# Biomarkers in osteoarthritis: a clinical trials perspective

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Osteoarthritis (OA), the most common type of arthritis, causes considerable disability and a significant public health impact. The burden of OA will increase with aging of the population and the present obesity epidemic. Currently, potential structure-modifying drugs for OA must demonstrate slowing of the rate of joint space narrowing in serial radiographs. This usually requires clinical trials of 2–3 years duration. More sensitive and precise biomarkers can potentially aid selection of participants into trials, identify those at highest risk of rapid disease progression and provide new surrogate markers for radiographic OA. These biomarkers will decrease the cost and duration of trials, and hasten the development and approval of new disease-modifying pharmaceuticals. Standardization of assays, methods of specimen collection and assessment of marker variation by age, race/ethnicity, sex, body mass index, total body OA load, comorbid conditions and medications will continue to be evaluated to hasten the incorporation of biomarkers into clinical trial design.

In the USA, arthritis is the leading cause of disability, and osteoarthritis (OA) is the most common cause of arthritis [1]. OA of the knee and hip is perhaps the most disabling, resulting in the majority of the 256,000 total knee replacements (TKR) and 117,000 total hip replacements (THR) for arthritis in 1997 [2]. Since OA is strongly linked to aging and to obesity, each of which is increasing in prevalence, it is expected that the numbers of individuals with arthritis in general, and OA in particular, will rise significantly in the next 20–30 years [3,4].

## Challenges in the development of OA disease-modifying interventions & definitions of biomarkers

Currently, there is a strong impetus in both the public and private sectors to develop pharmaceuticals and other interventions to delay or prevent structural development and progression of OA; that is, to develop interventions that are disease or structure modifying, as opposed to merely symptom modifying. Although radiographs are currently the gold standard in this regard, they are not sensitive to change and can be fraught with measurement error. As a result, clinical trials of potentially structure-modifying interventions utilizing radiographic outcomes require large numbers of participants followed over 2–3 years [5]. Clearly, more sensitive and precise measures are required to speed development and testing of interventions and decrease their duration and costs.

Biomarkers are one such potential modality to expedite this process. They are defined as 'objective indicators of normal biologic processes, pathogenic processes or pharmacologic responses to therapeutic interventions' [6]. Biomarkers can include more sensitive imaging modalities, such as magnetic resonance imaging (MRI), now under intense evaluation for its potential to identify individuals with OA before permanent structural damage has occurred, to identify individuals at high risk of progression, and to provide alternate or surrogate outcomes to radiographic definitions of OA. Other variant and invariant molecules in body fluids are also under investigation for these purposes, including nucleic acid profiles and proteins associated with bone or cartilage turnover, matrix synthesis and degradation, or synovial inflammation. Table 1 lists putative OA biomarkers included in this review. Whether they, alone or in conjunction with other clinical data, can potentially provide quicker assessments of effect than radiographic outcomes is a question of significant theoretical and practical importance.

This review will address methodological issues regarding potential uses of systemic biomarkers in clinical trials, highlight selected recent studies utilizing biomarkers in clinical trials and identify ongoing challenges and unmet needs in research before widespread adoption of biomarkers in clinical trials can occur.

## Use of biomarkers to aid selection of participants for OA clinical trials

Ideally, for inclusion in both symptom- and structure-modifying trials, potential participants should have a well-defined minimum severity of disease, either radiographic or symptomatic.

Keywords: biomarkers, cartilage, clinical trials, inflammation, osteoarthritis, structure modification, symptom modification, synovitis

future medicine

**Table 1. Selected osteoarthritis biomarkers according to presumed pathological process*.**

| | |
|---|---|
| Bone metabolism | uCTX-I and uNTX-I‡<br>Osteocalcin<br>Bone-specific alkaline phosphatase |
| Cartilage metabolism | COMP, HA, CSE 846, KS |
| Type II collagen | C2C, CP-II, Col 2–1, Helix II and uCTX-II |
| Matrix metalloproteinases | MMP-3 and MMP-13 |
| Synovial inflammation | HA, glucosyl-galactosyl pyridinoline |
| Systemic inflammation | hsCRP, IL-6,TNF-sR1 and TNF-sR2 |
| Pain | Serotonin, substance P and β-endorphin |

**Markers may derive from multiple tissue sources or reflect multiple pathologic processes, such as inflammation and cartilage degradation.*

*‡ u refers to marker measured in urine.*

*C2C: Type II collagen cleavage neoepitope; COMP: Cartilage oligomeric matrix protein; CP-II: Type II procollagen carboxy-propeptide; CSE 846: Chondroitin sulfate epitope 846; CTX-II: C-telopeptides of type II collagen; HA: Hyaluronan; hsCRP: High-sensitivity C-reactive protein; IL: Interleukin; KS: Keratan sulfate; MMP: Matrix metalloproteinase; NTX-I: N-telopeptides of type I collagen; TNF: Tumor necrosis factor; TNF-sR: Tumor necrosis factor soluble receptor.*

Typically, this may require participants to have a score of at least 40 on a 100-point scale for pain severity on most days, for example, or have a Kellgren–Lawrence radiographic grade of 2 or 3. Inclusion of individuals with rare or intermittent symptoms, or with symptoms that are not sufficiently severe, may result in null results if the disease is not severe enough to detect an effect of the intervention [7]. On the other hand, individuals whose disease is very severe, or endstage, may be unlikely to respond to any intervention short of joint replacement, and are frequently eliminated from most trials of symptom- or structure-modifying interventions [8].

For structure-modification trials, the goal is to evaluate whether an intervention can decrease the rate of progression of joint space narrowing (JSN) on an x-ray performed under a rigorously standardized protocol [5]. Here, enrollment of sufficient numbers of individuals with a high likelihood of radiographic progression is critical. Factors used to select such individuals have included older age, female sex and obesity [9]. These factors, despite evidence based from clinical or population studies, have not proved to be foolproof for this purpose. Trials can be inconclusive if they do not include sufficient numbers of individuals whose disease progresses within the timeframe of the study [10]. Other factors strongly associated with OA progression, such as joint malalignment and positive bone scintigraphy, have yet to be fully explored for their potential to aid in the selection of OA progressors for clinical trials. New imaging and biochemical markers are now currently available that might also assist in this process, as outlined in the following paragraphs.

To aid in participant selection in trials, biomarkers would likely be used in conjunction with relevant demographic and clinical selection criteria. The ideal biomarker(s) would identify individuals at high risk of rapid progression, identify early aspects of the disease process that are associated with later progression outcomes or are impacted by the intervention, differentiate between treated and untreated individuals, and monitor processes associated with adverse events.

Several candidate biomarkers come to mind as potentially useful in this regard, but not all have been fully validated. Bone-marrow edema on MRI has been shown to predict radiographic progression [11], can change within months, and was correlated with urinary CTX II, a Type II collagen-degradation marker [12]. Changes in serum cartilage oligomeric matrix protein (COMP) have been associated with OA progression [13], as has serum hyaluronan (HA), a measure of synovial inflammation [14], and high-sensitivity C-reactive protein (hsCRP) [15] Urinary CTX-II has also been associated with progressive knee OA [12], and may identify those likely to respond to structure-modification therapy [16].

## Important characteristics of OA biomarkers for clinical trials

Before incorporating a particular biomarker into clinical trial design, several issues should be considered (Box 1). First, it is helpful to know whether the marker varies with demographic and clinical characteristics of the potential study population. Data from the Johnston County Osteoarthritis Project, a population-based study of OA in North Carolina, USA, have demonstrated that African–American women had higher serum COMP levels than white women (Figure 1), while no ethnic differences were observed in the men. These effects were not explained by differences in age, body mass index (BMI), presence or severity of knee and hip OA involvement or height [17]. Further, African–Americans had significantly lower levels of serum HA than white patients in this study, a difference that was independent of these factors and comorbid conditions [18]. hsCRP has been associated with increased OA presence and severity [19], but is known to be higher in women, African–Americans, obese individuals, those with medical comorbidities common in

**Box 1. Important considerations in selection of a potential biomarker for use in osteoarthritis clinical trials*.**

- Is the marker associated with osteoarthritis (OA) structural outcomes, joint symptoms, functional outcomes or adverse events?
- Does the marker demonstrate variation diurnally or with activity or fasting?
- Does the clearance of the marker vary with inflammation, or with liver or renal impairment?
- Does the marker vary by sociodemographic factors, such as age, sex or race/ethnicity, and, if so, are norms available?
- Is the marker associated with body mass index?
- Does the marker vary with comorbid conditions frequently observed with OA?
- Does the marker vary with medications commonly used by individuals with OA?
- Does the marker reflect the total body load of OA involvement?
- Is the tissue origin (specifically, cartilage, bone, synovium, tendon, ligament) of the marker known?

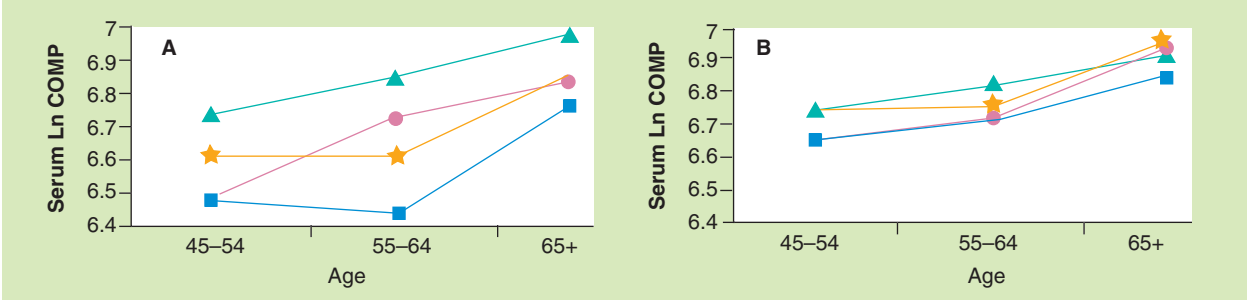
*Lack of complete answers to these questions does not necessarily preclude inclusion of biomarkers into OA clinical trials. Highest priority should be placed on the strength of the association between a biomarker and OA-related outcomes and on factors that could not be easily addressed by exclusion criteria, randomization or additional control of confounding.

people with OA, and those using hormone-replacement therapy, all of which can confound associations with OA [20]. Accordingly, the development of standardized norms (not currently available), for various populations, by age, sex and race/ethnicity, is an important area for future research. Standardization of assays is not currently a reality for many biomarkers, and processing must be centralized for multicenter clinical trials.

Another important and under-studied consideration is the standardization of data collection procedures. Recently, the first comprehensive study of diurnal and activity-related effects upon 11 serum and urine biomarkers was conducted in 20 individuals with symptomatic knee OA. Serum HA (Figure 2), COMP, keratan sulfate (KS-5D4), transforming growth factor (TGF)β1, and CPII (a Type II collagen synthesis marker) increased after 1–4 h after arising from bed, while no diurnal variation was observed for chondroitin sulfate epitope 846, hsCRP, osteocalcin, or serum $C_2C$, $C1,_2C$ (the latter two measures of Types I and II collagen metabolism) [21,22].

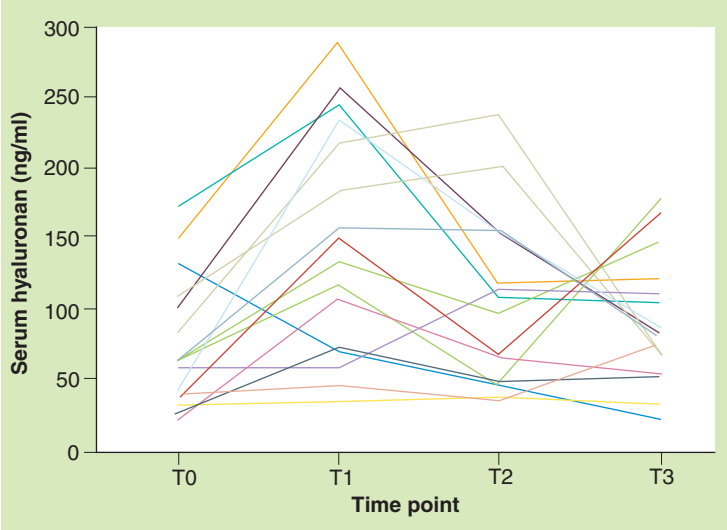
Third, whether and how clearance of a biomarker, and thus the level measured in the serum or urine, is affected by synovial inflammation, liver disease, kidney impairment, other comorbidities and medications is not completely known. The confounding of measurement of OA biomarkers in postmenopausal women on hormone-replacement therapy, which is associated with elevations in hsCRP, lower levels of serum COMP and HA [23,24], and urinary CTX-II [25],

**Figure 1. Serum cartilage oligomeric matrix protein in African–American and Caucasian women and men in Johnston County Osteoarthritis Project.**




Mean serum levels of natural ln COMP in **(A)** Women, **(B)** Men, by radiographic knee OA status (according to the Kellgren/Lawrence [K/L] scale), ethnicity and age group (years). Pink circle: unaffected (K/L grade 0 knee and hip OA) African–Americans; Blue square: unaffected Caucasians; Green triangle: affected (K/L grade 2–4 knee OA) African–Americans; Orange star: affected Caucasians.
ln COMP: Log-transformed cartilage oligomeric matrix protein; OA: Osteoarthritis.
Data from [17].

**Figure 2. Variation of serum hyaluronan over time following activity in individual participants.**




Changes in serum hyaluronan with activity in individual participants (n = 20). T0: 8:00 am sample, prior to arising from bed; T1: 9:00 am sample, 1 h after arising from bed and performing morning activities; T2:12:00 pm sample, 4 h after arising from bed; T3: 8:00 pm sample, after approximately 12 h of daily activities.
Data from [21].

illustrate this point. Concomitant vitamin D, calcium and bisphosphonate therapy, commonly consumed by such women, may also affect OA biomarkers [10].

To date, most OA biomarker studies have focused on a signal joint, usually the knee. The contribution of the total body load of OA to systemic biomarker measurement is beginning to be appreciated [17,18,26]. In the Johnston County Osteoarthritis Project, serum levels of COMP, HA and hsCRP each demonstrated increasing levels with bilateral knee involvement, concomitant knee and hip involvement, and number of knees and hips with OA [17,18,20]. Moskowitz and colleagues have attempted to quantify the contributions of large and small joints to systemically measured OA load [26]. How this information might be used to select participants into a clinical trial or monitor their course has not been tested. This does suggest that information about other joints with OA beyond the signal joint, should be collected in OA trials, in the event that randomization fails to account for their potential confounding effects upon systemic biomarker measurement.

Finally, most putative OA biomarkers are not restricted to joint tissues, and the tissue origin of most OA biomarkers cannot currently be differentiated. Type I and II collagens can be differentiated from each other, thereby enabling an estimation of presumed bone and joint turnover, respectively, in the OA process. Several collagen II-derived epitopes have been used to characterize synthesis and degradation of Type II collagen. Although articular cartilage is not the sole source of Type II collagen, these markers have been associated with various OA outcomes and have been assumed to reflect predominantly articular cartilage processes. These include urinary CTX-II [27], $C_2C$, CPII [28], PIIANP [29], Col 2–1 [30] and Helix-II [31].

Not all of these issues carry similar import for their effect on the integrity of data using biomarkers in a clinical trial. The most important consideration in the selection of a biomarker in OA clinical trials is the strength of the association with OA-related structural outcomes, joint symptoms and function. After that, highest priority should then be placed on dealing with sources of biomarker error that cannot easily be addressed by other means, such as exclusion criteria, randomization or statistical control of confounding. For example, if a marker is known to vary with certain medications, hormone replacement or comorbid conditions, persons on those medications or with those conditions could be excluded. Randomization may eliminate confounding for some issues. If randomization fails to do this, additional control for potential confounders can occur in the statistical analysis of the data.

## Biomarkers in symptom-modifying clinical trials

### *OA biomarkers*

Several studies have examined changes in OA biomarkers in symptom-modification trials of nonsteroidal anti-inflammatory drugs (NSAIDs) [32–34]. In a placebo-controlled study of ibuprofen in 201 individuals with symptomatic knee OA in flare, urinary CTX-II and urinary glucosyl–galactosyl–pyridinoline (a marker of synovial inflammation) increased in those with knee swelling in the placebo group over 4–6 weeks, compared with minimal or no increase in the ibuprofen group. These results suggested that ibuprofen might be able to prevent increased cartilage and synovium degradation associated with joint inflammation during flare [32].

A second study compared ibuprofen against nimesulide in 90 patients with knee or hip OA over 4 weeks. Nimesulide, but not ibuprofen, was associated with decreased urinary CTX-II and serum HA, serum matrix metalloproteinase

(MMP)-3 and -13. This suggests that nimesulide could impact joint inflammation and cartilage collagen degradation [34]. Long-term studies of this kind in NSAID trials have not been performed.

Few studies to date have published data on biomarkers in glucosamine OA symptom-modification trials [35]. In a placebo-controlled glucosamine-withdrawal trial in knee OA, Cibere and colleagues found no significant differences between placebo and glucosamine in serum or urine ratios of type II collagen degradation markers, C1, 2C or C2C [35].

### *Pain biomarkers*

Most clinical trials in OA symptom-modification trials have examined biomarkers of joint tissue metabolism. One novel approach evaluated plasma serotonin, substance P and β-endorphin levels in a trial of acetaminophen and rofecoxib in symptomatic knee OA [36]. Acetaminophen reduced β-endorphin levels, which were correlated with pain relief. It is anticipated that such studies will increase in number as pain biomarkers are validated and as interest in predictors of symptomatic response continues to grow.

### *OA biomarkers in structure-modifying clinical trials*

OA biomarker data from structure-modification trials of glucosamine, doxycycline, diacerein, and risedronate, have recently been published [10,16,37–40]. Christgau and colleagues found no difference between glucosamine and placebo groups in urinary CTX-II in a 3-year structure-modification study in knee OA. However, those with elevated CTX-II at baseline demonstrated worsening of symptoms. In such individuals on glucosamine, urinary CTX-II levels decreased over 12 months, and were correlated with average JSN at 36 months. The authors concluded that high urinary CTX-II might identify participants with high Type II collagen turnover who are more likely to respond to structure-modifying therapy [16].

Doxycycline was evaluated in a placebo-controlled trial for symptom and structure-modification in overweight women with unilateral knee OA [9]. In a preselected group of 60 whose OA progressed and 60 nonprogressors, those in the placebo group in the highest tertile of MMP-3 at baseline had four-times the odds of progression of those in the lowest tertile [37]. However, urinary CTX II levels were not associated with progression of radiographic or symptomatic OA [38]. This study provided further evidence that some biomarkers might be useful to identify progressors and to monitor response to therapy in OA trials.

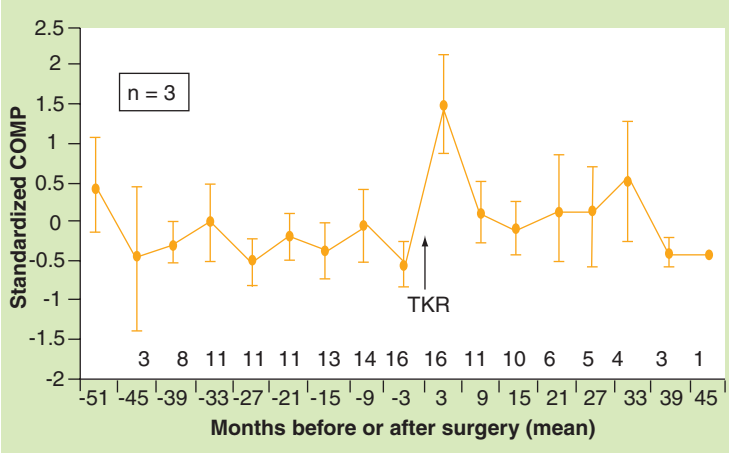
The British study of risedronate in structure and symptoms of knee OA evaluated markers of bone resorption (urinary N-terminal crosslinking telopeptide of Type I collagen [NTX-I]), bone formation (bone-specific alkaline phosphatase) and cartilage degradation (urinary CTX-II), in a 1-year placebo-controlled trial of risedronate in men and women with symptomatic knee OA [10]. In this study, markers of NTX-I and CTX-II decreased significantly with 15 mg risedronate daily compared with placebo. Although no significant difference was observed in radiographic outcome between the placebo and risedronate groups, there was a trend favoring risedronate, as well as improvement in several clinical and symptomatic measures.

One study evaluating potential structure modification in hip OA is the Evaluation of the CHOndromodulating effect of DIAcerein in osteoarthritis of the Hip (ECHODIAH) trial, a 3-year randomized, placebo-controlled trial of diacerein, an interleukin (IL)-1 inhibitor. Mazieres and colleagues reported that those in the highest tertiles of urinary CTX-II and serum HA at baseline were almost four-times as likely to have their hip OA progress as those in the lower two tertiles [39]. In a cross-sectional report of ten biomarkers in this cohort, Garnero and others demonstrated that urinary CTX-II was associated with hip pain and radiographic joint space narrowing and sclerosis. Serum COMP was associated with inflammation, as measured by night pain and morning stiffness [40].

### *OA biomarkers in clinical trials of nonpharmacological interventions*

Few nonpharmacological trials in OA have examined effects on OA biomarkers. In an 18-month study of diet-induced weight loss, exercise, diet plus exercise or healthy lifestyle control in older, overweight or obese, sedentary men and women with radiographic knee OA and reported difficulty with activities of daily living, those with diet-induced weight loss, but not with exercise alone, had significant decreases in inflammation, as measured by hsCRP, IL-6, and soluble tumor necrosis factor-α receptor 1 (TNF-sR1) [41]. Furthermore, those with higher serum levels of TNF-sR1 and TNF-sR2 were more likely to have more symptoms of pain and stiffness, more reported physical disability and more severe radiographic score [42].

**Figure 3. Serial serum cartilage oligomeric matrix protein and total knee replacement.**




Standardized serum COMP levels in relation to TKR surgery in 16 patients whose COMP levels were measured before and after surgery. Values are the mean and 95% confidence interval.
COMP: Cartilage oligomeric matrix protein levels; n: Number of patients; TKR: Total knee replacement.
Data from [13].

### *Osteoarthritis biomarkers in joint injury & surgical & rehabilitation interventions*

Building on a well-described literature about biomarker changes in synovial fluid and, more recently, serum in canine models of experimental OA by anterior cruciate ligament (ACL) transection [43], the potential utility of OA biomarkers in human joint injury and in surgical and rehabilitation interventions is beginning to be studied [44,45]. Lohmander and others, reported early and sustained elevations in synovial fluid CTX-II in patients with ACL tear [44]. One randomized trial of two rehabilitation schedules following ACL reconstruction, demonstrated sustained elevation of synovial biomarkers of type II collagen degradation ($COL2–3/4C_{Longmono}$) and synthesis (CPII) and aggrecan turnover. $COL2–3/4C_{Longmono}$ and aggrecan levels returned to control levels by 12 and 24 months, respectively, while CPII remained elevated 24 months after ACL repair. The rehabilitation schedule did not affect the responses of these biomarkers [45].

Sharif and colleagues first reported that serial serum COMP levels were elevated and remained elevated for months after TKR (Figure 3) [13]. Others have examined biomarkers as predictors of prosthesis loosening, heterotopic bone formation or infection following TKR or THR [46–48]. In a recent study of 40 following TKR, Li and others observed elevated serum osteocalcin at 12 and 24 months, and elevated cross-linked c-terminal telopeptide of Type I collagen from 6 to 24 months, in those with loosening compared to those with stable fixation. The authors suggested that biomarkers might be useful to study if medications that impair osteolysis and decrease bone turnover can improve implant fixation [46].

Wilkinson and colleagues observed early elevations in markers of bone formation and degradation following THR, with significantly higher rises in CTX-I, N-terminal propeptide of Type I procollagen and osteocalcin in those who subsequently developed heterotopic bone formation, compared with those who did not. The authors posited that these markers might potentially be early surrogate markers in clinical trials of prophylactic regimens for prevention of this adverse outcome [47].

Finally, serum IL-6 was evaluated as a marker of infection in 58 patients who required re-operation for infection or other implant-related events following TKR or THR [48]. A serum level of IL-6 ± 10 pg/ml was found to be highly sensitive and specific, with a positive predictive value of 89%, for the diagnosis of periprosthetic infection. The results of these studies hold promise that biomarkers may be useful in studying responses to injury and surgical and rehabilitation intervention trials in OA.

## Genetics, genomics, proteomics & metabolomics

The OA biomarkers discussed above are all proteins measured individually in the blood or urine. Other biomarkers include genes and their functional products, examined in conjunction with multiple other proteins and related data [49]. Ling and colleagues reported specific protein profiles were predictive of the development of OA in participants of the Baltimore Longitudinal Study of Aging [50], and Lamers and others observed different urinary metabolomic profiles, using MRI, in individuals with and without radiographic OA in the Johnston County Osteoarthritis Project [51].

## Conclusion

The use of biomarkers in OA research and practice is evolving rapidly. This includes the exploration of genomic [49] and metabolomic [51] markers, in addition to protein profiles [50]. The validity of an increasing number of biomarkers has been established with the demonstrated association of measurable differences in

biomarker levels with the development and progression of OA, and following pharmacological, nonpharmacological and surgical OA interventions. Ongoing challenges to the use of biomarkers in clinical trials include the need for standardization of data collection methods, procedures and assays, and the acknowledgement of potential variation in biomarker levels according to age, sex, race/ethnicity, BMI, comorbid conditions and medications.

## Future perspective

Over the next 5–10 years, new biomarkers for OA will continue to be developed, tested and validated in longitudinal studies and clinical trials. It is anticipated that biomarkers will be routinely used to select participants for clinical trials, identify those at greatest risk of rapidly progressive disease and provide surrogate measures for radiographic OA. The continuing advent and validation of biomarkers fulfilling these roles will hasten the development and testing of pharmaceuticals to alter OA incidence and progression. As a result, it is expected that regulatory agencies responsible for the approval of structure-modification pharmaceuticals, may re-examine the utility of the current radiographic criteria to demonstrate effectiveness of an intervention in altering OA structural deterioration. Further work utilizing novel biomarkers in symptomatic OA outcomes, rather than simply structural outcomes, will also occur. Rapidly advancing high-throughput, multiplex laboratory methods, in conjunction with increasingly sophisticated statistical and bioinformatics technologies, will be critical in this paradigm shift and provide cause for optimism that these goals are achievable.

## Executive summary

### *Public health burden of osteoarthritis*

- Arthritis is the leading cause of disability.
- Osteoarthritis (OA) is the most common cause of arthritis.
- OA is expected to increase in prevalence due to the aging of the population and the obesity epidemic.

### *Challenges in the development of OA disease-modifying interventions & definitions of biomarkers*

- There is a strong impetus in the public and private sectors to develop and test structure-modification interventions for OA.
- Currently, structure modification must be demonstrated by a decrease in the rate of joint-space narrowing measured by serial radiographs, which can be imprecise and insufficiently sensitive.
- Clinical trials of potential structure modification pharmaceuticals and interventions are costly and take 2–3 years, with the associated methodological pitfalls inherent in trials of long duration.
- Biomarkers are indicators of normal or abnormal biological processes or responses to therapeutic interventions. Some, such as magnetic resonance imaging (MRI), are more sensitive to change than x-ray in a shorter duration of time, but require further validation.

### *Use of biomarkers to aid selection of participants for OA clinical trials*

- Potential participants for trials should have a prespecified level of disease severity, excluding those with minimal or end-stage disease.
- A critical issue for structure-modification trials is the preselection of individuals with a high likelihood of progression over the timespan of the trial. Clinical characteristics alone as inclusion criteria do not guarantee the selection of such individuals, and the supplemental use of selected biomarkers may help in this regard.
- Potential biomarkers that predict progression or possible response to therapy include bonemarrow edema on MRI, elevated urinary CTX-II, high-sensitivity C-reactive protein, serum matrix metalloproteinase-3 and hyaluronan (HA). Others are also under evaluation.

### *Important characteristics of OA biomarkers for clinical trials*

- It should be known whether a biomarker varies with demographic and clinical characteristics of the study population, including age, race/ethnicity, sex, body mass index, comorbid conditions and medications.
- Standardization of data collection is also important since some biomarkers are sensitive to activity and fasting/eating. Few studies have examined this in detail.
- Detailed information about factors influencing local and systemic clearance of many biomarkers is not known.
- Typically, OA clinical trials focus on a single signal joint. Systemic biomarkers reflect the total body load of OA, and this needs to be factored into trial design and analyses.
- Differentiating the tissue source of biomarkers is an ongoing challenge.

## Executive summary

***OA biomarkers in symptom-modifying clinical trials***

- Few symptom-modification trials have assessed effects on biomarkers. Those that have examined this, such as nonsteroidal ant-infammatory drugs and glucosamine, have demonstrated mixed results, but anti-inflammatory medications may alter markers of inflammation and cartilage degradation.
- Evaluation of pain biomarkers in symptomatic OA is in its infancy and may increase in importance with validation and testing of such biomarkers.

***OA biomarkers in structure-modifying clinical trials***

- Glucosamine, doxycycline, diacerein and risedronate have been examined for their potential structure-modification properties in clinical trials. These trials have identified several potential biomarkers indicative of progression and possibly indicative of response to therapy. These include urinary CTX-II, matrix metalloproteinase (MMP)-3, and serum HA.

***OA biomarkers in clinical trials of nonpharmacological interventions***

- One study demonstrated that measures of inflammation, measured by high-sensitivity C-reactive protein (hsCRP), IL-6 and tumor necrosis factor-sR1, could be reduced with the combination of diet and exercise.

***OA biomarkers in joint injury & surgical & rehabilitation interventions***

- Examination of systemic biomarkers in the setting of joint injury, surgery and rehabilitation are few. Some biomarkers, such as CTX-II, CP II and serum cartilage oligomeric matrix protein, have been shown to be elevated following joint replacement.
- Other outcomes where biomarkers have been tested following surgical intervention for joint injury or OA include prosthesis loosening, heterotopic bone formation and infection.

***Genetics, genomics, proteomics & metabolomics***

- These methodologies examining profiles of genes and their products are beginning to be examined in OA, and have been found to be predictive of the development of OA and in the differentiation of OA and non-OA individuals.

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•• Examines several important risk factors for knee OA progression and their relationship to each other.

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