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Biomarkers for osteoarthritis: current position and steps towards further validation

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Keywords

osteoarthritis; biomarkers

Introduction

Osteoarthritis (OA), the most common of all arthritides, is a heterogeneous disease characterized by failure of the synovial joint organ. The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that due to any other medical condition in people aged 65 and over [1,2]. Recent estimates suggest the global burden of knee osteoarthritis affects approximately 250 million people [3]. Although ageing is a significant risk factor, the majority of those affected with OA (64%) are of working age (15–64 years) accounting for 11% of the workforce [4,5]. There are presently no therapies approved by regulatory authorities that modify the onset or progression of OA structural damage, and available symptom-modifying (analgesic) treatments have only moderate long-term effect sizes with the majority of patients dissatisfied with their efficacy [6,7]. As a result of the failure of pharmacological approaches

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Author contributions

All authors were involved in collecting data, reviewing the literature and drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Disclosure

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to manage the condition, the number of joint replacement surgeries, over 95% of which are done for OA, is increasing by ~10% annually. In the US alone, the financial burden has been estimated to be $81 billion in medical costs and $128 billion in total cost, given approximately 21 million people with OA associated limitations, 36 million outpatient visits and 750,000 hospitalizations per year [8]. This formidable individual and socioeconomic impact of OA will continue to grow as the population ages and obesity rates continue to grow, with the number of persons affected predicted to double by 2020 [4,9].

Despite the urgency driven by its frequency, individual impact of disability, and societal cost, current treatment paradigms are limited to palliative measures broadly focused on analgesia and, when this fails, surgical knee replacement. It is clear that finding effective disease- and symptom-modifying therapies for OA is a global unmet need whose amelioration should be an international medical priority. There have been major research advances that have significantly increased our understanding of the molecular pathophysiology of joint destruction and pain in OA. Despite this pre-clinical progress however, no new structure-modifying therapies have translated into treatments for patients. Indeed, the recent failure of a number of phase II and III clinical trials for OA structure-modifying drugs has resulted in a considerable decline in the number and size of pharmaceutical company research programs in this area [6]. The reasons for the translational failure of anti-OA drugs are likely multifold, but include the poor relationship in individual patients between joint structural pathology (especially joint space narrowing on radiographs) and symptomatic disease, and limited responsiveness of existing biomarkers [10].

This narrative review outlines the rationale for why we need OA biomarkers and work done in OA with regard to biomarker validation and qualification. The main biomarkers in current development for OA are biochemical and imaging markers. It then describes an approach to biomarker validation and qualification for OA clinical trials that has recently commenced with the Foundation of NIH OA Biomarkers Consortium study cosponsored by the Osteoarthritis Research Society International (OARSI).

The role of the Critical Path Initiative and the Biomarkers Consortium in biomarkers development

Cognizant of the challenges involved, stakeholders in the pharmaceutical enterprise (health care providers, regulatory authorities, industry, and payers) recognized the need for a shift in the approach to drug development [11]. New investigational paradigms in drug development have advanced to facilitate both discovery and clinical development, without sacrificing basic regulatory standards of safety and efficacy [12]. The U.S. Food and Drug Administration (FDA) put forward a Critical Path Initiative [13] that identified a choice between the status quo, “stagnation,” and a new path, “innovation”, and described critical path research as being “directed toward improving the product development process itself by establishing new evaluation tools”.

The many challenges related to biomarker research and development have been clearly articulated by the FDA Critical Path Initiative [13] and The Biomarkers Definitions Working Group [14]. Several consortia in recent years have taken on the challenges related

to biomarker development for a variety of diseases [12]; our own initiative, the Foundation of NIH (FNIH) OA Biomarkers Consortium, endeavors to identify, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics for osteoarthritis. The OA Biomarkers effort is part of the broader FNIH Biomarkers Consortium, a major public-private biomedical research partnership with broad participation from stakeholders across the health enterprise, including government, industry, academia and patient advocacy and other non-profit private sector organizations and managed by the Foundation for the National Institutes of Health (FNIH; http://www.FNIH.org).

Outlining the need for change in OA

Historically disease knowledge development and treatment innovation in osteoarthritis (OA) has been considered to be slow [10]. One of the many reasons purported as responsible for this slow pace has been the alleged lack of valid and responsive biomarkers to ascertain efficacy, which itself has been dependent upon the slow evolution of the understanding of the complex nature of joint tissue biology.

The lack of valid and responsive biomarkers not only slows therapeutic advances but also blocks development of strategies to stem the tide of rising clinical trial costs. The time and cost needed to develop new compounds has increased in recent years [15]. DiMasi et al. calculated that the average cost of bringing a drug to the market increased from US $ 318 million in 1991 to US $ 802 million in 2003 (inflation adjusted, including opportunity cost of capital) [16]. The cost calculation comprises the expenses for failures of drug candidates in the development process. The average probability that a drug candidate will successfully pass clinical phase I studies is in the range of 75%; the respective values for phases II and III trials are 50% and 65% [17]. In total (including further probabilities, e.g. for the regulatory review), the cumulative probability that a leading drug candidate will successfully proceed from the preclinical phase to approval is about 8% (i.e. for every 12–13 compounds that were serious candidates in preclinical research, only one drug will make it onto the market) [17]. The rising cost of drug development is imposing a significant burden on industry engaged in therapeutic development. The attraction of integrating valid and responsive biomarkers into the therapeutic development process includes the expectation that less promising projects may be stopped earlier (especially before they enter into costly clinical phase III [18]) and that the total cost of drug development will be optimized.

Some barriers to the development of OA therapeutics are unique to the OA biomarker field. First, our current reference standard for disease diagnosis and severity is often the radiograph, which has a low responsiveness to change and at most moderately correlates with clinical endpoints. Second, there is a lack of consensus for surrogate measure and efficacy of intervention development and the definition as to what constitutes a meaningful clinical endpoint. Third, OA is extraordinarily complex with marked heterogeneity in onset, clinical presentation, rate of disease progression, pattern of joint involvement and synovial tissue structure affected. These issues will be described in more detail later in the manuscript.

This vicious cycle, of imperfect biomarkers to test efficacy of disease modifying therapies in clinical trials and the lack of effective therapies to demonstrate the validity of biomarkers, has challenged therapeutic development for years. What remains clear however, is that it creates exciting opportunities to refine existing biomarker methods and identify new biomarkers for accelerating the development of safe and effective treatments for OA.

Challenges in Osteoarthritis

Many hurdles exist within OA research and development that pertain to biomarker validation and qualification. The draft regulatory (FDA) guidance and current gold standard for measuring clinical efficacy in disease modifying therapy development in OA is radiographic joint space narrowing (JSN) [19]. From JSN outcomes the health, integrity and thickness of hyaline articular cartilage are inferred [20,21]. This FDA guidance describes a process for drug approval for specific indications in OA, including treatment of symptoms, delays in structural progression and even discusses prevention of OA. The JSN measure is currently recommended by both the FDA and European Agency for the Evaluation of Medicinal Products (EMEA) guidance documents as the imaging endpoint for clinical trials of disease-modifying OA drugs (DMOADs). At present, an alteration in structural progression would likely be determined by plain radiography, but it is possible that newer technologies may be approved including biochemical markers, or MRI, once appropriately validated.

If we choose the current recommended endpoint, namely JSN, due to limited responsiveness we would require many hundreds of subjects, followed for at least 2–3 years, to demonstrate a significant incremental benefit of a novel therapy over and above that provided by currently available therapies. The direct costs of conducting such trials and the costs resulting from the overall duration of the therapeutic development and regulatory review process has dampened enthusiasm for development of therapeutic agents in this area and, in some instances, has rendered advancement of novel treatments prohibitively expensive. On the other hand, if other, more efficient means of establishing the benefit of new drugs exist, the promise of timely access to new therapies remains. There is, therefore, potentially tremendous value to public health in accelerating the discovery and development processes for OA therapeutics through shorter studies, using validated endpoints other than radiographic JSN. The use, in part, of clinical trial evidence based on biomarker and surrogate endpoint effects (in lieu of morbidity endpoints such as joint replacement or virtual joint replacement [22]) has the potential to revolutionize the OA drug development process and to thereby enhance the armamentarium of safe and effective therapeutics.

This accelerated path to new therapies in OA needs to be balanced by global concerns. Unlike other diseases where surrogate endpoints exist, OA does not have a mortality endpoint but rather affects a person’s quality of life [23]. Therefore, the ‘clinical endpoint’ is harder to establish. Furthermore, improvement in quality of life over the long interval of time that persons with this chronic disease receive therapy, can be easily dampened by toxicity [24]. Thus the need for therapeutic advance needs to be balanced by not only demonstrating early efficacy but also ensuring sustainability of the effect and adequate safety.

Another challenge with the radiograph as the current reference standard is that it creates an imperfect reference for comparison with other methodologies for the purposes of validation [25]. Progression in joint space width (JSW) loss also reflects OA changes in joint tissues other than articular cartilage, particularly extrusion and degenerative changes of the menisci associated with OA development and progression [26]. If a purported therapeutic targeted synovium or bone marrow lesions directly, ascertaining its therapeutic benefit by the measurement of JSW may not be appropriate.

Another challenge is that the current approval of potential therapies in OA requires that this structural alteration be linked to some clinical benefit either at the time when the structure was measured or at a later time-point. With this concept in mind it is obviously important that improvements in OA structural features are ascertained that are more likely linked to the clinical symptoms experienced by patients, or alternatively can serve as a surrogate for a clinically meaningful outcome. Currently there is little consensus on what constitutes a meaningful clinical endpoint for OA structure modifying trials; some suggest that the development of symptomatic radiographic OA should suffice whereas others are developing definitions for what would constitute a virtual total joint replacement [22]. The lack of clear consensus creates an enormous challenge with regards to defining and validating efficacy biomarkers let alone the development of surrogate endpoints. Although the use of surrogate outcomes in clinical trials reduces sample size requirements and trial duration, they can only be justified if there is strong evidence that therapeutic targeting of the surrogate will translate into a beneficial patient outcome [27].

Current State of the Art

In 2008, an effort by the Osteoarthritis Research Society International (OARSI) to evaluate the science around the design of clinical development programs for the treatment and prevention of OA was launched in response to a 2007 Federal Register notice posted by the FDA seeking a critical appraisal of these issues. Among the outputs were reviews of the state of the science as it relates to both imaging and biochemical markers.

The OARSI-FDA OA Assessment of Structural Change (ASC) Working Group reviewed and synthesized published data on the performance metrics of the most common imaging tools used to assess structural change in OA, focusing predominantly on conventional radiographs and magnetic resonance imaging (MRI). A search of plain radiography and MRI literature in OA was conducted using articles published up to the time of the search, April 2009. These systematic reviews depict the responsiveness of quantitative JSW on plain radiographs, and the responsiveness, reliability and validity of MRI measurements [28–30]. A meta-analysis of the plain radiographic literature demonstrated:

1. Insufficient data to make any conclusion on the predictive validity of JSW and change in JSW for clinical outcomes beyond a specific trial duration (typically 1–2 years). There were, however, some trends identified including:
    a. Baseline JSW may predict treatment outcomes, with patients with smaller JSW showing less symptomatic and structural efficacy in treatment trials.

   b. For example, in one study the amount of JSW loss may be predictive of requirement for knee replacement surgery [31]. In this 5-year cohort following two 3-year randomized trials, a 0.5 mm or more joint space loss during the 3-year trial was predictive of joint replacement during 5 subsequent years: 4 out 15 patients (26.7%) with an initial joint space loss above 0.5 mm underwent later 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).

2. Responsiveness of JSW measures pooled over multiple studies was low for all knee radiography techniques and without significant differences between techniques. Head-to-head comparisons suggested higher responsiveness with fluoroscopic semi-flexed views. Longer studies (~2 years) offered better responsiveness. Responsiveness is assessed by calculating the standardized response mean (SRM), which is defined as the mean change divided by the standard deviation of change.

MRI measures of cartilage morphology were recommended by the Working Group for clinical trials of knee OA treatments with structural outcomes on the basis of their preferable validity and responsiveness [32]. It is important to study all the joint tissues of the OA joint and the literature is growing on MRI quantification (and its responsiveness) of non-cartilage features. The most promising MRI measures identified in systematic reviews with respect to reliability, responsiveness and validity, were quantitative cartilage morphometry, cartilage defects and bone marrow lesions on semi-quantitative analysis, bone shape/ attrition and subchondral bone area; these particular parameters were subsequently selected for inclusion in the FNIH OA Biomarkers Consortium study. Research recommendations were developed through a consensus process by the ASC Working Group.

The biomarkers group of the OARSI-FDA initiative stated that there are no FDA qualified OA-related biochemical biomarkers, although there are many that have shown associations with some aspect of OA and that fulfill one or more aspects of the BIPEDS [33] classification scheme; this scheme classifies the major types of biomarkers into 6 categories corresponding to Burden of disease, Investigational, Prognostic, Efficacy of Intervention, Diagnostic and Safety biomarkers (the latter category added as part of the OARSI FDA initiative [34]). To date, a total of 12 distinct molecular biomarkers of bone and cartilage turnover that can be quantified by commercially available kits, have been shown to have an association with some aspect of OA based on the BIPEDS classification scheme. These represent the best-qualified OA-related biomarkers to date but few of them have been compared in the same sample set.

Steps taken towards biomarker validation for osteoarthritis: the FNIH OA Biomarkers Consortium

The first critical step for OA biomarker development is to establish a process for OA biomarker validation and qualification. Validation and qualification are interrelated but distinct processes; validation refers to the establishment of an accurate and reliable measure and qualification refers to the establishment of acceptable performance in a specific context

of use for a particular biomarker. In 2010, we established a working group that included biomarker experts from the academia, NIH, FDA, and industry that could bring new solutions to OA biomarker development and accelerate implementation for OA therapeutics.

The immediate focus of this group was to use standardized methods for biomarker validation [35] and qualification [36] in OA, and then with shared purpose, pursue the validation of specific biomarkers that could predict therapeutic response in the plethora of rich resources already available to us from well developed observational and clinical trial datasets. For successful biomarker validation and qualification, there is a great need for good specimen collections and we have been fortunate to leverage the samples and data collected for the Osteoarthritis Initiative (OAI). The OAI is a large observational cohort study of knee OA funded by the NIH and Industry with annual measurements of clinical outcomes, knee imaging and collection of biospecimens that enrolled 4,796 subjects ages 45–79 who are being followed for 8 years [37,38].

The overarching OA Biomarker project objective is to establish the predictive validity of disease progression biomarkers and assess the responsiveness of several imaging and biochemical markers pertinent to knee OA. This project is evaluating imaging and biochemical biomarkers in a nested case-control analysis in the OAI cohort. Cases are 194 knees with clinically meaningful progression of both radiographic joint space narrowing and symptoms over the course of 48 month and controls are 406 knees eligible to be cases that did not meet these progression criteria. In order to facilitate separate evaluation of biomarkers for structural progression and symptom progression, the sample of controls includes a predetermined number of knees with structural but no symptom progression, knees with symptom but not structural progression, and knees that did not progress on either outcome dimension. For imaging biomarkers, MRI and radiograph images are being distributed to vendors with established track records in selected measures of interest. For molecular biomarkers, serum and urine biospecimens have been retrieved and sent to a central Clinical Laboratory Improvement Amendments (CLIA) certified laboratory where assays relevant to OA are being conducted. This project will determine the biomarkers with optimal predictive validity and responsiveness for knee OA and will make it possible to take the next step, regulatory qualification of these markers, which will be to assess these biomarkers in clinical trial settings either prospectively or using data from completed clinical trials.

The project has three primary aims:

Aim 1

To examine the relationship between putative efficacy of intervention markers (biochemical markers, imaging features on x-ray and MRI and their progression (over 1 and 2 years)) and clinically relevant outcomes over a 4-year follow-up period.

Hypothesis 1 After adjusting for baseline structural severity and pain level, change of radiographic measures [minimum joint space width (JSW), JSW (X), Bone trabecular integrity by Fractal signature analysis (BTI/FSA), joint space area (JSA),

OARSI JSN] over 1 and 2 years will predict progression to clinically relevant outcome during 4 years of follow-up.

Hypothesis 2 After adjusting for baseline structural severity and pain level, change of MRI measures (semi-quantitative or quantitative): subchondral bone area, cartilage morphometry, T2 mapping, bone shape, bone marrow lesion volume, osteophyte volume) over 1 and 2 years will predict progression to clinically relevant outcomes during 4 years of follow-up.

Hypothesis 3 After adjusting for baseline structural severity and pain level, change of biochemical markers over 1 and 2 years will predict progression to clinically relevant outcomes during 4 years of follow-up.

Aim 2

To identify the most responsive marker(s) of OA progression.

Hypothesis 4 One or more quantitative MRI measures will surpass the sensitivity to change of existing plain radiographic measures of progression, namely quantitative JSW. Subchondral bone area, osteophyte volume and cartilage thickness will be more responsive than quantitative JSW.

Aim 3

To develop a risk score based on baseline values of several biomarkers including JSN, BTI/FSA, knee alignment, quantitative and semi quantitative MRI measures and biochemical biomarkers that would determine those who progress rapidly to case status.

Hypothesis 5 The higher risk score will have more discriminative power to predict rapid development of clinically relevant outcomes (case status) over the 4 year period compared to individual typology of biomarkers (X-ray based, MRI-based, other biochemical marker-based).

Over a period of two and a half years, this Biomarkers Consortium project will utilize both data and biospecimens from OAI to assess the ability of a set of plain radiographic measures, MRI measures and biochemical markers to predict clinical outcomes and their ability to change over time. Images from OAI will be sent to five different image analytical groups (Table 1). In addition, high quality biospecimens from OAI will be sent to Good Laboratory Practice (GLP) certified laboratories, LabCorp Clinical Laboratories (11 biomarkers) and Artialis (1 biomarker), to perform selected biochemical assays blinded to the clinical data (Table 2). The results of these assays will be analyzed by a Statistical Center at Brigham and Women's Hospital. Results of all analyses of both the imaging and biochemical markers will be reviewed and interpreted by the Biomarkers Consortium Project Team prior to being published in a suitable peer-reviewed journal(s). The data from collected during the tenure of the project analyses will be made available for public use and reanalysis via the OAI data coordinating center web-based data repository, and relevant results will be presented and published by the investigators in collaboration with the Project Team promptly thereafter.

The potential public health benefit of this project is substantial, as it will address some of the most fundamental obstacles to the development of new treatments for OA, a disease that presents a large and growing global health burden. The project will determine which biomarkers demonstrate optimal predictive validity and responsiveness for knee OA and represent suitable candidates for future qualification, via assessment in a clinical trial setting either using existing data from completed clinical trials or prospectively. The results of the project will facilitate the development of recommendations for using specific biomarkers in investigations to develop disease-modifying regimens in OA and will assist in planning and design of clinical trials focused on facilitating scientific discovery and establishing efficacy of future disease modifying regimens for knee OA.

These biomarker validation projects are a shared interest of all in the OA field. The Biomarker Consortium is precompetitive with respect to traditional pharmaceutical or biotechnology research and development and may overcome the current “silo” approach in pursuit of the “pet” biomarker. The shared results, shared costs and collaborative flow of information for both for-profit and non profit parties can overcome key impediments to biomarker qualification. All participants can benefit from being able to gain access to complex and innovative technology, test proprietary compounds using the data from biomarker research, and diminish financial risk by sharing the costs of these efforts between multiple funders. This is obviously not without challenges including satisfying the expectations of a diverse group of stakeholders, identification of funding for projects at an early stage of development, and harnessing the intellectual and resource potential of a disparate field. However, these challenges are not as great as those faced by our patients, who warrant collaborative pursuit of therapeutic advance for a disease where we need safe and effective therapeutic interventions.

Conclusion

Improved knowledge of the pathogenesis of OA and of its molecular and anatomic pathology and the wealth of information relating biomarkers of disease with clinical outcomes will permit a better means for the assessment of the effects of new therapeutic interventions in OA. It is evident from conversations within our field between industry, government regulators, and academia that there is a shared recognition of the need for both the development and application of new and existing biomarkers to enable therapeutic advances. To get to this point we have established and commenced a process for biomarker validation and qualification in OA. This is a path other disease areas have successfully taken and there are experiences, processes and infrastructure mechanisms in existence that we have built upon. Given the ubiquity of OA and its global burden, ultimately, we will all be the major beneficiaries from the new insights provided into disease risk, characterization and treatment.

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Keypoints

1. Historically disease knowledge development and treatment innovation in osteoarthritis (OA) has been considered to be slow. One of the many reasons purported as responsible for this slow pace has been the alleged lack of valid and responsive biomarkers to ascertain efficacy, which itself has been dependent upon the slow evolution of the understanding of the complex nature of joint tissue biology.
2. With the Foundation of NIH (FNIH) OA Biomarkers Consortium, we have established and commenced a process for biomarker validation and qualification in OA that endeavors to identify, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics for osteoarthritis.

Practice Points

The current reference standard for disease diagnosis and severity is often the radiograph, which has a low responsiveness to change and at most moderately correlates with clinical endpoints.

OA is extraordinarily complex with marked heterogeneity in onset, clinical presentation, rate of disease progression, pattern of joint involvement and synovial tissue structure affected.

At present, an alteration in structural progression would likely be determined by plain radiography, but it is possible that newer technologies may be approved including biochemical markers, or MRI, once appropriately validated.

Research agenda

At present it remains unclear which biomarkers (biochemical markers, imaging features on x-ray and MRI and their progression) demonstrate optimal predictive validity and responsiveness for knee OA.

Once identified they represent suitable candidates for future qualification, via assessment in a clinical trial setting either using existing data from completed clinical trials or prospectively.

These results will facilitate the development of recommendations for using specific biomarkers in investigations to develop disease-modifying regimens in OA and will assist in planning and design of clinical trials focused on facilitating scientific discovery and establishing efficacy of future disease modifying regimens for knee OA.

Table 1

X-ray and MRI measures being obtained in the FNIH OA Biomarkers Consortium.

Imaging Biomarker	Proposed Analytic Group	Parameter{s) Measured
Radiography		
Minimum Joint space width and joint space area and BTI/FSA	Duke Image Analysis Lab (DIAL)	Medial and lateral and minimum JSW and joint space area (JSA) and medial and lateral bone trabecular integrity by fractal signature analysis, (BTI/FSA)
MRI		
Quantitative cartilage morphometry	Chondrometrics	Cartilage Volume, thickness, denuded surface area
Quantitative bone morphometry	4Q imaging	Bone area, osteophyte volume and the bone/cartilage interface signal contrast
Quantitative bone morphometry	Imorphics	3 dimensional bone shape
Semi-quantitative joint scoring	Boston Image Core Lab (BICL)	Assessment of the joint organ morphology using the using the MRI Osteoarthritis Knee Score (MOAKS) system

Table 2

Biochemical markers to be assessed in the FNIH OA Biomarkers Consortium.

Biomarker	Process (preliminary)	BIPEDS Classifications	Surrogacy Based on Human Clinical Trials (preliminary)	ELISA type
urinary CTX-II	type II collagen degradation	Knee: BPED Hip: BPD	characterization: changed significantly in 3 pharmacologic trials that met primary clinical endpoints (Christgau 2004, Gineyts 2004, Manicourt 2006)	competitive-inhibition
serum COMP	cartilage degeneration	Knee: BPD Hip: BPD	exploration: not used to date in 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 (Manicourt 2006)	sandwich protein binding assay
serum and urine Cl,2C	Types I and II collagen degradation	Knee: D(u) Hip: none	exploration: non-significant change in one pharmacologic trial that met primary clinical endpoint (Mazzuca 2006)	competitive-inhibition
serum and urine C2C	type II collagen degradation	Knee: E(s), D(u) Hip: B(s)	demonstration: non-significant change in one pharmacologic trial that met primary clinical endpoint (Mazzuca 2006)	competitive-inhibition
urine Co1l2-1N02	type II collagen degradation	Knee: D(s), B(u), P(u) Hip: D(s)	exploration: not used to date in pharmacologic trial	competitive-inhibition
serum CPII	type II collagen degradation	Knee: D(s) Hip: B(s)	exploration: non-significant change in one pharmacologic trial that met primary clinical endpoint (Mazzuca 2006)	competitive-inhibition
Serum PIIANP	Type II collagen synthesis	Knee: BPD Hip: none	exploration: not used to date in pharmacologic trial	competitive-inhibition
urine and 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 (Spector 2005)	competitive-inhibition
urine and serum CTX-1	bone resorption	Knee: B(u), D(s/u), P(u) Hip: none	exploration: not used to date in pharmacologic trial	competitive-inhibition
serum CS846	cartilage aggrecan synthesis/turnover	Knee: P Hip: none	exploration: non-significant change in one pharmacologic trial that met primary clinical endpoint (Mazzuca 2006) 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 (Lohmander 2005, Manicourt 2006)	sandwich for total MMP-3 assay