)		No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	53

Table 3: Summary table of studies reporting data on predictive validity of MRI in hip OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Score of methodological quality
Cunningham T; Journal of Bone & Joint Surgery; 2006; 16818980 [61]	47	47	0		41	No	Yes	No	Yes	No	No	No	No	No	Longitudinal Prospective	76

[Click here to return to your place in the text, p 43 (Predictive Validity/MRI).]

[Click here to return to your place in the text, p 45.]

Table 4: Summary table of studies reporting data on reliability of MRI in knee OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Downs criteria score
Karvonen RL; Journal of Rheumatology; 1994; 7966075 [1]	92	52	40	all OA Pts: 55(14,), (range:25-86); Bilateral OA Pts: 53(13) (range:25-73) ; Control: 49(15), (range:22-78)	All OA Pts: 35; Bilateral OA Pts: 19; Control: 25	Yes	No	No	Yes	No	Yes	No	No	No	Case control	66
Peterfy CG; Radiology; 1994; 8029420 [2]	8	5	3	62 (Range: 45-82)	4(50%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	79
Marshall KW; Journal of Orthopaedic Research; 1995; 8544016 [3]	2			31		Yes	No	No	Yes	No	No	No	No	No	Other	76
Disler DG; AJR Am J Roentgenol.; 1996; 8659356 [4]	114	79	35	36	48	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	77
Dupuy DE; Academic Radiology; 1996; 8959181 [5]	7	2	5	TKA Pts: (Range:64-75); Asymptomatic Pts:(Range:25-35)	TKA Pts: 1(50%); Asymptomatic Pts: 2	Yes	No	No	Yes	No	No	No	No	No	Other	75
Trattnig S; Journal of Computer Assisted Tomography; 1998; 9448754 [6]	20	20	0	72.2 (Range: 62-82)	18	No	No	Yes	Yes	No	No	No	No	No	Other	78
Drape JL; Radiology; 1998; 9646792 [7]	43	43	0	63 (Range: 53-78)	30	No	No	Yes	Yes	No	No	No	No	No	Cross-sectional	78
Cicuttini F; Osteoarthritis & Cartilage; 1999; 10329301 [8]	28			Males: 41.4(14.8); Females: 31.2(8.6)	11(39%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	77
Pham XV; Revue du Rhumatisme; 1999; 10526380 [9]	10	10	10	67.2(7.34), (Range: 57-80)	6	No	No	Yes	No	No	No	No	No	Yes	Cross-sectional	65

Gale DR; Osteoarthritis & Cartilage; 1999; 10558850 [10]	291	233	58	Men cases: 67(10); Men controls 65(10); Women cases: 66(10); Women controls: 66(8)	61(21%)	No	No	No	No	No	No	No	Yes	No	Case control	67
Hyhlik-Durr A; European Radiology; 2000; 10663760 [11]	11	3	8	OA group: (Range:61-75); Healthy group: (Range:25-36)	5(45.5%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	79
Jones G; Arthritis & Rheumatism; 2000; 11083279 [12]	92	0	92	Boys:12.8(2.7); Girls: 12.6(2.9)	43(46.8%)	Yes	No	No	Yes	No	Yes	No	No	No	Cross-sectional	63
Wluka AE; Annals of the Rheumatic Diseases; 2001; 11247861 [13]	81	42	39	Cases: 58(6.1); Controls: 56(5.4)	81(100%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	59
Felson DT; Annals of Internal Medicine; 2001; 11281736 [14]	401	401	0	66.8	.	No	No	Yes	No	No	No	Yes	No	No	Cross-sectional	64
Hill CL; Journal of Rheumatology; 2001; 11409127 [15]	458	433	25	67	(34%)	No	No	Yes	No	Yes	No	No	No	No	Case control	64
Bergin D; Skeletal Radiology; 2002; 11807587 [16]	60	30	30	Cases: 50; Controls: 57	.	No	No	Yes	No	No	No	No	Yes	Yes	Case control	68
Beuf O; Arthritis & Rheumatism; 2002; 11840441 [17]	46	18	28	Mild OA: 56.3(4.5); Severe OA: 70(6.3)	17(37%)	Yes	No	No	No	No	No	No	No	No	Case control	76
Wluka AE; Arthritis & Rheumatism; 2002; 12209510 [18]	123	123	0	63.1(10.6)	71	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	61
Gandy SJ; Osteoarthritis & Cartilage; 2002; 12464553 [19]	16	16	0		6	Yes	No	No	Yes	.	.	.	.	.	Longitudinal Prospective	67

Bhattacharyya T; Journal of Bone & Joint Surgery - American Volume; 2003; 12533565 [20]	203	154	49	Cases: 65; Controls: 67	.	No	No	Yes	No	No	No	No	Yes	No	Case control	70
Cicuttini FM; Clinical & Experimental Rheumatology; 2003; 12673893 [21]	81	42	39	ERT: 58(6.1); Controls: 56(5.4)	81(100%)	Yes	No	No	Yes	No	Yes	No	No	No	Case control	63
Raynauld JP; Osteoarthritis & Cartilage; 2003; 12744941 [22]	28	17	11	Healthy subjects: (Range:25-35); OA Pts: 63.5	.	Yes	No	No	Yes	No	No	No	No	No	Other	75
Felson DT; Annals of Internal Medicine; 2003; 12965941 [23]	256	256	0	Followed: 66.2(9.4); Not followed: 67.8(9.6)	Followed: 41.7%; Not followed: 15.2%	No	No	Yes	No	No	No	Yes	No	No	Other	65
Hill CL; Arthritis & Rheumatism; 2003; 14558089 [24]	451	427		Knee pain/ROA/ MALE: 68.3; Knee pain/ROA/ Female: 65; No knee pain /ROA/male: 66.8; No knee pain /ROA/ female:66.1	.	No	No	Yes	No	No	No	Yes	No	No	Cross-sectional	73
Glaser C; Magnetic Resonance in Medicine; 2003; 14648571 [25]	23	7	16	Healthy subjects: (Range:23-33); OA Pts: 60-85	13(56.5%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	85
Lindsey CT; Osteoarthritis & Cartilage; 2004; 14723868 [26]	74	33	21	OA1(KL=1/2):62.7(10.9); OA2(KL=3/4):66.6(11.6);Controls: 34.2(12.5)	39(52.7%)	Yes	No	No	Yes	No	Yes	No	No	No	Case control	73
Cicuttini FM; Arthritis & Rheumatism; 2004; 14730604 [27]	117	117		63.7(10.2)	(58.1%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	76
Raynauld JP; Arthritis & Rheumatism; 2004; 14872490 [28]	32	32	0	62.9(8.2)	(74%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	69

Cicuttini F; Rheumatology; 2004; 14963201 [29]	117	117	0	67(10.6)	(58.1%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	63
Peterfy CG; Osteoarthritis & Cartilage; 2004; 14972335 [30]	19	19	0	61(8)	4	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Other	80
Dashti M; Scandinavian Journal of Rheumatology; 2004; 15163109 [31]	174	117	57	61.6(9.5)	123(70.7%)	Yes	No	No	Yes	No	No	No	No	No	Case control	66
Cicuttini FM; Journal of Rheumatology; 2004; 15229959 [32]	102	102	0	63.8(10.1)	(63%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	73
Baysal O; Swiss Medical Weekly; 2004; 15243849 [33]	65	65	0	53.1(7), (Range: 45-75)	(100%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	80
Kornaat PR; Skeletal Radiology; 2005; 15480649 [34]	25	25	0	Median age=63, (Range: 50-75)	.	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Other	78
Yoshioka H; Journal of Magnetic Resonance Imaging; 2004; 15503323 [35]	28	28	0	55.6 (Range: 40-73)	10	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Other	82
Ding C; Osteoarthritis & Cartilage; 2005; 15727885 [36]	372	162	210	No cartilage defects: 43.6(7.1); Any cartilage defects: 47(6.1)	(58%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	70
Hill CL; Arthritis & Rheumatism; 2005; 15751064 [37]	433	360	73	Case males:68.2; Case females:65; Control males:66.8; Control females:65.8	143(33%)	No	No	Yes	No	No	No	No	No	Yes	Case control	65
Maataoui A; European Radiology; 2005; 15856246 [38]	12	12	0	median age=70.5, (Range: 60-86)	9	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	78

Cicuttini F; Osteoarthritis & Cartilage; 2005; 15922634 [39]	28	28	0	62.8(9.8)	(57%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	68
Huh YM; Korean Journal of Radiology; 2005; 15968151 [40]	94	73	21	OA group: 57.8, (Range:40-80), Median=58; RA group:49.6, (Range:37-76), Median=48	73(80%)	No	No	Yes	No	Yes	No	No	No	No	Longitudinal Retropective	71
Wluka AE; Rheumatology; 2005; 16030084 [41]	126	126	0	63.6(10.1)	68(54%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	58
Eckstein, F; Annals of the Rheumatic Diseases; 2006; 16126797 [42]	19	10	9	51 (Range: 40-71)	12	Yes	No	No	Yes	No	Yes	No	No	No	Other	76
Eckstein F; Arthritis & Rheumatism; 2005; 16200592 [43]	30	15	15	Cases: 49.6(Range:37-76); Controls:62.3(11.5)	30(100%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	72
Sengupta M; Osteoarthritis & Cartilage; 2006; 16442316 [44]	217	217	0	67.3(9.1)	(30%)	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Cross-sectional	76
Raynauld JP; Arthritis Research & Therapy; 2006; 16507119 [45]	110	110	0	62.4(7.5)	(64%)	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Longitudinal Prospective	66
Hunter DJ; Arthritis & Rheumatism; 2006; 16508930 [46]	257	257	0	66.6(9.2), (Range: 47-93)	(41.6%)	No	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	70
Brandt KD; Rheumatology; 2006; 16606655 [47]	30	20	10	62	29	No	No	No	No	Yes	No	No	No	No	Other	55
Jaremko JL; Osteoarthritis & Cartilage; 2006; 16644245 [48]	12	3	9	OA: (Range:59-71);)Healthy: 37(8), (Range:23-48)	4(33.3%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	72
Hunter DJ; Osteoarthritis & Cartilage; 2007; 16857393 [49]	127	127		67(9.05)	(46.7%)	No	Yes	No	Yes	No	No	No	No	No	Cross-sectional	61

Boks SS; American Journal of Sports Medicine; 2006; 16861575 [50]	134	136	132	40.8 (Range: 18.8-63.8)	.	No	No	Yes	Yes	No	No	No	Yes	Yes	Cross-sectional	77
Brem MH; Skeletal Radiology; 2007; 17219231 [51]	5	5	0	64.3 (Range: 40-73)	2	Yes	No	No	Yes	No	No	No	No	No	Other	80
Folkesson J; IEEE Transactions on Medical Imaging; 2007; 17243589 [52]	139			56 (Range: 22-79)	(59%)	Yes	No	No	Yes	No	No	No	No	No	Other	78
Dam EB; Osteoarthritis & Cartilage; 2007; 17353132 [53]	139			Evaluation set: 55(Range:21-78); Scan-rescan set: 51,(Range:26-75)	(55%)	Yes	No	No	Yes	No	No	No	No	No	Other	72
Baranyay FJ; Seminars in Arthritis & Rheumatism; 2007; 17391738 [54]	297		297	58(5.5)	(63%)	Yes	No	No	Yes	No	No	Yes	No	No	Cross-sectional	58
Hanna F; Menopause; 2007; 17413649 [55]	176	0	176	52.3(6.6), (Range: 40-67)	176(100%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	64
Hunter DJ; Annals of the Rheumatic Diseases; 2008; 17472995 [56]	71			67.9(9.3)	(28.2%)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Other	70
Hill CL; Annals of the Rheumatic Diseases; 2007; 17491096 [57]	270	270	0	66.7(9.2)	112	No	No	Yes	Yes	Yes	No	No	No	No	Longitudinal Prospective	65
Qazi AA; Osteoarthritis & Cartilage; 2007; 17493841 [58]					.	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	75
Guymer E; Osteoarthritis & Cartilage; 2007; 17560134 [59]	176	0	176	52.3(6.6)	(100%)	Yes	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	70

Eckstein F; Osteoarthritis & Cartilage; 2007; 17560813 [60]	9	9		52.2(9.3)	5	Yes	No	No	Yes	No	No	No	No	No	Other	72
Akhtar, S; Osteoarthritis & Cartilage; 2007; 17707660 [61]	6			(Range: 25-69)	2(33%)	Yes	No	No	Yes	No	No	No	No	No	Other	79
Raynauld JP; Annals of the Rheumatic Diseases; 2008; 17728333 [62]	107	107	0	62.4(7.5)	(64%)	Yes	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Retrospective	58
Felson DT; Arthritis & Rheumatism; 2007; 17763427 [63]	330	110	220	Cases: 62.9(8.3); Controls: 61.2(8.4)	211(64%)	No	No	Yes	No	No	Yes	Yes	No	No	Case control	65
Lo GH; Osteoarthritis & Cartilage; 2008; 17825586 [64]	845	170		63.6(8.8)	(58%)	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	72
Davies-Tuck M; Osteoarthritis & Cartilage; 2008; 17869546 [65]	100	100	0	63.6(10.2)	61(61%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	72
Folkesson J; Academic Radiology; 2007; 17889339 [66]	.			56 (Range: 22-79)	(59%)	No	No	No	No	No	No	No	No	No	Other	80
Sanz R; Journal of Magnetic Resonance Imaging; 2008; 18022850 [67]	22	9		Normal: 43.6(15); Chondromalacia: 33.3(11.8); OA Pts: 58.9(11.5)	14(64%)	No	Yes	No	Yes	No	No	No	No	No	Case control	82
Englund M; Arthritis & Rheumatism; 2007; 18050201 [68]	310	102	208	Cases: 62.9(8.3); Controls: 61.2(8.3)	211(68%)	No	No	Yes	No	No	No	No	Yes	No	Case control	60
Hernandez-Molina G; Arthritis & Rheumatism; 2008; 18163483 [69]	258	258	0	66.6(9.2)	(42.6%)	No	No	Yes	Yes	No	No	Yes	No	Yes	Longitudinal Prospective	65

Amin S; Osteoarthritis & Cartilage; 2008; 18203629 [70]	265	265		67(9)	(43%)	No	No	Yes	Yes	No	No	No	Yes	Yes	Longitudinal Prospective	66
Teichtahl AJ; Obesity; 2008; 18239654 [71]	297		297	58(5.5)	186	Yes	No	Yes	Yes	No	Yes	No	No	No	Longitudinal Prospective	61
Anandacoomarasamy; Journal of Rheumatology; 2008; 18278831 [72]	32	32		Males: 64(11.5); Females: 66(9.5); Total: 65(Range:42-87)	17(53%)	Yes	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	67
Eckstein F; Annals of the Rheumatic Diseases; 2008; 18283054 [73]	158			Mild to moderate OA2: 57.6(8.3); Controls: 56.1(8.7)	158(100%)	Yes	No	No	Yes	No	No	No	No	No	Case control	63
Reichenbach S; Osteoarthritis & Cartilage; 2008; 18367415 [74]	964	217	747	63.3	(57%)	No	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	75
Petterson SC; Medicine & Science in Sports & Exercise; 2008; 18379202 [75]	123	123	0	64.9(8.5)	67	No	No	No	No	No	No	No	No	No	Case control	70
Bolbos RI; Osteoarthritis & Cartilage; 2008; 18387828 [76]	32			Cases: 47.2(11.5), (Range: 29-72); Controls: 36.3(10.5), Range(27-56)	14(44%)	Yes	Yes	No	Yes	No	Yes	No	No	No	Case control	73
Pai A; Magnetic Resonance Imaging; 2008; 18502073 [77]	10	0	10	27 (Range: 21-31)	4(40%)	No	Yes	No	Yes	No	No	No	No	No	Other	74
Folkesson J; Magnetic Resonance in Medicine; 2008; 18506845 [78]	.		143	Healthy subjects: 48(Range: 21-78); KL1: 62(Range:37-81); KL2: 67(Range:47-78); KL3&4: 68(58-78)	.	No	No	No	Yes	No	No	No	No	No	Other	65

Mills PM; Osteoarthritis & Cartilage; 2008; 18515157 [79]	49	25	24	APMM: 46.8(5.3); Controls: 43.6(6.6)	18(36.7%)	Yes	No	Yes	Yes	No	No	No	No	No	Case control	66
Dore D; Osteoarthritis & Cartilage; 2008; 18515160 [80]	50	50		64.5(7.1)	23	Yes	No	Yes	Yes	No	Yes	No	No	No	Cross-sectional	73
Pelletier JP; Osteoarthritis & Cartilage; 2008; 18672386 [81]	27	1		64.1(9.6)	14	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Other	76
Englund M; New England Journal of Medicine; 2008; 18784100 [82]	991	171		62.3(8.6), (Range: 50.1-90.5)	565(57%)	No	No	Yes	No	No	No	No	Yes	No	Cross-sectional	72
Rauscher I; Radiology; 2008; 18936315 [83]	60	37	23	Healthy controls: 34.1(10); Mild OA: 52.5(10.9); Severe OA: 61.6(11.6)	32(53.3%)	No	Yes	No	Yes	No	No	No	Yes	No	Case control	71
Kijowski R.; Radiology; 2009; 19164121 [84]	200		200	1.5T image group: 38.9(Range: 16-63); 3T image group: 39.1(Range:15-65)	87(43.5%)	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Retrospective	68

Table 5: Summary table of studies reporting data on reliability of MRI in hip OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Downs criteria score
Arokoski JP; Annals of the Rheumatic Diseases; 2002; 11796401 [85]	57	27	30	Cases: 56.2(4.9), (Range: 47-64); Controls: 56.3(4.5), (Range:47-64)	0	Yes	No	No	No	No	No	No	No	No	Case control	71
Zhai G; Arthritis & Rheumatism; 2005; 15818695 [86]	151	23	128	Men:64(8.1); Women:62(7.7)	72(47.7%)	Yes	No	No	Yes	No	No	No	No	No	Cross-sectional	75

Nishii T; Osteoarthritis & Cartilage; 2008; 17644363 [87]	33	23	10	Volunteers: 34(Range:23-51); Patients: 40(Range:22-69)	33(100%)	No	Yes	No	Yes	No	No	No	No	No	Case control	71
Carballido-Gamio J; Journal of Magnetic Resonance Imaging; 2008; 18581346 [88]	7	2	5	Healthy: 26.6(7.4); Mild Hip OA: 61(n=1); Advanced Hip OA: 54(n=1)	2(28.6%)	No	Yes	No	Yes	No	No	No	No	No	Other	78

Table 6: Summary table of studies reporting data on reliability of MRI in hand OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional techniques	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Downs criteria score
Grainger AJ; Skeletal Radiology; 2007; 17497149 [89]	15	15	0	59 (Range: 51-68)	14	No	No	Yes	No	No	No	No	No	No	Cross-sectional	76

Table 7: Summary table of studies reporting data on responsiveness of MRI in OA

Reference: Author, Journal, Year, PMID	Whole sample size	No. of cases	No. of controls	Age, yrs, Mean(SD), Range	No. (%) of females	Quantitative cartilage	Compositional technique	Semi-quantitative	Cartilage	Synovium	Bone	Bone marrow lesions	Meniscus	Ligament	Study design	Downs criteria score
Wluka AE; Arthritis & Rheumatism; 2002; 12209510[1]	123	123	0	63.1(10.6)	71	Yes	No	No	Yes	No	Yes	No	No	No	Longitudinal Prospective	61
Cicuttini FM; Journal of Rheumatology; 2002;	21	8	13	Case:41.3(13.2); Controls: 49.2(17.8)	14(66.7%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	63

12233892[2]															
Biswal S; Arthritis & Rheumatism; 2002; 12428228[3]	43	4	39	54.4(Range17-65)	21	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	68
Gandy SJ; Osteoarthritis & Cartilage; 2002; 12464553[4]	16	16	0	63.4 (Range 52-70)	6	Yes	No	No	Yes	.No	No	No	No	No	Longitudinal Prospective	67
Wluka AE; Journal of Rheumatology; 2002; 12465157[5]	136	136	0	Vitamin E group:64.3(11); Placebo group: 63.7(10)	75(55%)	Yes	No	No	Yes	No	No	No	No	No	Randomized controlled trial	38
Cicuttini F; Journal of Rheumatology; 2002; 12465162[6]	110	110	0	63.2(10.2)	66	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	69
Pessis E; Osteoarthritis & Cartilage; 2003; 12744942[7]	20	20		63.9(9)	13	Yes	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	68
Cicuttini FM; Arthritis & Rheumatism; 2004; 14730604[8]	117	117		63.7(10.2)	(58.1%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	76
Raynauld JP; Arthritis & Rheumatism; 2004; 14872490 [9]	32	32	0	62.9(8.2)	(74%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	69
Wluka AE; Annals of the Rheumatic Diseases; 2004; 14962960 [10]	132	132	0	63.1(Range:41-86)	71(54%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	71
Cicuttini FM; Journal of Rheumatology; 2004; 15229959 [11]	102	102	0	63.8(10.1)	(63%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	73

Blumenkrantz G; Osteoarthritis & Cartilage; 2004; 15564067 [12]	38	30	8	58(Range:28-81)	(39.5%)	Yes	Yes	No	Yes	No	No	No	No	No	Longitudinal Prospective	66
Zhai G; BMC Musculoskeletal Disorders; 2005; 15720725 [13]	150	80	70	TASOAC dataset: 62.3(7.6); KCV dataset: 42.8(6.1)	79(52.7%)	Yes	No	No	Yes	No	No	No	No	No	Other	65
Wang Y; Arthritis Res Ther; 2005; 15899054 [14]	126	126		63.6(10.1)	68	No	No	No	No	No	Yes	No	No	No	Longitudinal Prospective	63
Cicuttini F; Osteoarthritis & Cartilage; 2005; 15922634 [15]	28	28	0	62.8(9.8)	(57%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	68
Wluka AE; Rheumatology; 2005; 16030084 [16]	126	126	0	63.6(10.1)	68(54%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	58
Ding C; Arthritis & Rheumatism; 2005; 16320339 [17]	325			45.2(6.5)	190	Yes	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	64
Raynauld JP; Arthritis Research & Therapy; 2006; 16507119 [18]	110	110	0	62.4(7.5)	(64%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	66
Hunter DJ; Arthritis & Rheumatism; 2006; 16508930 [19]	257	257	0	66.6(Range:47-93)	(41.6%)	No	No	Yes	Yes	No	No	No	No	No	Longitudinal Prospective	70
Hunter, D J; Osteoarthritis & Cartilage; 2006; 16678452 [20]	150	150	0	58.9(Range:44-81)	(72%)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Longitudinal Prospective	71

Wluka AE; Arthritis Research & Therapy; 2006; 16704746 [21]	105	105	0	All eligible: 62.5(10.7); MRI at FU: 63.8(10.6); Lost to FU: 61.6(11.3)	61(58.1%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	55
Ding C; Rheumatology; 2007; 16861710 [22]	325			45.2(6.4)	190	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	61
Hunter DJ; Arthritis & Rheumatism; 2006; 16868968 [23]	264	264	0	66.7(9.2), (Range:47-93)	(40.9%)	No	No	Yes	Yes	No	No	No	Yes	No	Longitudinal Prospective	75
Bruyere O; Osteoarthritis Cartilage; 2007; 16890461 [24]	62			64.9 (10.3)	(74%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Stahl R; Osteoarthritis & Cartilage; 2007; 17561417 [25]	18	8	10	OA Pts: 55.7(7.3); Controls:57.6(6.2)	18(100%)	No	Yes	No	Yes	No	No	No	No	No	Case control	70
Pelletier JP; Arthritis Research & Therapy; 2007; 17672891 [26]	110	110		Q1greatestlossglobal: 63.7(7.2); Q4 least loss global: 61.3(7.5); Q1 greatestloss_med: 64.1(7.4); Q1 least loss_medial: 61.6(7.8)	74(67.3%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	56
Raynauld JP; Annals of the Rheumatic Diseases; 2008; 17728333 [27]	107	107	0	62.4(7.5)	(64%)	Yes	No	No	Yes	No	No	Yes	No	No	Longitudinal Retrospective	58
Davies-Tuck M; Osteoarthritis & Cartilage; 2008; 17869546 [28]	100	100	0	63.3(10.2)	61(61%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	72

Hunter DJ; Arthritis Research & Therapy; 2007; 17958892 [29]	160	80	80	67(9)	(46%)	No	No	Yes	Yes	No	No	No	No	No	Case control	64
Teichtahl AJ; Osteoarthritis & Cartilage; 2008; 18194873 [30]	99	99	0	63(10)	(60%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	62
Hunter DJ; Annals of the Rheumatic Diseases; 2009; 18408248 [31]	150	150		60.9(9.9)	76(51%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	76
Folkesson J; Magnetic Resonance in Medicine; 2008; 18506845 [32]	288		143	KL0(Healthy): 48(Range:21-78); KL1: 62(Range:37-81); KL2: 67(Range:47-78); KL3&4: 68(Range:58-78)	(44%)	No	No	No	Yes	No	No	No	No	No	Other	65
Sharma L; Arthritis & Rheumatism; 2008; 18512777 [33]	153	153	0	66.4(11)		Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	63
Teichtahl AJ; Osteoarthritis & Cartilage; 2009; 18590972 [34]	78			63 (10.5)	(52%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Raynauld JP; Annals Rheumatic Disease; 2009; 18653484 [35]	154			60.3 (8.1)	100 (65%)	Yes	No	No	Yes	No	No	No	No	No	Randomized controlled trial	
Pelletier JP; Osteoarthritis &	27	1		64.1(9.6)	14	Yes	No	Yes	Yes	Yes	No	Yes	No	No	Other	76

Cartilage; 2008; 18672386 [36]															
Wirth W; Osteoarthritis & Cartilage; 2009; 18789729 [37]	79			60.3 (9.5)	79 (100%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Eckstein F; Arthritis & Rheumatism; 2008; 18975356 [38]	174	174	0	66(11.1)	(76%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	69
Hellio Le Graverand MP; Annals Rheumatic Diseases; 2008; 19103634 [39]	180				(100%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Eckstein F; Arthritis Research Therapy; 2009; 19534783 [40]	79			60.3 (9.5)	79 (100%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Eckstein F; Arthritis Rheum; 2009: 19714595 [41]	80			60.9 (9.1)	48 (60%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	
Hunter DJ; Osteoarthritis & Cartilage; 2009; 19744588 [42]	150	150		60.9(9.9)	76(51%)	Yes	No	No	Yes	No	No	No	No	No	Longitudinal Prospective	76

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Predictive Validity

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APPENDIX 7

ULTRASONOGRAPHY

5.1 Methods

Articles published prior to November 2009 were sought. PubMed was searched using the terms "[ultrasound or sonography] and osteoarthritis," limited to humans and English language. Two hundred-ninety manuscripts were identified. Medline was searched using [MESH subject heading "ultrasonography" or the keyword "ultrasonography"] and [MESH headings "osteoarthritis'' or "osteoarthritis, knee" or "osteoarthritis, hip" or the keyword "osteoarthritis"], limited to humans and English language. One hundred and seventy one articles were identified. Of the identified articles, 165 were duplicates; therefore, the titles and abstracts of 296 articles were assessed with regards to inclusion and exclusion criteria.

Articles were excluded if they were not original articles pertaining to the use of B mode US in the assessment of a joint of a cohort of subjects with a diagnosis of OA at baseline. Review articles [n= 64], case reports [n= 21], letters [n=2], positions statements [n=2], recommendations [n=2], editorials [n=2] practice audits [n=1], pictorial reviews [n=1], studies ex vivo [n=13], and second reports [n=2] were excluded. Additionally, articles that utilized US only for guiding injections, and did not report any validity data or findings of the US examination were excluded [n=8]. Manuscripts utilizing US to measure only rotational angles were also excluded [n=3]. Of the remaining articles, 62 did not assess a cohort with a diagnosis of OA at baseline, 49 did not utilise B mode US and 17did not examine a joint structure. An additional nine publications were identified by experts in the field and searching the bibliographies of recent review articles. Therefore, 56 manuscripts were included in this review (see **Appendix 7, Table 1**)

5.2 Results

Data that focused on the metric properties of US in OA were extracted and are presented in **Appendix 7, Table 2)**.

Of the 56 studies identified, the majority were published in the last 100 years. The knee has been the most studied joint, followed by the hand and hip, with other joints being studied rarely. Grey scale B mode ultrasonography was the most commonly employed imaging technique, although more recent studies commonly used Doppler technique, and contrast was employed occasionally in contemporary studies.

Pathologies examined most commonly were effusion, followed by synovial thickening or hypertrophy, cartilage parameters, vascularity, Baker's cysts, osteophytes, tendon and ligament

abnormalities, meniscal changes, bursitis, erosions, and panniculitis. Definitions of the imaging appearance of the pathology imaged were provided in approximately half of the studies, however, definitions of pathologies varied. More recent studies tended to refer to the OMERACT definitions of pathology, or use a definition in keeping with the OMERACT definitions.

The validity of ultrasonography in detecting synovial pathology and vascularity has been compared to histopathology at the knee and hip joints,[20,234],and ultrasonography detected effusion have been able to be aspirated in the hip and hand.[235,236] The knee joint has been the focus of comparison between ultrasonography detected synovial pathology and MRI and arthroscopy.[237-239].Ultrasonography is more sensitive and specific than clinical examination in detecting effusion and synovial hypertrophy at the knee joint. Reliability data was reported relatively infrequently, although this has been addressed in other reviews.[240,241]

Given the difficulties in visualizing cartilage in vivo, there were few validity studies focusing on cartilage. However, ultrasonography demonstrated reasonable validity in detecting focal cartilage thickness compared to MRI and radiographs at the knee joint,[242-244] although generally only peripheral, nonload-bearing regions of cartilage can be visualized, meaning the clinical relevance of this measurement is uncertain. Reliability of measuring cartilage thickness was found to be acceptable in the small joints of the hand, and the knee.[243,245]

The studies examining the validity of ultrasonography detected tendon and ligament changes usually utilized clinical examination as the comparator, with varying results. Whilst there was good correlation between US and clinical and radiographic changes of enthesitis at the shoulder, and foot,[246,247] the correlation between ultrasonography and clinical diagnoses of anserine tenobursitis was poor.[248]

Cortical irregularities were infrequently studied, however, ultrasonography is more sensitive to osteophytosis than radiography in the small joints of the hand[249], but less sensitive to erosions.[250]

No consistent relationship between clinical symptoms and ultrasonography detected pathology is found in this review, although symptomatic joints tend to have more ultrasonography detected pathology than controls/healthy joints.

A minority of studies reported any reproducibility data, although when reported it was reasonably good. Importantly, Intra-/inter-reader acquisition was reported less often than re-reporting.

However, previous systematic reviews have well documented the reliability data regarding ultrasonography in assessing other joint diseases.[240,241,248]

Only nine studies utilized therapeutic interventions to allow the ability of ultrasonography to detected changes over time to be examined. The general trends were a reduction in ultrasonography detected pathology with time after therapy, although only one of the studies was a RCT, the others being observational case series. The paucity of these studies may be somewhat influenced by the lack of well established DMARDS in OA.

5.3 Summary

Ultrasonography is an imaging technique that may be useful in the diagnosis and management of OA, both in clinical trials and practice. To date, published manuscripts have demonstrated some construct and criterion validity of ultrasonography in assessing pathology specific to OA, albeit relatively scarce compared to the data in inflammatory arthritis. Additionally, reproducibility and discriminate validity data also exist, although again, it is a relatively small body of evidence. Further work is required to fully validate this promising imaging tool in OA and understand its clinical and scientific utility.

Ultrasonography Tables

[Click on link below (Table 1) to return to text (Appendix 7/Ultrasonograpy/5.1 Methods).]

Table 1. Summary of the included manuscripts, and summary of metric properties assessed in the manuscripts. (P, power Doppler; C, colour Doppler; B, both power and colour Doppler; U, unclear)

First Author	Year	Joint region Imaged	Doppler utilised	Definition of imaging appearance of pathology provided	Scoring system described	Criterion validity	Construct validity	Intra-observer acquisition	Inter-observer acquisition	Assesses response to therapy
Acebes[1]	**2006**	Knee	N	N	Y	N	Y	N	N	Y
Aisen[2]	1984	Knee	N	N	Y	N	N	N	N	N
Altinel[3]	2007	Knee	N	N	Y	N	N	N	N	N
Arslan[4]	1999	SI joint	P	Y	Y	N	Y	N	N	N
Atchia[5]	2007	Hip	N	N	N	N	Y	N	N	N
Baratelli[6]	1986	Hip	N	Y	Y	N	N	N	N	N
Baratto[7]	2000	C Spine	N	N	Y	N	N	N	N	Y
Chatzopolous[8]	2008	Knee	N	Y	Y	N	Y	N	N	N
D'Agostino[9]	2005	Knee	N	Y	Y	N	Y	N	N	N
De Miguel Mendieta[10]	2006	Knee	N	Y	Y	N	Y	N	N	N
Falsetti[11]	2002	Shoulder	N	N	Y	N	Y	N	N	N
Falsetti[12]	2003	Foot	N	Y	Y	N	N	N	N	N
Fam[13]	1982	Knee	N	N	Y	N	Y	N	N	N
Filippucci[14]	2003	Hand, Knee, Foot	N	N	N	N	N	N	Y	N

Giovagnorio[15]	2001	Knee	P	Y	Y	N	Y	N	N	N
Iagnocco[16]	2000	Hand	N	Y	Y	Y	N	N	N	Y
Iagnocco[17]	2005	Hand	N	Y	Y	N	Y	N	N	N
Iagnooco[18]	1992	Knee	N	N	Y	N	N	N	N	N
Jan[19]	2006	Knee	N	N	Y	N	Y	Y	N	Y
Jonsson[20]	1992	Knee, Hip	N	Y	Y	N	Y	Y	N	N
Ju[21]	2008	Knee	N	Y	Y	N	Y	N	N	N
Jung[22]	2006	Knee	N	Y	Y	N	Y	N	N	N
Karim[23]	2004	Knee	N	Y	Y	Y	Y	N	Y	N
Keen[24]	2008	Hand	N	Y	Y	N	Y	Y	N	N
Keen	2008	Hands	P	Y	Y	N	Y	Y	N	N
Keen[25]	2007	Hand	P	Y	Y	N	N	Y	Y	N
Kim[26]	2008	Knee	N	Y	Y	N	Y	N	N	N
Kristoffersen[27]	2006	Knee	C	Y	N	N	Y	N	N	N
Lee[28]	2007	Knee	N	Y	Y	N	Y	N	N	N
Lennox[29]	1994	Knee	N	N	Y	N	N	N	N	N
Mandl[30]	2006	Hand	N	Y	Y	N	Y	N	N	N
Martino[31]	1993	Knee	N	N	Y	Y	N	N	N	N
McCune[32]	1990	Knee	N	N	Y	Y	N	N	N	N
Moller[33]	2009	Hands	N	Y	Y	N	Y	Y	N	N
Monteforte[34]	1999	Knee	N	N	Y	N	N	N	N	N
Monteforte[35]	2003	C Spine	N	N	Y	N	N	N	N	N
Naredo[36]	2005	Knee	N	U	N	N	Y	N	N	N
Ostergaard[37]	1995	Knee	N	Y	Y	N	Y	N	N	Y
Pendleton[38]	2008	Knee	P	Y	Y	N	Y	N	N	Y
Pourbagher[39]	2005	Hip	N	N	N	N	Y	N	N	N
Qvistgaard[40]	2001	Knee, Hip	N	Y	N	Y	Y	N	N	N
Qvistgaard[41]	2006	Hip	N	N	Y	Y	N	N	N	N
Reardon[42]	2001	Hip	N	N	N	N	N	N	N	N
Rennesson-Rey[43]	2009	Hip	P	Y	Y	N	N	N	N	N

Robinson[44]	2007	Hip	B	Y	Y	N	Y	N	N	N
Schmidt[45]	2000	Knee	C	N	Y	Y	Y	N	N	Y
Song[46]	2008	Knee	P	Y	Y	N	N	N	N	y
Song[46]	2009	Knee	P	Y	Y	N	Y	N	N	N
Su[47]	2006	Hip	N	N	Y	N	N	N	N	N
Tarasevicius[48]	2006	Hip	N	Y	Y	N	N	N	N	N
Tarasevicius[49]	2008	Hip	N	Y	N	N	Y	N	N	N
Tarhan[50]	2003	Knee	N	Y	Y	N	Y	N	N	N
Walther[51]	2002	Hip	P	N	Y	Y	N	N	N	Y
Walther[52]	2001	Knee	P	N	Y	Y	N	N	N	Y
Yoon[53]	2005	Knee	P	Y	Y	N	Y	N	N	N
Yoon[54]	2008	Knee	N	N	Y	N	Y	N	N	N

[Click on link below (Table 2) to return to text (Appendix 7/Ultrasonography/5.2 Results).]

Table 2. Pathologies examined in the manuscripts and scoring systems used NS: not specified

Manuscript	Pathology Imaged	Scoring system used
Acebes[1]	• Bakers cyst • Synovial hypertrophy	• Continuous (area) • Continuous (area)
Altinel[3]	• Patella Tendon	• ordinal Categorical (4 point)
Arslan [4]	• Vascular flow(RI)	• Resistive index
Atchia[5]	• Hip joint	• Described elsewhere
Baratelli[6]	• Joint capsule thickness	• Continuous (mm)
Chatzopolous[8]	• Popliteal Cyst • Effusion	• dichotomous • ordinal Categorical (3 point)
D'Agostino [9]	• Synovial hypertrophy • Effusions	• dichotomous • dichotomous
De Miguel Mendieta [10]	• Meniscal lesion • effusion • bursitis • baker's cyst	• dichotomous • dichotomous • dichotomous • dichotomous
Falsetti [11]	• Enthesitis • Enthesophytes	• dichotomous • dichotomous

	• Tenosynovityis • Accromial irregularity	• dichotomous • dichotomous
Falsetti[12]	• Enthesitis • Plantar fasciitis	• Nominal Categorical (4 point) • Nominal Categorical (4 point)
Fam[13]	• Popliteal cysts	• Dichotomous
Giovagnorio[15]	• Typical signs of arthritis • (including cartilage thinning) • Vascularity • Synovial thickening, effusion.	• Dichotomous • Dichotomous • Dichotomous
Iagnocco[18]	• Erosions • Cartilage thickness	• Dichotomous • Continuous (mm)
Iagnocco[16]	• Effusion	• Continuous (mm)
Jan[19]	• Synovial sac thickness	• Continuous (mm)
Jonsson[20]	• Cartilage thickness	• Continuous (mm)
Ju [21]	• Synovitis • Effusion	• Dichotomous • Continuous (mm)
Jung[22]	• Osteophyte length • Cartilage thickness • Capsular distension • Effusion • Synovial proliferation	• Continuous (mm) • Continuous (mm) • Continuous (mm) • Continuous (mm) • Dichotomous
Karim [23]	• Synovitis • Effusion	• Nominal Categorical(4 point) • Dichotomous
Keen[24]	• Osteophytes • Joint space narrowing • Synovial hypertrophy and effusion • Vascularity	• Dichotomous • Dichotomous • Ordinal categorical (4 point) • Ordinal categorical (4 point)
Keen[25]	• Osteophytes • Synovitis • Vascularity	• Ordinal categorical (4 point) • Ordinal categorical (4 point) • Ordinal categorical (4 point)
Keen[55]	• Osteophytes • Joint space narrowing	• Continuous(number) • Dichotmous
Kim [26]	• Bony spurs • Patella tendon • Medial and lateral collateral ligaments • Effusion • Synovitis • Cartilage	• NS • NS • NS • Continuous(mm) • U • Continuous(mm)
Kristoffersen[27]	• Synovial hypertrophy • Fluid • Hyperemia	• NS • NS • Continuous
Lee[28]	• Synovial proliferation	• Dichotomous
Lennox[29]	• Quadriceps diameter	• Continuous(mm)

Martino[31]	• Cartilage thickness	• Continuous(mm)
McCune[32]	• Cartilage thickness • Cartilage clarity • Cartilage sharpness	• Continuous(mm) • Ordinal categorical (7 point) • Ordinal categorical (7 point)
Moller[33]	• Cartilage thickness	• Continuous(mm)
Monteforte[34]	• Cartilage thickness • Thickness of patella and quadriceps tendons	• NS • Continuous (mm)
Naredo[36]	• Bursitis • Effusion • Popliteal cyst	• NS • NS • NS
Naredo[56]	• Tendon and ligament lesions	• NS
Ostergaard [37]	• Erosions • Effusion • Synovial thickness • Cartilage thickness	• Continuous (number) • Continuous (mm) • Continuous (mm) • Continuous(mm)
Pendleton[38]	• Synovial hypertrophy • effusion	• Dichotomous
Qvistgaard[41]	• Osteophytes • Synovial profile • Effusion • Global synovitis	• Ordinal categorical (4 point) • Ordinal categorical (3 point) • Ordinal categorical (3 point) • Ordinal categorical (3 point)
Reardon[42]	• Quadriceps muscle thickness	• NS
Rennesson-Rey[43]	• Effusion	• dichotomous
Robinson[57]	• Osteophytes • Effusion • Capsular thickness • Vascularity	• Ordinal categorical (4 point) • dichotomous • Continuous (mm) • dichotomous
Schmidt [45]	• Synovial thickness	• Ordinal categorical (4 point)
Song[46]	• Effusion • Synovitis • Vascularity	• Ordinal categorical (4 point) • Ordinal categorical (4 point) • Ordinal categorical (4 point)
Song[58]	• Effusion • Synovial hypertrophy • Vascularity	• Ordinal categorical (4 points • Ordinal categorical (4 points) • Ordinal categorical (4 points)
Su [47]	• Posterior structures tears	• Ordinal categorical (3 point)
Tarasevicius [49]	• Capsular distention	• NS

Tarasevicius[48]	• Capsular distension	• Continuous (mm)
Tarhan [50]	• Cartilage sharpness • Cartilage clarity • Synovial hypertrophy • Effusion	• Nominal categorical (7 point) • Nominal categorical (7 point) • Ordinal categorical (4 points) • Ordinal categorical (4 points)
Walther [52]	• Synovial thickness and effusion • Vascularity	• Ordinal categorical (5 points) • Ordinal categorical (5 points)
Walther[51]	• Synovial thickness • Effusion thickness • Vascularity	• Ordinal categorical (5 points) • Ordinal categorical (5 points) • (0-4 and software)
Yoon[53]	• Anserine Tendobursitis	• Continuous (mm) • dichotomous • Continuous (mm) • dichotomous
Yoon[54]	• Cartilage thickness	• Continuous (mm)

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APPENDIX 8

REFERENCES FOR RECOMMENDATIONS OF THE ASC WORKING GROUP AND FOR APPENDICES 4–7

(For tables representing x-ray, MRI, and ultrasonography systematic reviews, individual reference lists are given within the respective appendices.)

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APPENDIX 9

(Click on the hyperlink above to return to your place in the document, p 22.)

EFFECT SIZES FOR KEY OUTCOME MEASURES IN PLACEBO-CONTROLLED CLINICAL TRIALS OF OA

1. Methods

A total of 171 placebo-controlled, blinded and randomized clinical trials of oral and topical agents for treatment of OA of the knee, hip, and/or hand were identified through searches of MEDLINE, the Cochrane collaboration, and clinicaltrialsresults.gov through August 5, 2009. All primary and secondary endpoints for each study were coded and entered into a database. The studies were grouped into four categories according to the statistical significance ($P \leq .05$ or $P > .05$) of the primary endpoint and the joint studied:

- Group I: all studies, regardless of *P*-value for primary endpoint
- Group II: all positive ($P \leq .05$) studies for primary endpoint
- Group III: same as group I, but studies of knee OA only
- Group IV: same as group II, but studies of knee OA only

All values were converted to a 0-100 scale and the placebo, treatment, and standardized effect sizes were computed as follows:

- Placebo effect, change from baseline = $\text{Placebo}_{\text{baseline}} - \text{Placebo}_{\text{final}}$
- Treatment effect, change from baseline = $\text{Treatment}_{\text{baseline}} - \text{Treatment}_{\text{final}}$
- Standardized effect size = (Treatment-Placebo)/Pooled standard deviation

The placebo and treatment effects were determined only for studies that provided either (1) a baseline and final value for the placebo arm or (2) expressed the placebo effect as the change from baseline. The difference between treatment effect and placebo effect was computed by subtracting the placebo effect from the treatment effect; when no baseline values were present (for treatment or placebo), the difference was calculated by subtracting the final values for placebo and treatment.

For studies that had more than one treatment arm of the same therapy (eg, dose titration), the treatment and standardized effect size was averaged across all arms of the same therapy for Groups I and II. In order to show the range of possible responses for a given treatment, the highest treatment and standardized effect size occurring for arms of the same therapy are presented for Groups III and IV. The percentage of positive arms for each outcome measure was determined by identifying the arm within the same therapy that had the lowest *P*-value and assigning the value positive ($P \leq .05$) or negative ($P > .05$) to that therapy arm for each outcome measure.

Pain, function, global, and composite outcome measures were included in the summary if there were at least 10 values for computing placebo or treatment effect. All related responder results (pain: 30% and 50%; patient and clinician global assessment/improvement; OMERACT-OARSI) were included regardless of sample size. Pain-related response variables that were not measured on a subscale of the WOMAC or Lequesne were divided into two categories: if pain were described as "at rest," "spontaneous," or no description was provided, the label ""Pain" (1st column, Table 1) was assigned. Pain described as occurring during any weight-bearing activity (eg, walking, standing, getting out of bed, etc) was assigned the label "Pain-activity" (2nd column, Table 1).

2. Results

Table 1. Numerically larger placebo, treatment, and standardized effect sizes occurred for Pain and Pain-activity compared to pain measured on the WOMAC pain subscale, regardless of trial outcome or joint assessed. The highest placebo group response, one of the lowest treatment effects, and the lowest standardized effect were found for question 1 of the WOMAC pain subscale (pain walking), although it is important to note that this category had a relatively small sample size compared to others. As expected, higher treatment and standardized effect sizes were present in the analysis of trials that were positive for the primary endpoint analysis compared to all trials. For Pain and Pain-activity, placebo, treatment, and standardized effect sizes were generally higher in knee trials compared to all trials, whereas the reverse occurred for the WOMAC pain measures.

The percentage of placebo group responders was higher for the ≥30% responder outcome compared to the ≥50% responder outcome, whereas the difference between placebo and treatment response rates was higher for the ≥50% outcome than for the ≥30% outcome.

Table 2. For the clinician and patient global assessments, both the treatment effect and standardized effect were generally smaller in studies restricted to the knee joint. There were inadequate numbers of studies with relevant data for patient- or clinician-rated response to therapy to make any observations. A larger placebo response and a smaller difference between

placebo and treatment response rates were observed in patient-rated responders compared to clinician-rated responders.

Table 3. Lower placebo group responses occurred with the Lequesne composite outcome compared with the WOMAC total score across all four groups of trials. Treatment effect was also slightly lower as well but the standardized effect was higher for the Lequesne composite, due in part to its smaller pooled standard deviation. The placebo, treatment, and standardized effect sizes of the WOMAC function subscale were generally comparable to the WOMAC total. The lowest standardized effect sizes were most often observed on the WOMAC stiffness scale, and this was due in part to a somewhat higher pooled standard deviation.

There were few trials with OARSI-A, OARSI-B, or OMERACT-OARSI responder outcomes. There was a relatively small difference between placebo and treatment response rates compared to other responder criteria. The percentage of positive arms was higher than for pain-related responder outcomes but lower than for patient or clinician global responder outcomes.

3. Limitations

This summary does not address the influence of variables such as the scale of measurement, the use of flare vs nonflare and other research designs, the role of inclusion and exclusion criteria, and the methods used handling missing data.

Table 1. Placebo, treatment, and standardized effect sizes for pain-related outcome measures

[Click on hyperlink, above, (Table 1.) to return to text.]

EFFECT	Pain			Pain-activity			WOMAC-Pain subscale			WOMAC-Pain walking on flat surface			Responder-30% reduction			Responder-50% reduction		
I. *All trials*[a]	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD
Change, baseline																		
Placebo	62	13.6	7.4	22	13.3	6.9	61	10.9	6.0	12	20.2	5.1	10	44.8	10.3	6	31.4	8.3
Treatment – placebo difference	84	10.6	6.8	32	9.6	7.8	95	8.3	6.9	20	8.8	4.8	14	14.8	11.6	8	19.5	18.7
Std effect[d]	48	0.49	0.40	12	0.38	0.50	56	0.39	0.37	5	0.18	0.21						
Pooled SD	48	22.26	6.34	12	23.68	5.87	56	20.99	3.09	5	26.71	1.39						
% positive	83	79.5		29	72.4		91	74.7		20	85.0		14	50.0		8	50.0	
II. *All trials-knee*																		
Change, baseline																		
Placebo	39	14.8	7.2	14	14.9	6.1	40	10.9	5.7	7	21.0	6.0	7	46.2	9.5	5	30.0	8.4
Treatment – placebo difference	52	11.4	6.7	19	10.5	7.3	61	7.4	7.9	11	6.4	4.7	9	15.9	14.1	7	19.0	20.1
Std effect	32	0.54	0.42	8	0.44	0.58	37	0.35	0.43	4	0.16	0.24						
Pooled SD	32	22.65	5.43	8	22.75	6.92	37	20.45	3.24	4	26.80	1.58						
% positive	51	80.4		16	81.3		57	64.9		11	72.7		9	55.6		7	57.1	
III. *Positive trials*[e]																		

EFFECT	Pain			Pain-activity			WOMAC-Pain subscale			WOMAC-Pain walking on flat surface			Responder-30% reduction			Responder-50% reduction		
Change, baseline																		
Placebo	50	14.4	7.3	17	12.6	7.0	51	11.6	5.7	12	20.2	5.1	9	44.0	10.6	6	31.4	8.3
Treatment – placebo difference	70	12.5	6.6	25	12.1	6.7	83	9.4	6.8	20	9.2	5.0	13	17.1	11.0	8	19.5	18.7
Std effect	38	0.62	0.42	8	0.54	0.54	49	0.44	0.37	5	0.18	0.21						
Pooled SD	38	22.62	6.10	8	22.67	7.00	49	21.64	2.16	5	26.71	1.39						
% positive	69	95.7		22	86.4		79	84.8		20	85.0		13	53.8		8	50.0	
IV. *Positive trials*[e]*-knee*																		
Change, baseline																		
Placebo	32	15.7	7.0	11	13.7	6.1	31	11.7	5.4	7	21.0	6.0	6	45.3	10.1	5	30.0	8.4
Treatment – placebo difference	43	13.2	6.6	16	12.2	6.6	50	8.7	8.1	11	6.7	4.9	8	17.5	13.9	7	19.0	20.1
Std effect	26	0.65	0.47	5	0.66	0.64	31	0.40	0.43	4	0.16	0.24						
Pooled SD	26	23.26	4.13	5	20.97	8.39	31	21.25	2.03	4	26.80	1.58						
% positive	42	97.6		13	100.0		46	78.3		11	72.7		8	62.5		7	57.1	

[a] All trials with a positive ($P \leq .05$) or negative ($P > .05$) outcome indicated for primary endpoint.

[b] Number of active treatment arms (1 value per therapy) except for "% positive" where value represents number of treatment arms (1 value per therapy) with a positive outcome for the response measure indicated.

[c] For analysis of all trials or all knee trials (Groups I and III) , value represents mean response per same therapy treatment arm. For analysis of all positive trials or all positive knee trials (Groups II and IV), value represents the highest response observed within arms of the same therapy. For the variable "% positive,", the value represents the percentage of treatment arms (1 value per therapy) that had a positive ($P \leq .05$) outcome, irrespective of the primary endpoint outcome.

[d] Standardized effect size.

[e] All trials with a positive ($P \leq .05$) outcome for primary endpoint.

Table 2. **Placebo, treatment, and standardized effect sizes for patient and clinician global outcome measures**

[Click on hyperlink, above, (Table 2.) to return to text.]

EFFECT	Patient-global			Patient-response to therapy			Patient Responder			Clinician- global			Clinician- response to therapy			Clinician Responder		
I. *All trials*[a]	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD
Change, baseline																		
Placebo	38	14.7	4.5	4	33.7	12.5	47	34.4	12.4	26	17.4	5.9	3	33.0	13.5	34	29.5	13.7
Treatment – placebo difference	66	11.2	5.7	21	15.0	7.4	62	23.8	12.9	49	10.5	5.5	10	18.3	5.6	41	27.3	18.1
Std effect[d]	37	0.41	0.27	2	0.39	0.06				20	0.33	0.25	0					
Pooled SD	37	26.31	3.97	2	28.61	0.23				20	24.42	4.36	0					
% positive	66	81.8		21	85.7		57	89.5		49	87.8		10	80.0		36	88.9	
II. All trials-knee																		
Change, baseline																		
Placebo	19	14.8	4.7	2	30.7	20.6	33	33.3	12.2	12	16.7	6.6	1	17.6		25	27.9	14.3
Treatment – placebo difference	31	8.7	6.2	11	12.8	9.6	42	25.1	13.7	22	8.9	7.0	2	21.7	14.4	31	28.1	19.9
Std effect	20	0.23	0.13	2	0.39	0.06				14	0.24	0.17	0					
Pooled SD	20	27.72	3.09	2	28.61	0.23				14	25.16	3.91	0					
% positive	31	71.0		11	72.7		37	91.9		22	81.8		2	100.0		26	88.5	
III. Positive trials[e]																		
Change,																		

EFFECT	Patient-global			Patient-response to therapy			Patient Responder			Clinician- global			Clinician- response to therapy			Clinician Responder		
Placebo	35	14.6	4.5	4	33.7	12.5	41	34.5	12.7	26	17.4	5.9	3	33.0	13.5	28	29.9	13.9
Treatment – placebo difference	63	11.9	5.5	21	15.3	7.9	56	24.8	11.6	49	10.8	5.6	10	18.7	5.9	34	29.2	15.5
Std effect	36	0.42	0.27	2	0.39	0.06				20	0.34	0.25	0					
Pooled SD	36	26.30	4.03	2	28.61	0.23				20	24.42	4.36	0					
% positive	63	85.7		21	85.7		51	96.1		49	87.8		10	80.0		29	100.0	
IV. Positive trials-knee																		
Change, baseline																		
Placebo	16	14.8	4.7	2	30.7	20.6	29	33.5	12.2	12	16.7	6.6	1	17.6		21	28.4	14.2
Treatment – placebo difference	28	9.5	6.0	11	13.0	10.1	38	25.4	13.0	22	9.0	7.0	2	22.0	14.8	26	29.6	17.2
Std effect	19	0.25	0.14	2	0.39	0.06				14	0.25	0.18	0					
Pooled SD	19	27.78	3.17	2	28.61	0.23				14	25.16	3.91	0					
% positive	28	78.6		11	72.7		33	97.0		22	81.8		2	100.0		21	80.8	

[a] All trials with a positive ($P \leq .05$) or negative ($P > .05$) outcome indicated for primary endpoint.

[b] Number of active treatment arms (1 value per therapy) except for "% positive" where value represents number of treatment arms (1 value per therapy) with a positive outcome for the response measure indicated.

[c] For analysis of all trials or all knee trials (Groups I and III) , value represents mean response per same therapy treatment arm. For analysis of all positive trials or all positive knee trials (Groups II and IV), value represents the highest response observed within arms of the same therapy. For

the variable "% positive," the value represents the percentage of treatment arms (1 value per therapy) that had a positive ($P \leq .05$) outcome, irrespective of the primary endpoint outcome.

[d] Standardized effect size.

[e] All trials with a positive ($P \leq .05$) outcome indicated for primary endpoint.

Table 3. Placebo, treatment, and standardized effect sizes for physical functioning, composite, and other outcome measures

[Click on hyperlink, above (Table 3), to return to text.]

MEASURE	WOMAC-FUNCTION subscale			LEQUESNE			OMERACT-OARSI Responder			WOMAC TOTAL			WOMAC-STIFFNESS subscale		
I. *All trials*[a]	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD	n[b]	mean[c]	SD
Change, baseline															
Placebo	58	10.0	4.5	26	8.4	5.1	9	46.8	12.2	41	10.1	4.5	52	10.3	5.4
Treatment-placebo difference	91	7.4	5.3	33	6.5	5.3	14	10.7	6.1	61	7.5	7.4	80	7.6	6.9
Std effect[d]	56	0.32	0.21	25	0.38	0.26				34	0.30	0.19	49	0.28	0.25
Pooled SD	56	20.65	3.24	25	18.04	12.90				34	21.07	9.45	49	23.06	3.57
% positive	90	72.2		33	63.6		14	71.4		61	66.7		79	64.6	
II. *All trials-knee only*															
Change, baseline															
Placebo	36	10.4	4.0	19	8.8	5.0	9	46.8	12.2	30	9.6	4.0	31	9.9	5.4
Treatment – placebo difference	55	6.5	6.0	22	7.0	5.7	14	10.7	6.1	44	7.4	8.3	46	6.3	7.6
Std effect	35	0.26	0.17	15	0.43	0.26				27	0.30	0.17	32	0.21	0.20
Pooled SD	35	20.19	3.52	15	19.10	16.75				27	20.92	10.55	32	22.82	4.03
% positive	54	63.0		22	68.2		14	71.4		44	65.9		45	57.8	

MEASURE	WOMAC-FUNCTION subscale			LEQUESNE			OMERACT-OARSI Responder			WOMAC TOTAL			WOMAC-STIFFNESS subscale		
III. *Positive trials*[e]															
Change, baseline															
Placebo	50	10.3	4.4	22	8.5	5.5	7	48.1	12.8	34	10.5	4.3	44	10.9	4.7
Treatment-placebo difference	82	8.0	5.4	28	7.5	6.0	12	12.7	3.6	53	8.2	7.6	71	8.6	6.8
Std effect	49	0.34	0.21	20	0.45	0.30				28	0.31	0.19	43	0.32	0.24
Pooled SD	49	20.71	2.35	20	18.96	14.31				28	21.61	10.29	43	23.78	2.26
% positive	81	79.0		28	71.4		12	83.3		53	81.1		70	71.4	
IV. *Positive trials*[e]*-knee*															
Change, baseline															
Placebo	29	10.6	4.2	17	8.9	5.2	7	48.1	12.8	23	10.1	3.6	24	10.6	4.3
Treatment-placebo difference	47	6.8	6.1	19	8.2	6.5	12	12.7	3.6	36	8.2	8.9	38	7.4	7.8
Std effect	29	0.27	0.18	12	0.53	0.29				21	0.31	0.17	27	0.25	0.18
Pooled SD	29	19.97	2.32	12	20.43	18.63				21	21.61	11.85	27	23.73	2.38
% positive	46	71.7		19	78.9		12	83.3		36	77.7		38	65.8	

[a] All trials with a positive ($P \leq .05$) or negative ($P > .05$) outcome indicated for primary endpoint.

[b] Number of active treatment arms (1 value per therapy) except for "% positive" where value represents number of treatment arms (1 value per therapy) with a positive outcome for the response measure indicated.

[c] For analysis of all trials or all knee trials (Groups I and III) , value represents mean response per same therapy treatment arm. For analysis of all positive trials or all positive knee trials (Groups II and IV), value represents the highest response observed within arms of the same therapy. For the variable "% positive," the value represents the percentage of treatment arms (1 value per therapy) that had a positive (($P \leq .05$) outcome, irrespective of the primary endpoint outcome.

[d] Standardized effect size.

[e] All trials with a positive ($P \leq .05$) outcome indicated for primary endpoint.

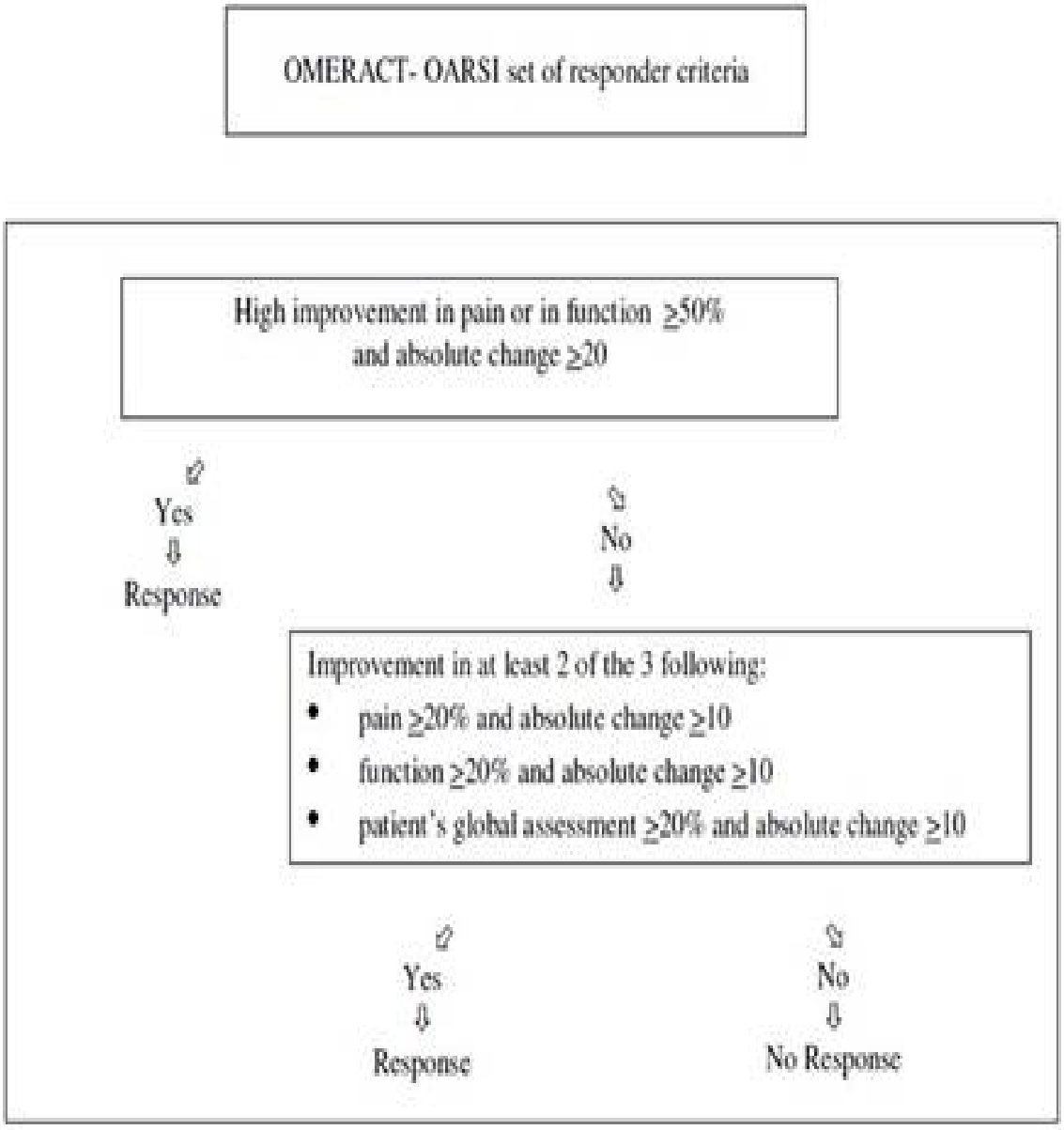

Fig. 4. OMERACT–OARSI Set of responder criteria.

Table 4. Measurement of pain in patients with OA

Measure	Key Points	References
Arthritis Impact Measurement Scales (AIMS/AIMS2)	These are multidimensional patient-completed questionnaires on health status, useful for evaluating the outcome of arthritis treatments and programs. There are nine component scales (mobility, physical activity, dexterity, household activities, activities of daily living, anxiety, depression, social activity, pain) that include 45 questions with a choice of 2–6 possible responses.	Meenan RF, Gertman PM, Mason JH. Measuring Health Status in Arthritis. The Arthritis Impact Measurement Scales. *Arthritis Rheum*. 1980;23:146-152. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2: The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. *Arthritis Rheum.* 1992; 35:1-10. Lorish CD, Abraham N, Austin JS, Bradley LA, Alarcon GS. A comparison of the full and short versions of the Arthritis Impact Measurement Scales. *Arthritis Care Res.* 1991;4:168-173.
Arthritis-Specific Health Index (ASHI) for the SF-36	The ASHI for the SF-36 includes the eight-scale SF-36 and five arthritis-specific measures of knee pain on weight bearing, time to walk 50 feet, physician global evaluation of symptom severity and impact, patient global evaluation of symptom severity and impact, and pain intensity VAS.	Ware JE Jr, Keller SD, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. *Med Care*. 1999;37(5 Suppl):MS40-MS50.

Measure	Key Points	References
Australian/Canadian Hand Osteoarthritis Index (AUSCAN)	The AUSCAN Index is a disease-specific, tri-dimensional, self-administered questionnaire, for assessing health status and health outcomes in OA of the hand. The questionnaire contains 15 questions, targeting areas of pain, stiffness, and physical function, and can be completed in less than 5 minutes. Usually patient self-administered, the Index is amenable to interview administration by telephone. The AUSCAN is available in 5-point Likert, 100-mm VAS or 11-point numerical rating scale format.	Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthritis Cartilage*. 2002;10:855-862. Bellamy N, Campbell J, Haraoui B, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthritis Cartilage.* 2002;10:863-869.

Measure	Key Points	References
Brief Pain Inventory (BPI)	The BPI was developed from the Wisconsin Brief Pain Questionnaire. The BPI assesses pain severity and the degree of interference with function, using a 0–10 numeric rating scale. It can be self-administered, given in a clinical interview, or administered over the telephone. The BPI asks the patient to rate their present pain intensity, "pain now," and pain "at its worst," "least," and "average" over the last 24 hours. Location of pain on a body chart and characteristics of the pain are documented. The BPI also asks the patient to rate how much pain interferes with seven aspects of life: (1) general activity, (2) walking, (3) normal work, (4) relations with other people, (5) mood, (6) sleep, and (7) enjoyment of life.	Williams VS, Smith MY, Fehnel SE. The validity and utility of the BPI interference measures for evaluating the impact of osteoarthritic pain. *J Pain Symptom Manage*. 2006;31:48-57. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 1983;17:197-210. Wang XS, Cleeland Cs. Outcomes measurement in cancer pain. In: Wittink Hm, Carr DB, eds. *Pain Management: Evidence, Outcomes, and Quality of Life. A Sourcebook.* London: Elsevier, 2008; 377-405.
Cochin Hand Functional Disability Scale	The Cochin hand functional disability scale, which was first developed to assess the rheumatoid hand, can be used to evaluate functional disability in hand OA.	Poiraudeau S, Chevalier X, Conrozier T, et al. Reliability, validity, and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. *Osteoarthritis Cartilage*. 2001;9:570-577.
Daily Pain Diaries	Many different types of daily diaries have been employed for assessment of pain in patients with OA, and they often include a scale (eg, VAS) for recording pain severity.	Allen KD, Golightly YM, Olsen MK. Pilot study of pain and coping among patients with osteoarthritis: a daily diary analysis. *J Clin Rheumatol.* 2006;12:118-123.

Measure	Key Points	References
Dallas Pain Questionnaire (DPQ)	The DPQ is a 16-item visual analog tool developed to evaluate how chronic pain affects four aspects of patients' lives: 1) daily activities including pain and intensity, personal care, lifting, walking, sitting, standing, and sleeping; 2) work and leisure activities; 3) anxiety-depression; and 4)	Lawlis GF, Cuencas R, Selby D, McCoy CE. The development of Dallas pain questionnaire. *Spine.* 1989;14:515-516.

	social interest that includes interpersonal relationship, social support, and punishing responses.	
Foot Function Index (FFI)	This questionnaire has been designed to provide information about how foot pain affects patients' ability to manage in everyday life. It includes four questions about pain and interference that are measured on a 10-point scale.	Budiman-Mak E, Conrad KJ, Roach KE. The Foot Function Index: a measure of foot pain and disability. *J Clin Epidemiol.* 1991;44:561-570.
Functional Index for Hand Osteoarthritis (FIHOA)	The FIHOA, a 10-item investigator-administered questionnaire, was validated in 1995. It is relevant, reliable, and has good external and internal validities.	Dreiser RL, Maheu E, Guillou GB, Caspard H, Grouin JM. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed*. 1995;62 (Suppl 1):43S-53S. Dreiser RL, Maheu E, Guillou GB. Sensitivity to change of the functional index for hand osteoarthritis. *Osteoarthritis Cartilage*. 2000;8 (Suppl A):S25-S28.

Measure	Key Points	References
Harris Hip Score	The Harris Hip Score is a multidimensional, observational assessment that contains eight items representing pain, walking function, activities of daily living, and range of motion of the hip joint. Final score ranges from 100 (no disability) to 0 (maximum disability). The index consists of questions about pain and activities of daily living, referring to the previous week, and assessments of hip function (limping) and range of motion.	Harris H. Traumatic arthritis of the hip after dislocation and acetabular fracture. Treatment by mold arthroplasty. *J Bone Joint Surg Am.*1969;4:737-755.
Health Assessment Questionnaire (HAQ)	The full HAQ measures five dimensions, including diasbility, pain, medication effects, costs of care, and mortality. Pain is measured using a VAS	Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol*. 2005;23 (5 Suppl):S14-S18. Yazici Y. Monitoring outcomes of arthritis and longitudinal data collection using patient questionnaires in routine care. *Bull NYU Hosp Jt Dis*. 2006;64:40-44.
Hip disability and Osteoarthritis Outcome Score (HOOS)	The HOOS is organized in the same manner as the KOOS (see below) and has been shown to be valid for hip disability with or without hip OA and with high demands of physical function.	de Groot IB, Reijman M, Terwee CB, et al. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage*. 2007;15:104-109.

Measure	Key Points	References
Joint-Specific Multidimensional Assessment of Pain (J-MAP)	The J-MAP includes the 6-item Pain Sensory and the 4-item Pain Affect subscales. Scores on the J-MAP Pain Sensory and Affect subscales range from 0 to 100, with higher scores indicating more pain intensity and worse pain distastefulness, respectively.	O'Malley KJ, Suarez-Almazor M, Aniol J, et al. Joint-specific multidimensional assessment of pain (J-MAP): factor structure, reliability, validity, and responsiveness in patients with knee osteoarthritis. *J Rheumatol.* 2003;30:534-543.
Knee injury and Osteoarthritis Outcome Score (KOOS)	The KOOS was developed as an extension of the WOMAC Osteoarthritis Index with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and OA. The KOOS has five separately scored subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related QOL.	Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
Knee Pain Scale (KPS)	The KPS was specifically developed for patients with OA and is comprised of a test battery that includes measures of physical functioning, physical performance, and depression.	Rejeski WJ, Ettinger WH Jr, Shumaker S, et al. The evaluation of pain in patients with knee osteoarthritis: the knee pain scale. *J Rheumatol.* 1995;22:1124-1129.
Lequesne Index	This measure has five questions about pain with categorical responses that are scored from 0–2.	Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation--value in comparison with other assessment tests. *Scand J Rheumatol Suppl.* 1987;65:85-89.

Measure	Key Points	References
McGill Pain Questionnaire (MPQ) and Short-form MPQ (SF-MPQ)	The MPQ and SF-MPQ evaluate sensory, affective–emotional, evaluative, and temporal aspects of the patient's pain condition. The SF-MPQ consists of 11 sensory (sharp, shooting, etc) and four affective (sickening, fearful, etc) verbal descriptors. The patient is asked to rate the intensity of each descriptor on a scale from 0 to 3 (severe). Three pain scores are calculated: sensory, affective, and total pain indices. Patients also rate their present pain intensity on a 0–5 scale and a VAS.	Melzack R, Katz J. Pain assessment in adult patients. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*, 5th Edn. London: Elsevier, 2006; 291-304.

Measure of Intermittent and Constant OA Pain, ICOAP: HIP Version	This measure consists of 11 questions about intermittent and constant hip pain with responses measured on 5-point categorical scales.	Maillefert JF, Kloppenburg M, Fernandes L, et al. Multi-language translation and cross-cultural adaptation of the OARSI/OMERACT measure of intermittent and constant osteoarthritis pain (ICOAP). *Osteoarthritis Cartilage.* 2009;17:1293-1296.
Measure of Intermittent and Constant OA Pain, ICOAP: KNEE Version	This measure consists of 11 questions about intermittent and constant knee pain with responses measured on 5-point categorical scales	Maillefert JF, Kloppenburg M, Fernandes L, et al. Multi-language translation and cross-cultural adaptation of the OARSI/OMERACT measure of intermittent and constant osteoarthritis pain (ICOAP). *Osteoarthritis Cartilage.* 2009;17:1293-1296.

Measure	Key Points	References
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)	The SF-36 is a generic, non-disease-specific questionnaire, which includes eight scales that assess limitations in physical activities, limitations in social activities, limitations in usual role activities because of physical problems, pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions.	Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.
Neuropathic Pain Scale (NPS)	The NPS is a 12-item questionnaire aimed primarily at distinguishing nociceptive from neuropathic pain. It has been used to identify a neuropathic component in OA pain.	Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. Clin J Pain. 200319:306-314. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS. Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. *J Pain*. 2005;6:98-106. Gammaitoni AR, Galer BS, Onawola R, Jensen MP, Argoff CE. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the Neuropathic Pain Scale. *Curr Med Res Opin.* 2004;20 (Suppl 2):S13-9.

Measure	Key Points	References
Norwegian Pain Society Questionniare	This 31-item questionnaire covers the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)-recommended outcome domains, and in addition includes questions on coping and catastrophizing, health-related quality of life, economic impact of the pain condition, social security status, and any ongoing litigation or compensation process.	Fredheim OM, Borchgrevink PC, Landmark T, Schjodt B, Breivik H. Norwegian pain society minimum questionnaire for pain patients (NOSF-MISS). *Tids Nor Legeforen*. 2008;128: in press. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9-19.

Measure	Key Points	References
OARSI/OMERACT Pain Measure	This 12-item measure, developed based on focus group results, is comprised of two sections, one for "constant pain" and one for "pain that comes and goes." For each of these pain types, single items assessed pain intensity, effect on sleep, impact on quality of life, extent to which the pain "frustrates or annoys," and the extent to which it "worries or upsets." For pain that comes and goes, two additional items asked respondents to report the frequency of pain and the degree to which the pain could be predicted. The time frame used is 1 week, in keeping with other widely used OA pain measures. All items are constructed as rating scales, with five levels of response (0–4) for questions asking about intensity, response options were "not at all" (0), "mildly," "moderately," "severely," and "extremely" (4), while those that asked about frequency had the following response options: "never" (0), "rarely," "sometimes," "often," and "very often" (4).	Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage*. 2008;16:409-414.
OsteoArthritis Knee and Hip Quality Of Life (OAKHQOL)	The OAKHQOL is the first specific HRQOL questionnaire developed for knee and hip OA. The OAKHQOL is a self-administered questionnaire comprising 40 items divided into five dimensions—physical activity, mental health, pain, social support, and social activities—and three additional independent items.	Rat AC, Coste J, Pouchot J, et al. OAKHQOL: a new instrument to measure quality of life in knee and hip osteoarthritis. *J Clin Epidemiol*. 2005;58:47-55.

Measure	Key Points	References
Oxford Knee Score	The Oxford Knee Score is a 12-item questionnaire with five possible responses to each question. Each item is scored from 0 to 4, and the items are summed, thus giving 0 for the worst possible status and 48 for a normal knee. It is designed to be used as a short and simple postal questionnaire.	Harcourt WG, White SH, Jones P. Specificity of the Oxford knee status questionnaire. The effect of disease of the hip or lumbar spine on patients' perception of knee disability. *J Bone Joint Surg Br*. 2001;83:345-347.
Present Pain Intensity (PPI)	The PPI is a variable on the MPQ that is the number-word combination chosen as the indicator of overall pain intensity. The levels of the PPI scale include none, mild, discomforting, distressing, horrible, and excruciating (range 0-5). Present Pain Intensity is a measure of how much a person hurts and is an estimation of the magnitude of the pain.	Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277-299. Escalante A, Lichtenstein MJ, White K, Rios N, Hazuda HP. A method for scoring the pain map of the McGill Pain Questionnaire for use in epidemiologic studies. *Aging* (Milano). 1995;7:358-366.
Score for Assessment and Quantification of Chronic Rheumatic Affections of the Hands (SACRAH)	The SACRAH is comprised of 23 VAS's (100 mm) covering the three categories of symptoms that primarily determine the situation of patients with rheumatic diseases of the hand: function, joint stiffness, and pain.	Leeb BF, Sautner J, Andel I, Rintelen B. SACRAH: a score for assessment and quantification of chronic rheumatic affections of the hands. *Rheumatology* (Oxford). 2003;42:1173-1178.

Measure	Key Points	References
SF-MPQ-2	The SF-MPQ-2 is a single measure of the major symptoms of both neuropathic and nonneuropathic pain that can be used in studies of epidemiology, natural history, pathophysiologic mechanisms, and treatment response. It expands the revised the SF-MPQ pain descriptors by adding symptoms relevant to neuropathic pain and by modifying the response format to a 0–10 numerical rating scale to provide increased responsiveness in longitudinal studies and clinical trials.	Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain*. 2009;144:35-42.
Short Arthritis Assessment Scale (SAS)	The SAS is a 4-item arthritis severity questionnaire that is simple to score, clinically useful and meaningful, and suitable for use in primary care, where OA is the primary prevalent arthritis illness. The SAS was developed by performing multivariable analyses that involved individually adding/subtracting items in differing regression models.	Wolfe F, Michaud K, Kahler K, Omar M. The Short Arthritis Assessment Scale: a brief assessment questionnaire for rapid evaluation of arthritis severity in research and clinical practice. *J Rheumatol*. 2004;31:2472-2479.
Short-form BPI	A modified BPI short form assesses three pain	Mendoza T, Mayne T, Rublee D,

	severity items (worst pain, pain on the average, and pain right now) and five interference items (walking ability, mood, sleep, relations with others, and ability to concentrate).	Cleeland C. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. *Eur J Pain*. 2006;10:353-361.

Measure	Key Points	References
Short HAQ	This measure contains the HAQ Disability Index and patient global and pain VAS	Pincus T, Sokka T. Quantitative measures and indices to assess rheumatoid arthritis in clinical trials and clinical care. *Rheum Dis Clin North Am*. 2004;30:725-751.
Visual Analog Scale (VAS) and Categorical Scales	Visual analog scales of many different types are used to measure pain severity in patients with OA. Most often, these scales are 100 mm in length, and patients point or move a cursor to a distance along the scale reflecting their pain. Categorical scales divide pain severity into distinct categories and are not continuous as is the case for VAS.	Hendiani JA, Westlund KN, Lawand N, Goel N, Lisse J, McNearney T. Mechanical sensation and pain thresholds in patients with chronic arthropathies. *J Pain*. 2003;4:203-211. Huskisson EC. Measurement of pain. *Lancet*. 1974;2:1127-1131. Averbuch M, Katzper M. Assessment of visual analog versus categorical scale for measurement of osteoarthritis pain. *J Clin Pharmacol*. 2004;44:368-372.

Measure	Key Points	References
WOMAC Index	The questionnaire contains 24 questions targeting areas of pain, stiffness, and physical function and can be completed in less than 5 minutes. Usually patient self-administered, the Index is amenable to electronic data capture formats using mouse-driven curser, touch screen, and to interview administration by telephone. Available in over 60 alternative language forms, there are several different forms of the WOMAC Index suitable for different clinical practical and clinical research applications. Ratings can be made on a 5-point adjectival, 100-mm VAS, and 11-point numerical rating scale format.	McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum*. 2001;45:453-461. Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. *J Rheumatol*. 2002;29:2473-2476.