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# Can We Identify Patients with High Risk of Osteoarthritis Progression Who Will Respond to Treatment? A Focus on Biomarkers and Frailty

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**Abstract** Osteoarthritis (OA), a disease affecting different patient phenotypes, appears as an optimal candidate for personalized healthcare. The aim of the discussions of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group was to explore the value of markers of different sources in defining different phenotypes of patients with OA. The ESCEO organized a series of meetings to explore the

possibility of identifying patients who would most benefit from treatment for OA, on the basis of recent data and expert opinion. In the first meeting, patient phenotypes were identified according to the number of affected joints, biomechanical factors, and the presence of lesions in the subchondral bone. In the second meeting, summarized in the present article, the working group explored other markers involved in OA. Profiles of patients may be defined

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according to their level of pain, functional limitation, and presence of coexistent chronic conditions including frailty status. A considerable amount of data suggests that magnetic resonance imaging may also assist in delineating different phenotypes of patients with OA. Among multiple biochemical biomarkers identified, none is sufficiently validated and recognized to identify patients who should be treated. Considerable efforts are also being made to identify genetic and epigenetic factors involved in OA, but results are still limited. The many potential biomarkers that could be used as potential stratifiers are promising, but more research is needed to characterize and qualify the existing biomarkers and to identify new candidates.

### Key Points

Osteoarthritis affects different patient phenotypes with heterogeneous clinical presentation, rate of progression, and response to therapy, and thus appears as an optimal candidate for personalized medicine.

The level of pain, functional limitation, and presence of coexistent chronic conditions including frailty status should be considered to guide treatment decisions.

Magnetic resonance imaging-based diagnosis could be used in drug development and in clinical practice to identify patients more likely to benefit from treatment.

Promising potential biomarkers (e.g., biochemical, genetic, epigenetic) currently under investigations could be used in the near future to guide clinical decision making.

## 1 Introduction

As non-communicable diseases increase with the rise in life expectancy and with the changes in lifestyle, the traditional approach to their management should be reconsidered. Current medicine is still largely based on the ‘one-size-fits-all’ model where patients diagnosed

with the same condition often are prescribed the same medication at the same dose. For some medications, this model potentially can lead to poor response, preventable occurrence of side effects, and increased healthcare costs.

For these reasons, a more patient-centric or personalized approach of medical practice has been proposed and the conventional model is being replaced by new approaches in which the health of the patients can be managed according to their individual biologic or risk factors. The concept of ‘stratified medicine’ refers to this targeting of treatments (including pharmacological and non-pharmacological interventions) according to the biological or risk characteristics shared by subgroups of patients. The potential to use biomarkers for identifying patients with the greatest chance of benefit and the lowest risk of experiencing adverse events in response to a given therapy is anticipated to have a major effect on both clinical practice (e.g., choice of treatment, dosing, or duration of treatment) and the development of new drugs and diagnostics [1, 2].

Osteoarthritis (OA) is a common slowly progressive condition that may affect the structure of all joint tissues, and is a major cause of pain and chronic disability in the elderly [3]. The lack of a universal definition of OA is probably because of the complexity of processes underlying its pathogenesis [4] and to the diversity in clinical presentation, rate of disease progression, pattern of joint involvement, and joint tissue affected [5]. Considering this marked heterogeneity, it appears unlikely that one treatment will benefit all phenotypes of patients. OA thus appears as an optimal candidate for personalized medicine.

The ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) has previously explored a variety of pivotal topics in OA, including the question of how best to define responders to treatment for drug development [4] and the value of magnetic resonance imaging (MRI) in the diagnosis of the disease and the prediction of the hard outcome of joint replacement surgery [6].

An ESCEO working meeting convened in October 2012 discussed the value of biomarkers currently investigated in drug development in OA with a focus on the potential avenues for future research [7]. In 66 relevant publications, numerous candidate biomarkers from multiple sources were identified. Some were considered promising but none of the best candidates has entered clinical use.

In a meeting held in October 2013, an ESCEO-EUGMS (European Union Geriatric Medicine Society) working group discussed the possibility of identifying patients who would most benefit from treatment for OA, to better orientate research and to identify relevant outcomes in clinical trials. Patient profiles were identified according to the

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number of affected joints, biomechanical factors, and the presence of lesions in the subchondral bone [8].

In this second meeting held in May 2014, the working group explored other markers involved in OA that could be used to define patients to be treated, such as imaging, clinical, biochemical, genetic, and epigenetic markers. This is the subject of the present article.

## 2 Process and Outcomes

As in previous initiatives and publications, the ESCEO working group consisted of clinical scientists and experts in the field of OA in academia and the pharmaceutical industry, and representatives of national or European licensing authorities giving their contribution on a personal basis. Members of the group were asked to prepare a full review of the literature on imaging markers (JMP), clinical-biochemical markers (MH), stratified medicine in OA (CC), genetic-epigenetic markers (ED), and the association of OA with frailty status (SM).

They identified relevant articles, reviews, and abstracts in a search of PubMed/MEDLINE and EMBASE for English language articles published between 1990 and October 2014. The initial search strategy included the terms osteoarthritis, risk factor, predictor, progression, guidelines, biomarkers, MRI, and phenotype. Separate sub-searches were also performed using a cross search of the above terms combined, and additional references were selected from the reference lists of selected articles and the presentations made during the working meeting. The narrative is therefore largely based upon expert opinion. Relevant items were selected by the authors according to their quality and pertinence for discussion by the ESCEO working group. After the presentations given at the working meeting, a comprehensive discussion was held within the group and shared conclusions were reached. Two electronic consultation rounds occurred on the draft manuscript to achieve a final consensus.

## 3 Risk Factors for Progression and Predictors of Response to Treatments

### 3.1 Risk Factors for Progression

Increasing our knowledge regarding the predictors of progression of OA is important for optimal treatment allocation and clinical investigations of new therapies [9]. Not all patients will progress symptomatically, radiologically, or to joint replacement and treatments need to be focused to those most at need.

A number of risk factors for the progression of OA have been identified including obesity, radiographic features, biomechanical derangement, multi-joint OA, and synovitis/effusion [10, 11]. In a study on 561 patients, although more than half of the patients had stable Kellgren–Lawrence grades over 15 years, patients with a baseline Kellgren–Lawrence grade 1 were twice as likely to progress as those with a baseline Kellgren–Lawrence grade 0 [12]. A systematic review to identify risk factors for radiographic progression showed that knee malalignment was an independent risk factor for the progression of knee OA [11]. A review of 36 high-quality studies was performed to provide an overview of prognostic factors of knee OA progression [9]. While sex, knee pain, radiologic severity, knee injury, quadriceps strength, and regular sport activities did not seem to be predictive, the best evidence synthesis yielded strong evidence that the serum levels of hyaluronic acid, a marker of synovial inflammation, and generalized OA (i.e., different joints affected at the same time) are predictive for the progression of knee OA [9]. In studies focussing on patient-reported outcomes (pain or activity limitations), as opposed to radiographic progression, prognostic factors that were identified included radiographic, biomechanical, biological, and clinical factors but also psychological and social factors [13, 14]. Most of these findings need to be validated and interactions between individual potential predictors of progression need to be identified, providing a direction for future research.

### 3.2 Predictors of Response to Treatment

However, predictors for progression of the disease and need for treatment may not be the same as the predictors of response to treatment. Current OA treatment includes non-pharmacological therapies, such as physical therapy, weight loss in obese patients or device-based treatments, and pharmacologic therapies, primarily intended to alleviate pain and improve/preserve functional ability. When all previous modalities have failed, surgery such as joint replacement is the main option. A recent algorithm was developed to advise on the possible stepwise approach to the sequence of interventions [15]. All current treatments are symptom-modifying drugs as there are no licensed treatments that prevent the progression of the disease. Disease-modifying OA drugs (DMOADs) have therefore become a major focus of research, but their development involves a number of difficulties, including slow disease progression and a lack of sensitivity of tools recommended by the regulatory agencies [16]. The current treatments (except for joint replacement) have at best modest albeit clinically relevant efficacies, and are sometimes associated with substantial side effects or costs [17]. Part of this modest efficacy might be explained by the inclusion of

heterogeneous groups of OA patients in trials. This highlights the need to identify subgroups of patients who might be responsive to current treatments. Furthermore, all treatments have associated side effects, stressing the importance of focusing therapy to patients with the adequate phenotype.

## 4 Imaging Markers

Radiography is the most commonly used technology and is recommended by regulatory agencies for assessing DMOAD. Although radiography has weaknesses, including a poor sensitivity to changes in cartilage width, it is cheap and accessible and has been shown to predict the progression of OA and response to some intra-articular and oral treatments. The main limitation of plain radiography is its inability to assess other important joint structures such as the synovium, meniscus, and bone marrow lesions (BML). Important progress has been made in the development of MRI technology allowing direct, precise, and reliable assessment of multiple tissues and their changes over time targeting mostly hip and knee OA. MRI has been extensively used in a number of studies assessing cartilage volume loss, BML, synovial membrane thickness, meniscal extrusion, Hoffa's fat pad and, less extensively studied, synovial fluid effusion size.

### 4.1 Extent of Cartilage Damage

A number of studies suggest that MRI may assist in delineating different phenotypes of patients with OA. Some clinical trials have assessed the effect of drugs on articular structural change over time in patients with knee OA including licofelone [18], chondroitin sulfate [19], strontium ranelate [20], and sprifermin [21]. In these trials in patients at a moderate to severe stage of the disease, these agents were shown to have a beneficial effect on cartilage volume loss, which was mostly seen at the lateral compartment. In a study using data from the OsteoArthritis Initiative progression cohort, glucosamine plus chondroitin treatment significantly reduced the cartilage volume loss, predominantly in patients with mild to moderate knee OA, but showed no protective effect in those with already severe disease [22].

This study also suggests that in patients with less extensive cartilage damage, treatment provided protection in both medial and lateral compartments.

### 4.2 Presence of Bone Marrow Lesions

MRI has also been used in a number of studies to select knee OA patients with BML.

A proof-of-concept trial in knee OA patients evaluated the effect of zoledronic acid, a bisphosphonate, on BML change at 1 year. Although data showed a significant reduction in BML size at 6 months, and a numerical trend towards a reduction at 12 months, the cartilage volume and cartilage loss were not assessed [23]. However, other putative DMOADs were tested for their effects on the change over time of both BML in the medial compartment and cartilage volume. Two such drugs were studied, licofelone [18] and strontium ranelate [20]. In general, data showed a strong association for the compounds tested between BML change and cartilage volume loss in the same or related topographical site.

### 4.3 Presence of Meniscal Extrusion

Although the presence of meniscal extrusion has been shown to be associated with greater cartilage volume loss and to be a strong marker of OA progression [23, 24], to our knowledge there has been no clinical trial using MRI investigating the effect on meniscal extrusion of drug response to treatment. However, post hoc analyses of studies exploring the effect of putative DMOADs (licofelone [18], strontium ranelate [25], and chondroitin and glucosamine sulfate [26]) and one study looking at the presence of meniscal extrusion in knee OA patients with neuropathic pain [27], argue in favor of an MRI-based diagnosis of meniscal extrusion in clinical practice. This would help physicians identify knee OA patients who are more likely to benefit from treatment, namely those with mild to moderate OA with meniscal extrusion, or those with more symptomatic disease but without meniscal extrusion. Moreover, co-localized knee structural pathologies such as meniscal extrusion/damage and BML further increased the risk of cartilage loss [25, 28] highlighting that the response to treatment of knee OA patients can be greatly influenced by the presence or absence of multiple risk factors associated with the progression of structural changes.

## 5 Clinical and Biochemical Biomarkers

### 5.1 Clinical Biomarkers

Among useful clinical markers, the most important and obvious are the presence and severity of pain and of functional limitation, which are the primary indications of licensed medications in OA. Demographic factors (age, sex, menopause, race/ethnicity, marital status, education) are important in terms of predicting the need for total joint replacement but have no role in evaluating the efficacy of a clinical intervention. As discussed in a previous ESCEO

meeting, the presence of abnormal biomechanics or severe malalignment may indicate the use of a certain class of treatment and predict the lack of efficacy of interventions (e.g., weight loss or doxycycline [29]) on structural progression. Inflammation (presence of effusion and/or soft-tissue swelling) is a predictor of progression to total joint replacement [30]. Some inconsistent data suggest that the presence of effusion is predictive of the efficacy of an intra-articular corticosteroid joint injection [31]. Polyarticular joint involvement is a predictor of OA progression, not necessarily of the clinical response.

## 5.2 Biochemical Biomarkers

A systematic review of serum and urine biomarkers in knee and hip OA provides an overview of publications on biochemical markers performance [32]. Data were categorized according to the five categories of the BIPED classification proposed by the National Institutes of Health (NIH)-funded OA Biomarkers Network [33]: Burden of disease, Investigative, Prognosis, Efficacy of intervention, and Diagnostic. A total of 26 biochemical markers were identified, 15 concerned collagen metabolism, eight related to collagen type II degradation (CTX-II, HELIX-11, C2C, Coll2-1, Coll2-1 NO(2), TIINE) and synthesis (PIIANP, PIICP), five to collagen type I degradation (NTX-1, CTX-1, ICTP) and synthesis (PICP, PINP), one to collagen type I and II degradation (C1, 2C), and one to collagen type III synthesis (PIIINP). It was concluded that none of the current biochemical markers, of cartilage, bone, or synovial metabolism, is sufficiently discriminating to aid diagnosis and prognosis in individual patients with OA, to facilitate the design of clinical trials or to act as a surrogate outcome used as an additional secondary endpoint. This is a view shared by the ESCEO working meeting on biomarkers [7]. However, it must be taken into account that the current perceived limitations in the use of biomarkers stems in part from the limited tools available for their qualification, i.e., the means of establishing the context in which they are validated.

A nested case-control study of progressive knee OA within the OsteoArthritis Initiative has been initiated by the Foundation of NIH OA Biomarkers Consortium to determine the biomarkers with optimal predictive validity and responsiveness for progression of knee OA [5]. The 12 assessed biochemical markers are related to cartilage degradation (CTX-II, C1, 2C, C2C, Coll2-1NO2 in urine and COMP, C1, 2C, C2C, CPII, PIIANP, CS846, MMP-3 in serum), bone resorption [serum and urine NTX-I and CTX-I], and synovitis (serum hyaluronic acid (HA)). The next step should be the qualification of the most promising markers, either prospectively or using data from completed clinical trials.

## 5.3 Genetic and Epigenetic Markers

New technologies are now available to investigate the link between cellular mechanisms and the disease phenotypes, including the omics approach (genomics, transcriptomics, proteomics, epigenomics, microbiomics, metabolomics) the exposome (the combined exposures from all sources received by a person during life), new non-hierarchical approaches to phenotyping complex disease (e.g., cluster analyses), applications of informatics to interrogate large data-sets from biological collections, clinical trials, and linked population-based case records and prescribing practice.

A genetic component to OA in most of the large joints has been established [34]. Recent developments of the identification of the susceptibility genes for OA by using different approaches including genome-wide association studies, family-based studies, and extreme OA phenotypes have been recently reviewed, showing rapid progress in the knowledge of genetics of OA. Despite numerous efforts made on human genetic studies worldwide, only a few numbers of loci have been associated with OA. This might be attributed to several factors such as insufficient sample sizes and disease heterogeneity that might result from different underlying causes, both genetic and environmental, depending on which joints are affected [35]. OA is a complex polygenic disease that lacks any large-effect susceptibility loci. Instead, OA susceptibility alleles individually contribute only modestly to the overall disease risk, making their identification challenging. Although the success of genetic studies is still limited, recent data suggest that epigenetic mechanisms may be heavily mechanistically involved [36].

## 5.4 Genetic Biomarkers

In a recent meta-analysis of nine genome-wide association studies using Human Genome Epidemiology (HuGE) navigator in patients with knee and hip OA, only 2 of the 199 candidate genes considered were shown to be associated with hip OA: COL11A1 (collagen, type XI, alpha 1) and vascular endothelial growth factor (VEGF, signal found only in men) [37].

Other examples are:

- That genetic modification of the SMAD3 gene was found to be associated with hip and knee OA in European populations [38], and also with hand and knee OA in a northeast Chinese population [39];
- TRPV1 (transient receptor potential cation channel, subfamily V, member 3) and COMT (catechol-O-methyltransferase) variants are involved in the perception of pain in knee OA [40, 41];

- FTO (fat mass and obesity-associated) signal is robustly associated with BMI, and showed evidence of association with OA underpinning the known epidemiological link between BMI and OA [42];
- The IL1RN (interleukin-1 receptor antagonist) C-T-A haplotype may have a role in severe knee OA which is consistent with the possible role of IL-1 as a regulator of cartilage degradation [43];
- COL11A1, which could play a role in erosion of joints cartilage in OA, is a strong candidate gene for OA [44];
- GDF5 (Growth and differentiation factor 5), to promote the development, maintenance, and repair of joint tissues is associated with OA of the knee with genome-wide statistical significance [45];
- The Semaphorin 4D (Sema4D) gene region may play a role in the etiology of acetabular dysplasia [46], a multifactorial disease that has been shown to increase the risk of OA [47].

Moreover, studies are being set up to unravel the genetic causes of OA, including a 5-year study by Arthritis Research UK focusing on rare genetic variants that lead to the development of OA, and looking at how they interact with environmental factors to increase the risk of developing OA.

## 5.5 Epigenetic Biomarkers

Although limited compared with genetic studies, epigenetic studies suggest that post-transcriptional regulation of gene expression might play a substantial role in OA progression. In particular, microRNA-mediated mechanisms have been found to be differentially expressed in normal and OA cartilage [48, 49] and offer potential diagnostic and therapeutic strategies, which need to be further investigated.

## 6 Frailty and OA

### 6.1 The Frailty Phenotype

In patients with OA, the presence of coexistent chronic conditions, particularly heart disease, pulmonary disease, and obesity, increase markedly the likelihood of subsequent disability [50]. Consequently, there is a need to assess comorbidity, which is one of the main risk factors for frailty.

There is a growing consensus that comorbidity, disability, and frailty are distinct clinical entities with distinct prevention and therapeutic issues, important overlap, and a causal relationship [51]. Frailty is generally described as “a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors” [52]. There

are two main ways of defining frailty: the Cardiovascular Health Study index [53] defines frailty as a clinical syndrome in which three or more of the following phenotype indicators are present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Alternatively, the Geriatric Status Scale [54] combines aspects of cognitive and functional performance to describe various degrees of frailty from “robust” to “severely frail” to predict death or need for institutional care.

In the SHARE study, a multidisciplinary European Union Research project, the prevalence of frailty and pre-frailty in 18,227 randomly selected community-dwelling men and women aged 50 years and older reached around 10 and 50 %, respectively [55]. In four large prospective cohort studies, frailty was shown to be associated with all negative outcomes (falls, disability, hospitalization, home care admission, mortality) [56]. A study based on data from cohorts of community-dwelling persons aged 65 years or older showed that adding frailty markers to age, sex, and chronic diseases provided an increase in the patient-level prediction of disability [57]. The increase was modest but worthwhile because frailty is potentially a reversible condition when effective interventions are put in place [58]. There is thus an urgent need to identify pre-frail and frail older adults to prevent rapid disability in our OA aging population [59].

### 6.2 Association of OA with Frailty Status

Comorbidity and frailty status affect the treatment of OA in many different ways, including the ability to adhere to exercise, polypharmacy (with the potential for drug–drug interactions and increased risk of adverse events), medical contraindications, worsening of quality of life, and mood disorders such as depression and anxiety that can accompany any chronic condition. Several studies have recently examined the association of OA with frailty, all suggesting that the frailty status should be assessed when considering treatment of OA, as it may be essential in targeting therapeutic interventions. The EPOSA study (2942 patients aged 65–85 years) showed a significant association between clinical OA at any site and frailty status (preliminary results). In a cohort of 4130 men aged over 65 years, hip OA and total hip replacement were found to be associated with greater frailty, suggesting that interventions to reduce frailty should be evaluated in these patients [60]. People with lower extremity OA had a two to five times increased incidence of falls than age-matched healthy controls [61]. The mechanisms underlying this increased risk are not clear but could involve poor physical performance, loss of proprioception, and impaired balance [62, 63]. Another study showed that clinical frailty significantly

predicted mortality in subjects with OA. Thus, clinical frailty may be considered a new prognostic factor to identify subjects with OA at high risk of mortality [64].

The intervention will need to be targeted to the exact phenotype of the frailty identified.

### 6.3 Ongoing Projects with a Strong Potential for Synergies and Complementarities in the Fields of Frailty and OA

There are several international projects in progress that have the potential to further advance the importance and understanding of the interaction between OA and frailty. The Innovative Medicines Initiative (IMI), a joint undertaking between the European Union and the pharmaceutical industry association EFPIA, is supporting the SPRINTPROJECT (Sarcopenia and Physical Frailty in older people: multi-component treatment). The IMI is additionally funding the APPROACH (Applied Public–Private Research enabling OsteoArthritis Clinical Headway) project, which will enhance the collective knowledge base around OA biomarkers and disease as well as build stronger collaborations among academic and industrial groups to enable effective therapeutic development. The “European Innovation Partnership on Active and Healthy Ageing” project promotes systematic routine screening for pre-frailty stages in at-risk patients and older people using the Multidimensional Prognostic Index [65]. This index is a multidimensional tool measuring frailty and prognostic indicators in health-related outcomes.

## 7 Conclusions

Our increasing knowledge of disease and drug mechanisms has led to the understanding that the heterogeneity in disease expression and response to therapy is the result of differing underlying pathological mechanisms, as well as other individual patient features that influence treatment efficacy and tolerability. Considering the heterogeneous nature of OA, the very large number of affected individuals, and the need for new efficient and safe treatments, OA appears as an optimal candidate for personalized healthcare [66].

The ultimate aim of these discussions of the ESCEO working group was to explore the value of (bio)markers of different sources in defining different phenotypes of patients with OA. The characterization of the OA patient phenotype could be used to guide clinical decision making. Optimizing the selection of patients for whom an intervention with a DMOAD could prevent the development of OA would assist the emergence of personalized or precision medicine for these patients.

A research agenda for the identification of patient phenotypes was proposed (Table 1). This approach should lead to the definition of a risk score, allowing the categorization of patients according to their risk for structural or clinical progression. This should include all possible predictors, possibly including an aggregate of different (bio)markers.

As part of this agenda, it was felt important to recommend a core data set that should be collected in future studies of OA that assesses the natural history of the disease and the response to treatment. This will allow more standardized assessment and collation of cohorts and databases in the future. Following the meeting, the working group produced a recommended list of core data, presented in Table 2, which was based on the evidence provided at the meeting and individual expert opinion.

Profiles of patients may be defined according to their level of pain, functional limitation, and presence of co-existent chronic conditions including frailty status. Moreover, converging data argue for an MRI-based diagnosis in clinical practice to help physicians identify patients who are more likely to benefit from treatment. More research is required, however, to validate these preliminary findings and to correlate improvements with hard clinical endpoints.

Among potential biochemical biomarkers, despite active research and numerous candidates, none is sufficiently validated and recognized for systematic use in drug development of OA or in clinical practice to identify patients who should be treated. Among current investigations, the Foundation of NIH OA Biomarkers Consortium has established and initiated a process for validation and qualification of the most promising commercially available biomarkers in OA [5]. This approach will support new drug

**Table 1** Research agenda for the identification of patient phenotypes

Identify published randomized clinical trials and observational cohorts assessing the efficacy of different class of interventions on clinically relevant outcomes, divided in structural and symptomatic outcomes
Using above data, produce clinical prediction tools to quantify a patient’s risk of progression and good outcomes from treatment interventions
With available data, identify phenotypes of patients according to their outcome. Panel of (bio)markers (clinical, biochemical, imaging) should be investigated, rather than individual items
Assess the uniformity of data across clinical trials and cohorts
Proceed to a validation step on a separate validation cohort
Ensure that all new cohorts and trials use the same core dataset to allow easy integration into extant data
Possible limitations:
The availability of the data and of the biological specimens in cohorts
The high heterogeneity in the assessments methods and reporting (e.g., multiple assessment tools for pain), which would require a hierarchical/standardization of criteria



**Table 2** Minimum core data set

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Age [67]
BMI [10]
Sex [67, 68]
Racial origin [69]
Occupation [70]
Comorbidities [71]
Menopausal status [72]
Presence of chondrocalcinosis [73]
Baseline pain and function [13, 74]
OA pain in other joints [10]
Possibly meniscal extrusion in the target knee [23, 24]
X-ray grade of target joint [10]
OA medication use (analgesia and disease modification)
Previous joint surgery (in particular meniscectomy) [75]
Persistent inflammation or effusion [30, 31]
Trauma in the elderly [76, 77]

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*BMI* body mass index, *OA* osteoarthritis

developments, preventive medicine, and medical diagnostics for OA.

In the future, identification of genes associated with OA may help reveal underlying biological mechanisms that lead to the development of new therapeutic targets or biomarkers for early detection and risk stratification. Considerable efforts are being made to identify genetic and epigenetic factors involved in OA that could be used as potential stratifiers, but results are still limited. However, with new technologies, diagnosis will increasingly focus on integrating information for multiple sources, not only genomics and other omics technologies but also environmental and lifestyle data.

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