Personalized medicine for osteoarthritis: where are we now?

Allen Dale Sawitzke

Ther Adv Musculoskel Dis

(2013) 5(2) 67–75

DOI: 10.1177/
1759720X12470752

© The Author(s), 2013.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Personalized medicine is a much talked about subject that is a timely and important development to healthcare in general and also specifically for patients affected by osteoarthritis. This review uses biomarker examples pertinent to osteoarthritis to highlight the current status of the field, while also highlighting probable future developments. It is not meant to be an exhaustive account. The BIPED(s) [Burden of disease, Investigative, Prognosis, Efficacy, Diagnosis (safety)] classification system is used to organize the discussion of examples. Biomarkers pertaining to burden, investigation, prognosis, efficacy, diagnosis and safety are highlighted. The examples are followed by a discussion of issues related to interpretation and application of biomarker results and approaches to solve the challenges interpretation faces, including graphical, mathematical and synthetic representations. Through this review, it is hoped that a better appreciation can be gained of the potential and pitfalls of personal medicine in the care of patients with osteoarthritis.

Keywords: biomarker, osteoarthritis, human, analysis, safety, diagnosis, prognosis, efficacy, investigation

Introduction

Over the last several years, personalized medicine has become a much talked about subject that has many divergent meanings to the different stakeholders involved. In fact, trying to meet the many varied expectations all at once has led in part to the difficulty in achieving results. However, nearly all would agree that personalized medicine is a timely and important development in healthcare.

Much of the traditional medicine is based on a public health approach in which population-based findings (risk factors) are used to determine recommendations for individuals. As well-known examples, we regularly use cholesterol, blood sugar and blood pressure guidelines to advise patients [Aronow and Banach, 2012; Buyken *et al.* 2007; Daskalopoulou *et al.* 2012; Lenfant *et al.* 2003; Phillips, 2012] and guidelines have even been used to assess the quality of healthcare providers [Cotton *et al.* 2006; Guldberg *et al.* 2011; Kirchhoff *et al.* 2008; Rodondi *et al.* 2006].

In contrast, personalized medicine can be thought of as the broad application of approaches that allow decision making to be based on the individuals'

specific test results and clinical factors rather than being based on global recommendations. Some examples might be use of the cardiac risk score [Armstrong *et al.* 2011; Guzder *et al.* 2005; Nakajima and Nishimura, 2008; Sheridan *et al.* 2003], and the fracture risk assessment tool for osteoporosis (OA) [Johansson *et al.* 2009; Kanis *et al.* 2008], both of which combine testing results with clinical factors. The typical personalized medicine goal falls into a small number of categories (Table 1), including diagnostic, therapeutic, efficacy and safety. Subdivisions of these are readily considered, such as predicting susceptibility *versus* actual current diagnosis.

In order to accomplish these goals, tests of blood, urine or nucleic acids are used to define an individual's personal biotype and thereby make healthcare predictions. The analytes measured are typically referred to as biomarkers [Kraus, 2006; Schatzkin *et al.*; Biomarkers Definitions Working Group, 2001]. Some properties of an ideal biomarker include being generally available in terms of acquiring the sample, but also having readily available testing, being stable in storage, and perhaps most importantly, accurately representing a specific disease pathogenesis or treatment goal [Kraus, 2006].

Correspondence to:
Allen Dale Sawitzke, MD
Internal Medicines,
University of Utah, 30N
1900E SOM, 4B200, Salt
Lake City, UT 84132, USA
allen.sawitzke@hsc.utah.edu

Table 1. Common personalized medicine goals for biomarker use.

Diagnostic	Susceptibility prediction
Therapeutic	Accurate diagnosis
	Define prognosis
	Monitor disease activity and progression
Efficiency	Optimize therapeutic efficacy
Safety	Minimize costs
	Minimize adverse drug reactions

Currently, very few tests function well enough to meet even most of these requirements. Despite this, there are convincing reasons to consider biomarkers as valuable assets in caring for patients with OA [van Spil *et al.* 2010].

The Burden of disease, Investigative, Prognosis, Efficacy and Diagnosis (BIPED) classification of biomarkers as put forward by Bauer and others [Bauer *et al.* 2006] helps to give structure to our thinking regarding biomarkers. It has often been expanded to include a safety category often shown as (s) [Kraus *et al.* 2011]. Although the domains measured are not unique to OA, the acronym BIPEDs may allow us to stand on our own two feet when we talk about personalized medicine and OA. Using this logical structure, markers under development for OA are to be characterized according to relevance to one or more specific areas. For example, one marker might measure aspects of disease burden (B), while also aiding in disease diagnosis (D). The recent overview paper by Kraus and colleagues includes lists of biomarkers, which have accrued enough evidence to support their clinical use [Kraus *et al.* 2011]. For example, urine c-terminal crosslinking telopeptide from type II collagen (uCTX-II) has support for measuring disease burden, prognosis, treatment efficacy and diagnosis (BPED). The future development of markers that perform especially well in one single domain may be the most practicable markers of all as their results would be most readily interpreted. Examples of markers that highlight each of the BIPEDs categories will be used (*vide infra*) as a way to illustrate the current state of personalized medicine in OA.

BIPEDs examples

Diagnosis

Discussion will start with the 'D' of BIPEDs because of the critical importance of defining the phenotype

of interest to any further biomarker discussion. We must first know what we are talking about, that is, a 'biomarker of what'? What can biomarkers tell us about diagnosing OA? As we can see from this partial list (Table 2), many marker associations to OA diagnosis have been described. These include protein-based markers from blood [serum hyaluronic acid (sHA), serum cartilage oligomeric matrix protein (sCOMP)], from urine (uCTX-II) and gene-based markers [Cibere *et al.* 2009; Dam *et al.* 2009a; Deberg *et al.* 2005a, 2005b; Fernandez-Moreno *et al.* 2008; Karsdal *et al.* 2010; Kraus *et al.* 2010; Meulenbelt *et al.* 2006; Rego-Perez *et al.* 2008]. For example, when Sharif and colleagues examined tibiofemoral OA *versus* patellofemoral OA, they were able to show a relationship between elevated serum COMP and tibiofemoral OA, specifically highlighting the diagnostic discrimination that might be obtained using biomarkers [Sharif *et al.* 2006].

Among the strongest gene candidates for OA diagnosis are the interleukin (IL)-1 gene complex, the vitamin D receptor, the cyclooxygenase (cox) 2 genes (PTGS2), double von Willebrand factor A domains particularly in Asians, and growth and differentiation factor 5 (GDF-5) [Chapman *et al.* 2008; Fernandez-Moreno *et al.* 2008; Loughlin *et al.* 2002; Takahashi *et al.* 2010; Zintzaras *et al.* 2010]. Recent meta-analyses have refined and confirmed the strength of these influences [Zintzaras *et al.* 2010]. Table 2 further shows examples of how this type of data is typically reported, listing results for each biomarker, some at different body sites such as hip, knee or generalized, which are in effect surrogates for different diagnostic or phenotypic forms of OA. Many markers also vary with the genetic origin of the patient. For example, the GDF-5 single nucleotide polymorphism (SNP) 143383, in relationship to hip, knee and hand OA has a small magnitude effect with an overall odds ratio (OR) of about 1.26 for OA [Chen *et al.* 2010]. However, the mean OR for OA of the hip in Asians was much higher at 1.78 [Chapman *et al.* 2008].

Table 2. Selected biomarker associations to the diagnosis of osteoarthritis.

Gene/marker	Population	Phenotype specifics	OR	Reference
Serum HA	White	Osteophytosis	NA	Kraus <i>et al.</i> [2010]
Serum COMP		TF knee OA	NA	Kumm <i>et al.</i> [2006]
Urinary CTX-II	White	Radiographic subtypes	NA	Henrotin <i>et al.</i> [2007]; Meulenbelt <i>et al.</i> [2006]
IL-1 gene complex	White	Hip OA		Attur <i>et al.</i> [2010];
		Knee OA	1.22	Loughlin <i>et al.</i> [2002]
GDF-5 snp	White	Knee OA	1.13	Chapman <i>et al.</i> [2008]
rs143383		Hip OA	1.04	
	Asians	Knee OA	1.39	
		Hip OA	1.78	
TLR-9	Asians	Knee OA		Su <i>et al.</i> [2012]
SNP-1486 T			1.66	
SNP-1486 C			0.63	
DVWA	Asians	Knee OA	1.43	Valdes <i>et al.</i> [2009]

COMP, cartilage oligomeric matrix protein; CTX-II, c terminal crosslinking telopeptide from type II collagen; DVWFA, double von Willebrand factor A; GDF-5, growth differentiation factor; HA, hyaluronic acid; IL-1RN, interleukin 1 receptor antagonist; NA, not applicable; OA, osteoarthritis; OR, odds ratio; SNP, single nucleotide polymorphism; TLR-9, toll like receptor 9.

One of the newest gene marker associations with severe OA of the knee is toll like receptor (TLR)-9 haplotypes, defined based on their typing at three SNP sites: 1237, 1486 and 1635 studied in a Chinese patient population. Subjects in which the haplotype sequence is TTA have increased risks (OR up to 1.66) of OA, while those with the TCA haplotype have decreased risks of OA (OR 0.63) [Su *et al.* 2012]. We should recognize that ORs close to 1 complicate our application of markers to individual patients even though the markers may be truly informative. As a consequence, we are forced to think probabilistically rather than absolutely, which will be considered in more detail in the ‘Application/interpretation’ section of this paper.

Burden (B)

The idea of measuring burden is to have a way to summarize the extent of disease. For OA, this concept most likely relates best to a summary of the total number of joints involved, the magnitude of cartilage destroyed, or possibly to a patient’s level of disability. Some markers that have been suggested as effective in assessing OA burden include sCOMP, sHA and uCTX-II [Henrotin *et al.* 2007; Kraus *et al.* 2010]. Similarly, using a slightly different definition of burden, serum type 2 collagen peptide 1 (sColl 2-1) has been suggested as a marker of joint destruction in OA as it rapidly returns to normal after total joint

surgery for an isolated joint affected by OA [Kraus *et al.* 2010].

Investigative (I)

Investigative markers are those that show promising preliminary data but which have not yet accumulated enough data to be categorized solidly into other BIPEDs categories. In some cases these might be already well described markers being looked at for a new ‘indication’.

While it is clear that OA symptoms wax and wane seemingly without any clear reason, it is logical that biomarkers to assess disease activity, perhaps based on messenger RNA microarrays, might be particularly useful to predict these changes. Biswas and colleagues used a bioinformatics approach on publicly available microarray datasets of rheumatoid arthritis and OA samples [Biswas *et al.* 2011] to identify changes in collagenase 1, matrix metalloproteinase 3 IL-6, tumor necrosis factor α , and increased expression of phospholipase C. These markers could be measured either as the protein correlates or as messenger RNA using different techniques. These markers for disease activity or prognosis would currently be characterized as ‘I’. The use of multiple microarray markers directly rather than their associated protein equivalents may soon be more feasible as testing platforms of significantly lower cost are rapidly becoming available.

Figure 1. Likelihood of developing severe osteoarthritis based on a gene marker of interleukin 1 receptor antagonist (IL1RN). Reproduced from Attur et al. [2010] with permission from BMJ Publishing Group Ltd.

Prognosis (P)

Most studies of biomarkers examining prognosis have focused on radiographic outcomes as the measure of worsening that the prognostic markers are subsequently compared with. Several biomarkers have shown benefit in predicting radiologic progression, for example, sColl 2-1 [Deberg *et al.* 2005a, 2005b], uCTX-II [Dam *et al.* 2009a, 2009b], IL-6 [Livshits *et al.* 2009], and IL-1 gene variants [Attur *et al.* 2010]. An example will illustrate how applicable these may be. As shown in Figure 1, patients who have one or more copies of this IL-1 receptor antagonist haplotype (the light bars) have less severe OA as measured by K/L grade at all ages examined [Attur *et al.* 2010]. Consequently, patients bearing only this marker might not need therapy, while the opposite results would suggest the need for a more aggressive treatment strategy as nearly 75% of those in the oldest age range without this marker have a K/L score greater than 2.

Clinical features are also known to be associated with worsened prognosis, including the presence of synovitis, having a larger body mass index (BMI) or more advanced age, and having a history of joint injury [Jiang *et al.* 2011; Zhang *et al.* 2009]. As we will see below, combining clinical and biomarker data may show the most promise in applying biomarkers to clinical issues [Flugsrud *et al.* 2002; Livshits *et al.* 2009].

Figure 2. Cyclooxygenase 2 genotypes and response of dental pain to selected nonsteroidal anti-inflammatory drugs. Reproduced from Lee et al. [2006].

Efficacy (E)

Another frequent clinical question ripe for personalized medicine is ‘What is the best therapy?’ While we all recognize that ‘best’ requires that we balance efficacy and safety, can we pick a therapy based on biomarker results and get the ‘best’ one? Although I was unable to find an OA example, a study of nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat the pain associated with wisdom teeth extraction is very likely illustrative of what we can expect to accomplish in OA.

Figure 2 shows the results for two genotypes of the *cox 2* gene (PTGS2) [Lee *et al.* 2006]. Patients who have only the GG type responded best to treatment with rofecoxib, while those who had at least one 'C' at this site in their typing did best using ibuprofen. The observed differences in pain as measured by visual analog scale were statistically significant and also clinically relevant. These observations help to explaining the common clinical observation that one NSAID helps a given patient, while several other NSAIDs seemingly are of no benefit to that same patient. It is easy to appreciate that testing for a few such markers could change a largely trial and error approach to pain relief into a personalized one in which efficacy is maximized.

Safety [s]

The use of biomarkers to avoid or limit adverse drug reactions (ADRs) has been reasonably productive, perhaps in part due to the clarity of the phenotypes associated with specific adverse events such as associations between NSAIDs, particular human leukocyte antigen types, and development of allergic reactions and chronic urticaria associated with aspirin or NSAID use [Pacor *et al.* 2006; Sanchez-Borges *et al.* 2009]. In treating OA, we would most like to limit the occurrence of peptic ulcer disease, renal insufficiency, allergic reactions and vascular complications. Thus far, examples modifying gastrointestinal or renal ADRs are not available.

Several studies show evidence for the potential of predicting selected cardiovascular outcomes and thereby for modifying a patient's risks. In a master's thesis by Christine St Germaine at McGill University, polymorphisms of three genes *CRP*, *COX-1* and *KLOTHO* were each associated with increased risk of acute coronary syndrome (ACS) among NSAID users [St Germaine, 2008]. The OR was highest for the *COX-1* gene at 6.9. Notice this OR is significantly higher than those observed in association with markers of OA diagnosis. Another study by Brune and colleagues [Brune *et al.* 2008] examined a protein biomarker, N-terminal pro-B-type natriuretic peptide (NT-BNP), as related to *de novo* onset of congestive heart failure (CHF) following initiation of NSAIDs. They observed an OR of 7.41 for patients who initiate a coxib despite having a BNP greater than 100 ng/liter, highlighting how biomarker testing could be used to modify prescribing behavior and thereby avoid selected ADRs. Once again the importance of phenotype definition is

very evident, as the markers most associated with one cardiovascular complication, for example new onset CHF after starting NSAIDs, appear to be different than those associated with another cardiovascular complication, that is, ACS after NSAID initiation.

Application/interpretation of biomarkers

Thus far, I have shown a few examples of biomarkers related specifically to OA. But, to apply the BIPEDs construct to everyday practice, we need to consider how the interpretation part of the process is to be done. For the moment, assume that our list of ideal biomarkers can be readily measured and at a reasonable cost. What do we do with the results? Is there a best way to apply them? Can we use multiple results in a coordinated way? In many ways their interpretation is like our past experience with understanding basic electrolyte measurement. The first level is assessing whether the measured values of sodium, potassium, bicarbonate and so on are in the normal range. However, the value of the test is further increased by use of strategies to combine the measures, for example, by calculating the anion gap [Kraut and Madias, 2012; Porteous *et al.* 2011]. Similar combinatorial analyses have not yet been revealed for most biomarkers, although the use of ratios of cartilage synthesis to destruction markers has been used [Williams, 2009] and combinations of imaging and soluble biomarkers [Dam *et al.* 2009b]. These examples have shown improved accuracy compared with use of individual markers.

Just as the 'normal range' of common analytes like hematocrit is affected by gender, similar effects are likely for biomarkers in OA. One of the best examinations of the effects of demographic variables on OA biomarkers has been done by van Spil and colleagues, who examined 14 biomarkers in a large study of early OA of the hip and knee called the Cohort hip and cohort knee (CHECK) study [van Spil *et al.* 2012]. They were able to show strong statistical relationships between demographic variables (age, gender and BMI) and the levels of some of the biomarkers, thereby suggesting a more detailed application of the tests than normal and abnormal is required.

Examination of current clinical use of gene testing/interpretation might provide further insights as well. Most of us are familiar with interpretation of monogenic disease tests like those used to diagnose sickle cell anemia, in which the sequence

variant is clearly present or absent. We are also increasingly comfortable with tests for oligogenic conditions like hemochromatosis in which compound heterozygotes (one copy of two different mutant alleles) can also be affected by the disease [Santos *et al.* 2012; Speechley *et al.* 2012], but we have only begun to develop abilities to interpret results pertaining to polygenic disorders. These trends apply equally well to other types of biomarker interpretation.

Perhaps surprisingly, asking about family history remains one of the most potent ways to separate patients at most risk for a disease from those who are not at risk [Paynter *et al.* 2010]. Perhaps asking about family history serves to integrate multiple small influences (low ORs) into a single usable score for us. A 'score' in the future that reliably outperforms family history needs to be developed in order to get the maximal benefits from personalized medicine.

Some efforts to develop such a score have already taken place. The study by Livshits and colleagues [Livshits *et al.* 2009] made use of a serum assay result (IL-6) (biomarker) and clinical features [the subject's age and a physical measure (BMI) to stratify a patient's risk for developing radiographic OA of the knee] each plotted on their own axis as a three-dimensional figure [Livshits *et al.* 2009]. All three factors clearly change an individual's risk and importantly the diagrams make it possible to assess each factor's influence on the patient's risk and to look up a particular patient's absolute risk based on their personal factors. However, considering more than a small number of biomarkers with this approach will be quite difficult.

A potential solution to this limitation has been provided by another group: the 'Nottingham knee prediction models' are mathematical models designed to apply what we know about key OA risk factors to predict incident, symptomatic or progressive (increase by K/L grade 1) OA of the knee [Zhang *et al.* 2011]. For example, the equation for incidence of symptomatic OA is $\text{Logit} = -7.733 + 0.56 \text{ age} + 0.29 \text{ female} + 0.089 \text{ BMI} + 0.245 \text{ occupational risks} + 0.543 \text{ family history} + 0.87 \text{ knee injury}$. Inspection of the constants (factor weightings) shows injury followed by family history to be the most important factors to predict development of incident symptomatic knee OA. Receiver operating curves (ROCs) were used to test the equation's effectiveness on several different patient populations. For these tests maximal areas under the curve (AUCs) are desirable

(maximum of 1). The results for this model ranged from 0.6 to 0.79 for the three patient sets. Would better results have been achieved by adding biomarker data to the calculation?

It appears as if it would, as a similar analysis using both gene-based markers and clinical features performed by Takahashi and colleagues showed a simple increase in risk associated with the presence of increasing numbers of risk alleles with a ROC AUC of 0.554, while a ROC on the model based on the risk alleles and clinical factors including age, gender and BMI was more robust, with an AUC of 0.742 [Takahashi *et al.* 2010]. The addition of clinical factors significantly improved the ROC again, suggesting that the tried and true clinical factors are having the largest effect, not the biomarker analysis. This strongly suggests that further synthesis of biomarker results is still required to produce maximal benefits from their application.

Future developments and conclusions

OA is a disease in which biomarkers should enable efforts to achieve optimal clinical care. To date, family history and traditional risks such as prior injury remain the most important predictors of disease, but progress in defining other markers has been rapid. It is most likely that biomarkers will first aid us in minimizing adverse drug reactions, but later will help with selection of treatments for achieving best efficacy.

The tools for testing many biomarkers concurrently are soon to be generally available, but how to use the results in a meaningful way for application by the clinician is still very open to debate. We can draw from one example to think about the options. The University of Chicago has started a 1200 patient study focused on pharmacogenomic markers [Geonomeweb, 2012]. Subjects have to be chronically followed by their team and be on relatively few baseline medications. They are using the traffic light as their communication device, with red, yellow and green icons to let the providers know if the addition of any planned new medication is supported by that patient's genotype information. A red light means that the evidence is against the initiation of the medication. The actual SNPs and genes involved are not important to the care provider and are not reported. Instead a synthetic measure of what the evidence shows is used. Ultimately, integrative measures of biomarkers and clinical data perhaps as an 'OA score' will provide the most benefit to patients. These types

of synthetic measures will be essential to move beyond reporting associations of biomarkers to accomplishing differences in providing OA care.

Acknowledgements

I would like to thank Bioiberica S.A. for their support of my OA research as well as their role in encouraging my development of this material first for use in a talk and then for this manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Armstrong, D., Brouillard, D. and Matangi, M. (2011) The effect of the change in the Framingham Risk Score calculator between the 2006 and 2009 Canadian lipid guidelines. *Can J Cardiol* 27: 67–170.
- Aronow, W. and Banach, M. (2012) Ten most important things to learn from the ACCF/AHA 2011 expert consensus document on hypertension in the elderly. *Blood Press* 21: 3–5.
- Attur, M., Wang, H., Kraus, V., Bukowski, J., Aziz, N., Krasnokutsky, S. *et al.* (2010) Radiographic severity of knee osteoarthritis is conditional on interleukin 1 receptor antagonist gene variations. *Ann Rheum Dis* 69: 856–861.
- Bauer, D., Hunter, D., Abramson, S., Attur, M., Corr, M., Felson, D. *et al.* (2006) Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage* 14: 723–727.
- Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 69: 89–95.
- Biswas, S., Manikandan, J. and Pushparaj, P. (2011) Decoding the differential biomarkers of rheumatoid arthritis and osteoarthritis: a functional genomics paradigm to design disease specific therapeutics. *Bioinformation* 6: 153–157.
- Brune, K., Katus, H., Moecks, J., Spanuth, E., Jaffe, A. and Giannitsis, E. (2008) N-terminal pro-B-type natriuretic peptide concentrations predict the risk of cardiovascular adverse events from antiinflammatory drugs: a pilot trial. *Clin Chem* 54: 1149–1157.
- Buyken, A., von Eckardstein, A., Schulte, H., Cullen, P. and Assmann, G. (2007) Type 2 diabetes mellitus and risk of coronary heart disease: results of the 10-year follow-up of the PROCAM study. *Eur J Cardiovasc Prev Rehabil* 14: 230–236.
- Chapman, K., Takahashi, A., Meulenbelt, I., Watson, C., Rodriguez-Lopez, J., Egli, R. *et al.* (2008) A meta-analysis of European and Asian cohorts reveals a global role of a functional SNP in the 5' UTR of GDF5 with osteoarthritis susceptibility. *Hum Mol Genet* 17: 1497–1504.
- Chen, H., Kraus, V., Li, Y., Nelson, S., Haynes, C., Johnson, J. *et al.* (2010) Genome-wide linkage analysis of quantitative biomarker traits of osteoarthritis in a large, multigenerational extended family. *Arthritis Rheum* 62: 781–790.
- Cibere, J., Zhang, H., Garnero, P., Poole, A., Lobanok, T., Saxne, T. *et al.* (2009) Association of biomarkers with pre-radiographically defined and radiographically defined knee osteoarthritis in a population-based study. *Arthritis Rheum* 60: 1372–1380.
- Cotton, A., Aspy, C., Mold, J. and Stein, H. (2006) Clinical decision-making in blood pressure management of patients with diabetes mellitus: an Oklahoma Physicians Resource/Research Network (OKPRN) Study. *J Am Board Fam Med* 19: 232–239.
- Dam, E., Byrjalsen, I., Karsdal, M., Qvist, P. and Christiansen, C. (2009a) Increased urinary excretion of C-telopeptides of type II collagen (CTX-II) predicts cartilage loss over 21 months by MRI. *Osteoarthritis Cartilage* 17: 384–389.
- Dam, E., Loog, M., Christiansen, C., Byrjalsen, I., Folkesson, J., Nielsen, M. *et al.* (2009b) Identification of progressors in osteoarthritis by combining biochemical and MRI-based markers. *Arthritis Res Ther* 11: R115.
- Daskalopoulou, S., Khan, N., Quinn, R., Ruzicka, M., McKay, D., Hackam, D. *et al.* (2012) The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. *Can J Cardiol* 28: 270–287.
- Deberg, M., Labasse, A., Christgau, S., Cloos, P., Bang Henriksen, D., Chapelle, J. *et al.* (2005a) New serum biochemical markers (Coll 2–1 and Coll 2–1 NO2) for studying oxidative-related type II collagen network degradation in patients with osteoarthritis and rheumatoid arthritis. *Osteoarthritis Cartilage* 13: 258–265.
- Deberg, M., Labasse, A., Collette, J., Seidel, L., Reginster, J. and Henrotin, Y. (2005b) One-year increase of Coll 2–1, a new marker of type II collagen degradation, in urine is highly predictive

- of radiological OA progression. *Osteoarthritis Cartilage* 13: 1059–1065.
- Fernandez-Moreno, M., Rego, I., Carreira-Garcia, V. and Blanco, F. (2008) Genetics in osteoarthritis. *Curr Genomics* 9: 542–547.
- Flugsrud, G., Nordsletten, L., Espehaug, B., Havelin, L. and Meyer, H. (2002) Risk factors for total hip replacement due to primary osteoarthritis: a cohort study in 50,034 persons. *Arthritis Rheum* 46: 675–682.
- Genomeweb (2012) U of Chicago begins 1,200-patient feasibility study for PGx-based genomic prescribing system. Available at: www.genomeweb.com/mdx/u-chicago-begins-1200-patient-feasibility-study-pgx-based-genomic-prescribing-system (accessed 10 December 2012).
- Guldborg, T., Vedsted, P., Kristensen, J. and Lauritzen, T. (2011) Improved quality of type 2 diabetes care following electronic feedback of treatment status to general practitioners: a cluster randomized controlled trial. *Diabet Med* 28: 325–332.
- Guzder, R., Gatling, W., Mullee, M., Mehta, R. and Byrne, C. (2005) Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. *Diabet Med* 22: 554–562.
- Henrotin, Y., Addison, S., Kraus, V. and Deberg, M. (2007) Type II collagen markers in osteoarthritis: what do they indicate? *Curr Opin Rheumatol* 19: 444–450.
- Jiang, L., Rong, J., Wang, Y., Hu, F., Bao, C., Li, X. *et al.* (2011) The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 78: 150–155.
- Johansson, H., Kanis, J., Oden, A., Johnell, O. and McCloskey, E. (2009) BMD, clinical risk factors and their combination for hip fracture prevention. *Osteoporos Int* 20: 1675–1682.
- Kanis, J., Johnell, O., Oden, A., Johansson, H. and McCloskey, E. (2008) FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 19: 385–397.
- Karsdal, M., Byrjalsen, I., Bay-Jensen, A., Henriksen, K., Riis, B. and Christiansen, C. (2010) Biochemical markers identify influences on bone and cartilage degradation in osteoarthritis—the effect of sex, Kellgren-Lawrence (KL) score, body mass index (BMI), oral salmon calcitonin (sCT) treatment and diurnal variation. *BMC Musculoskelet Disord* 11: 125.
- Kirchhoff, A., Drum, M., Zhang, J., Schlichting, J., Levie, J., Harrison, J. *et al.* (2008) Hypertension and hyperlipidemia management in patients treated at community health centers. *J Clin Outcomes Manag* 15: 125–131.
- Kraus, V. (2006) Do biochemical markers have a role in osteoarthritis diagnosis and treatment? *Best Pract Res Clin Rheumatol* 20: 69–80.
- Kraus, V., Burnett, B., Coindreau, J., Cottrell, S., Eyre, D., Gendreau, M. *et al.* (2011) Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. *Osteoarthritis Cartilage* 19: 515–542.
- Kraus, V., Kepler, T., Stabler, T., Renner, J. and Jordan, J. (2010) First qualification study of serum biomarkers as indicators of total body burden of osteoarthritis. *PLoS One* 5: e9739.
- Kraut, J. and Madias, N. (2012) Differential diagnosis of nongap metabolic acidosis: value of a systematic approach. *Clin J Am Soc Nephrol* 7: 671–679.
- Kumm, J., Tamm, A., Veske, K., Lintrop, M. and Tamm, A. (2006) Associations between cartilage oligomeric matrix protein and several articular tissues in early knee joint osteoarthritis. *Rheumatology (Oxford)* 45: 1308–1309.
- Lee, Y., Kim, H., Wu, T., Wang, X. and Dionne, R. (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* 79: 407–418.
- Lenfant, C., Chobanian, A., Jones, D. and Roccella, E. (2003) Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 41: 1178–1179.
- Livshits, G., Zhai, G., Hart, D., Kato, B., Wang, H., Williams, F. *et al.* (2009) Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford Study. *Arthritis Rheum* 60: 2037–2045.
- Loughlin, J., Dowling, B., Mustafa, Z. and Chapman, K. (2002) Association of the interleukin-1 gene cluster on chromosome 2q13 with knee osteoarthritis. *Arthritis Rheum* 46: 1519–1527.
- Meulenbelt, I., Kloppenburg, M., Kroon, H., Houwing-Duistermaat, J., Garner, P., Hellio, Le, Graverand, M. *et al.* (2006) Urinary CTX-II levels are associated with radiographic subtypes of osteoarthritis in hip, knee, hand, and facet joints in subject with familial osteoarthritis at multiple sites: the GARP study. *Ann Rheum Dis* 65: 360–365.
- Nakajima, K. and Nishimura, T. (2008) Prognostic table for predicting major cardiac events based on J-ACCESS investigation. *Ann Nucl Med* 22: 891–897.

- Pacor, M., Di Lorenzo, G., Mansueto, P., Martinelli, N., Esposito-Pellitteri, M., Pradella, P. *et al.* (2006) Relationship between human leucocyte antigen class I and class II and chronic idiopathic urticaria associated with aspirin and/or NSAIDs hypersensitivity. *Mediators Inflamm* 2006: 62489.
- Paynter, N., Chasman, D., Pare, G., Buring, J., Cook, N., Miletich, J. *et al.* (2010) Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA* 303: 631–637.
- Phillips, R. (2012) Controversies in blood pressure goal guidelines and masked hypertension. *Ann N Y Acad Sci* 1254: 115–122.
- Porteous, H., Morgan, N., Lanfranco, J., Garcia-Buitrago, M., Young, L. and Lenz, O. (2011) Systemic lupus erythematosus associated with type 4 renal tubular acidosis: a case report and review of the literature. *J Med Case Rep* 5: 114.
- Rego-Perez, I., Fernandez-Moreno, M. and Blanco, F. (2008) Gene polymorphisms and pharmacogenetics in rheumatoid arthritis. *Curr Genomics* 9: 381–393.
- Rodondi, N., Peng, T., Karter, A., Bauer, D., Vittinghoff, E., Tang, S. *et al.* (2006) Therapy modifications in response to poorly controlled hypertension, dyslipidemia, and diabetes mellitus. *Ann Intern Med* 144: 475–484.
- Sanchez-Borges, M., Acevedo, N., Vergara, C., Jimenez, S., Zabner-Oziel, P., Monzon, A. *et al.* (2009) The A-444C polymorphism in the leukotriene C4 synthase gene is associated with aspirin-induced urticaria. *J Investig Allergol Clin Immunol* 19: 375–382.
- Santos, P., Krieger, J. and Pereira, A. (2012) Molecular diagnostic and pathogenesis of hereditary hemochromatosis. *Int J Mol Sci* 13: 1497–1511.
- Schatzkin, A., Freedman, L. and Schiffman, M. (1993) An epidemiologic perspective on biomarkers. *J Intern Med* 233: 75–79.
- Sharif, M., Granell, R., Johansen, J., Clarke, S., Elson, C. and Kirwan, J. (2006) Serum cartilage oligomeric matrix protein and other biomarker profiles in tibiofemoral and patellofemoral osteoarthritis of the knee. *Rheumatology (Oxford)* 45: 522–526.
- Sheridan, S., Pignone, M. and Mulrow, C. (2003) Framingham-based tools to calculate the global risk of coronary heart disease: a systematic review of tools for clinicians. *J Gen Intern Med* 18: 1039–1052.
- Speechley, M., Alter, D., Guo, H., Harrison, H. and Adams, P. (2012) Effect of ambiguous hemochromatosis gene test results on physician utilization. *Med Care* 50: 394–398.
- St Germaine, C. (2008) Genetic polymorphisms and cardiovascular risk of nonsteroidal anti-inflammatory drugs. Thesis, Department of Epidemiology, Biostatistics and Occupational Health, McGill University Medical Center, Montreal, Quebec, Canada.
- Su, S., Yang, H., Lee, C., Huang, G., Salter, D. and Lee, H. (2012) The (-1486T/C) promoter polymorphism of the TLR-9 gene is associated with end-stage knee osteoarthritis in a Chinese population. *J Orthop Res* 30: 9–14.
- Takahashi, H., Nakajima, M., Ozaki, K., Tanaka, T., Kamatani, N. and Ikegawa, S. (2010) Prediction model for knee osteoarthritis based on genetic and clinical information. *Arthritis Res Ther* 12: R187.
- Valdes, A., Spector, T., Doherty, S., Wheeler, M., Hart, D. and Doherty, M. (2009) Association of the DVWA and GDF5 polymorphisms with osteoarthritis in UK populations. *Ann Rheum Dis* 68: 1916–1920.
- van Spil, W., DeGroot, J., Lems, W., Oostveen, J. and Lafeber, F. (2010) Serum and urinary biochemical markers for knee and hip osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthritis Cartilage* 18: 605–612.
- van Spil, W., Jansen, N., Bijlsma, J., Reijman, M., DeGroot, J., Welsing, P. *et al.* (2012) Clusters within a wide spectrum of biochemical markers for osteoarthritis: data from CHECK, a large cohort of individuals with very early symptomatic osteoarthritis. *Osteoarthritis Cartilage* 20: 745–754.
- Williams, F. (2009) Biomarkers: in combination they may do better. *Arthritis Res Ther* 11: 130.
- Zhang, W., McWilliams, D., Ingham, S., Doherty, S., Muthuri, S., Muir, K. *et al.* (2011) Nottingham knee osteoarthritis risk prediction models. *Ann Rheum Dis* 70: 1599–1604.
- Zhang, Y., Zhang, B., Wise, B., Niu, J. and Zhu, Y. (2009) Statistical approaches to evaluating the effect of risk factors on the pain of knee osteoarthritis in longitudinal studies. *Curr Opin Rheumatol* 21: 513–519.
- Zintzaras, E., Kitsios, G., Ziogas, D., Rodopoulou, P. and Karachalios, T. (2010) Field synopsis and synthesis of genetic association studies in osteoarthritis: the CUMAGAS-OSTEO information system. *Am J Epidemiol* 171: 851–858.