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Perspective

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Novel approaches to the stratified management of knee osteoarthritis

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Abstract

Knee osteoarthritis is a highly prevalent whole-joint disease that is associated with substantial morbidity. If step changes are to be made in the management of knee osteoarthritis, novel patient stratification approaches are needed to identify the most effective treatment for individual patients. Numerous methods for stratifying patients with knee osteoarthritis can be employed; clinical presentation, including co-morbidity and pain phenotype, can influence treatment decisions, and there is a rich history of imaging biomarker use, both from conventional radiographs and, since its development, via MRI, in identifying patients at risk of disease progression, and the latter facilitates the detection of synovitis. The development of novel biochemical biomarkers and the rapid growth of '-omics' technologies provide fresh opportunities to deploy these advances in the stratification of patients with knee osteoarthritis. The health economic landscape in this area is developing, and scoping work has highlighted the need for further studies.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis, with knee OA alone affecting approximately 654 million individuals worldwide[1], with a lifetime risk of 44.7% (ref. 2). OA has substantial effects at the patient level owing to its association with pain, loss of mobility and disability, and at a population level, by placing a huge financial burden on health systems[3]. These burdens are set to rise, with increasing prevalence each year from 1990 to 2019 observed across a diverse selection of 21 geographic regions, and this trajectory is expected to continue[4]. The prevalence of knee OA is higher in those countries with higher socio-demographic indices; however, some of the greatest percentage increases are observed in Africa, South America, the Middle East and South-East Asia[4].

Although OA can affect many different anatomical joints[4,5], knee OA has the highest incidence[5] and is the focus of this article. Knee OA affects women more than men[4] and the incidence peaks above the age of 70 years[5]. Since it was first described, there have been various classification criteria for OA[6,7] (Box 1) with only moderate overlap between the patients that these criteria identify[8]. As well as discrepant performance, these criteria also only identify those with established disease and substantial steps are underway to define 'early OA' so that those individuals at risk of progression can be treated early and their disease trajectory improved[9,10].

Given the immense global impact of knee OA, patient stratification methods need to be developed so that treatments can be targeted to those with the greatest need, those who stand to benefit the most and those who are currently neglected owing to health inequity.

Box 1 | The definition of osteoarthritis

One of the earliest historical descriptions of osteoarthritis (OA) dates back to William Heberden in the latter part of the eighteenth century, when he described the changes in the interphalangeal joints of the hands that were not fluctuant, which would indicate the inflammatory effusions related to 'the gout', but were instead 'hard knobs', indicating the osteophytes now known as Heberden's nodes[92]. Since then, OA has been defined as relating to degradation of cartilage, but this definition alone might not do justice to the other tissues within the joint, which are implicated in the pathogenesis of OA, including the synovium and bone. Indeed, in this Perspective article, the synovium is highlighted as a tissue strongly predictive of pain but also of radiographic and clinical progression, even of arthroplasty, and as such surely needs to be considered in the characterization of the disease. Key OA primary-outcome measures vary, which makes comparison between biomarker studies difficult. The definition of OA is still debated and there are even calls to acknowledge the wide aetiology and broad number of disorders associated with the condition[93] by renaming it 'systemic osteoarthritis'[94]. Considering that the current definition of OA produces a broad umbrella term under which sit numerous subtypes, phenotypes, endotypes and theratypes is important. This definition is acceptable, provided that these subtypes are recognized and distilled in future research; if not, the field of OA might become stifled as it attempts to develop, regulate and deploy the right intervention for the right patient.

International guidelines provide recommendations to navigate the available treatments for knee OA[11–13] and advocate for a multi-modal approach to management[14], but the disease-modifying benefits of such therapies are often limited. Currently guidelines do not take advantage of the numerous technological and life-science developments, which, if harnessed correctly, might enable the stratification of patients with OA, with the aim of optimizing the entire clinical process, from diagnosis to treatment. Indeed, as the field of disease-modifying OA drugs (DMOADs) moves forward, methods of stratifying patients for treatment will be required, and to begin with, these interventions will probably be marketed at a substantial financial cost. In the field of OA, biomarkers can potentially be used to assess disease status (via imaging or clinical symptoms), disease activity (via biochemical biomarkers but also imaging) and for the development of therapeutics and monitoring of treatment effects. In June 2024, the European Society for the Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) convened a working group consisting of patients, rheumatologists, orthopaedic surgeons, researchers, regulatory experts and health-economic specialists. The purpose of this working group was to analyse the latest literature and leverage expert opinion to review which novel approaches should be considered in the stratified multimodal management of knee OA.

In this Perspective article, we explore the issue of stratification by scrutinizing the current definitions of knee OA, mapping the regulatory landscape, examining how biochemical, '-omics' and imaging biomarkers are being used to identify subsets of patients with knee OA, highlight how novel methods of cell culture could be used to assist with treatment targeting and scoping the health-economic implications of treatment stratification. In reviewing these topics, we aim to illuminate how these developments can be used to strategically stratify patients with knee OA and address this important issue of health equity.

The regulatory landscape

The current regulations for the treatment of OA come from the EMA[15] and the FDA[16]. These recommendations have slightly different approaches and might require updating in the light of new developments in the field of OA.

The 2010 EMA recommendations

The current European recommendations for the clinical investigation of medicinal products used in the treatment of OA were published by the EMA in 2010 (ref. 15) in which, the pharmacological treatment of OA is divided into two categories: symptom-modifying drugs (including fast-acting dugs for acute flares, such as NSAIDs, corticosteroids and symptom-modifying slow-acting drugs, such as symptomatic slow-acting drugs for OA) and structure-modifying drugs (which affect the structural progression of OA). These structure-modifying medicines can be divided further into those that affect structural progression alone or those with an associated effect on symptoms.

The 2018 FDA recommendations

A draft guidance for industry on structural endpoints for the development of OA treatments was published by the FDA in 2018 (ref. 2). These recommendations replace previous guidance and focus on the potential endpoints to be used for investigating treatments that inhibit structural damage or target the underlying pathophysiology of the disease. This rather short document does not address improvement of symptoms of OA and gives no detailed recommendations on study population, statistical analysis or clinical trial design.

Participants

Participants selected for OA treatment studies should, according to the current EMA guidelines, have both symptomatic and structural changes in the target joint, with radiographic evidence (via Kellgren–Lawrence criteria) and meet American College of Rheumatology[6] or European Alliance of Associations for Rheumatology[7] diagnostic criteria. These selection criteria enable both symptomatic and structural elements to be assessed in clinical trials. The EMA guidelines state that findings from studies of the lower limb (hip and knee) OA should not be extrapolated to hand OA owing to pathophysiological and functional differences, and that in studies that include only lower-limb OA, subgroup analyses of knee and hip OA should be performed and presented. Owing to the different presentations and natural history of OA across the life course, the importance of stating the age distribution of the study population is emphasized. Populations with 'special characteristics' (such as individuals who have undergone a meniscectomy or women with obesity and unilateral radiographical OA) that are consistent with high risk of progression of OA were suggested; however, despite these being interesting and valid populations to investigate, the ability to generalize the findings from such trials to the general OA population is potentially limited.

Endpoints

The endpoints included differ for symptom-modifying and structure-modifying drugs as indicated in the EMA guidelines. The primary endpoint for medications aimed at improving symptoms is pain intensity, as measured by a validated self-assessment tool. Functional disability should be a co-primary endpoint, measured by validated joint-specific measures. Secondary endpoints should be devised according to the pharmacological profile of the medication (such as onset of action or percentage of people who respond to treatment).

In the EMA guidelines, radiographic joint-space narrowing (JSN), which is shown in epidemiological studies to correlate with the subsequent need for total joint replacement, is mentioned as an acceptable primary endpoint for those medicinal products aimed at improving structure[15]. If this endpoint is chosen as primary over the generally preferred clinical outcome measures (such as time to necessity of virtual or actual joint replacement), the clinical relevance of radiographic change should be pre-specified and its validity as a surrogate parameter should be strengthened by an improvement in pain and function. Importantly, radiographic technique should be standardized, precise and accurate, with central reading of films and measuring of parameters. Secondary endpoints include MRI outcomes to evaluate cartilage and biochemical biomarkers (from serum and urine) to measure progression of disease or evaluation of response to the medicinal intervention. The challenges in developing robust structural endpoints for OA are attributable to the marked discordance between clinical symptoms and radiographic severity of the disease, combined with a dearth of standardized agreement on what constitutes clinically relevant disease progression. For this reason, the FDA also requires structural endpoints to be aligned with clinically meaningful outcomes[16], eventually demonstrating a halt or slowing of progression to severe disease.

According to the FDA, this clinically meaningful approach should establish a substantial delay in the need for joint replacement and slow the worsening of pain and deterioration of function. The concept proposed could best be reflected in a composite primary endpoint of total knee replacement rates together with thresholds of unacceptable pain and disability defining severe disease, measured particularly via patient-reported outcome measures (PROMs), including Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscales. These PROMs are also acceptable to confirm efficacy for an indication of 'pain of OA' in studies of shorter duration than required by the EMA, which is at least 12 weeks for a double-blind trial of therapy[17].

Therapeutic confirmatory studies

Therapeutic confirmatory studies should be placebo controlled but there are nuances in the recommendations for symptom-modifying and structure-modifying medications defined in the guidelines from the EMA.

The EMA recommendations state that studies of symptom modification should ideally include an additional third study arm for an established active comparator, and patients should be sufficiently symptomatic at baseline (for example, with a visual analogue scale (VAS) score for joint pain of at least 40 mm out of 100 mm). The efficacy (that is, the change in symptom intensity) and subsequent maintenance of improvement should be repeated and evaluated over the course of the study, depending on the time needed for the onset and duration of action of a treatment; monitoring for coincident structural changes should be tracked for at least 1 year.

Studies of structural modification should be longer-term (at least 2 years), with recruited patients having established radiographic knee OA (Kellgren–Lawrence grade 2 or 3) to ensure sufficient baseline joint space width to determine potential effects on JSN, with efficacy of the intervention determined via clinical variables (necessity for joint replacement, time to surgery and long-term clinical evolution of pain and disability), or on structural changes, whereby the clinical surrogacy of the change is proven.

The FDA has not yet approved structural biomarkers from MRI as validated endpoints for structure-modifying interventions[16]. However, the FDA does recognize that the ultimate goal of treatments related to structural damage inhibition (or targeting the underlying pathophysiology associated with OA) is to avoid (or substantially delay) the complications of joint failure and the need for joint replacement, and also to reduce the deterioration of function and worsening of pain.

Notably, the FDA considers OA to be a severe condition, meaning that initial clinical trials for OA interventions can be shorter (1–2 years) and approval can be accelerated depending on the surrogate endpoint used. Phase III studies are then performed once the product is on the market, to confirm the adequacy of the surrogate endpoints.

Implications

The EMA and FDA recommendations (Table 1) might now be outdated as they do not consider new developments in the phenotyping (the observable characteristics or outward expression of a disease) and endotyping (the identification of subtypes, which are defined by distinct biological or molecular mechanisms and identified via specific biomarkers) of OA. Indeed, these guidelines focus on one general phenotype of OA progressing to one clinical outcome (arthroplasty) and fail to provide a consensus approach to the identification of 'early OA', when disease trajectories might be more amenable to manipulation by a therapeutic intervention[10] (Fig. 1).

Importantly, PROMs should be measured against an active comparator rather than against baseline levels, as the latter have been shown to be susceptible to artefactual findings via regression to the mean[18].

Since publication of these guidelines, however, progress with novel interventions for OA has been slow and there is yet to be a step-change development in this area, with safety concerns surrounding past

Table 1 | Comparison of EMA and FDA guidelines for the assessment of interventions for osteoarthritis

	EMA guidelines[a]	FDA guidelines[b]
Treatment aim	Improvement of symptoms Prevention of structural damage	Inhibition of ongoing structural damage
Study population	Patients with both symptomatic and structural changes in the target joint Possibly patients at a high risk of or with rapidly progressive OA	Potential use of enrichment strategies, with studies in models of accelerated OA, and innovative trial designs[17]
Primary endpoints	Symptom modification, including improvement in pain and function Conventional radiography for measurement of JSN and/or clinical endpoints (time to joint replacement, pain and disability) to demonstrate structural improvement	Conceptual approach with a composite endpoint of total knee replacement rates and unacceptable levels of pain and disability to meet the definition of severe disease[17]
Study duration	At least 1 year for symptom modification At least 2 years for structure improvement	Approximately 2 years or more for prevention of progression[17]

[a]Title of EMA guidelines: Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis. [b]Title of FDA guidelines: Osteoarthritis: structural endpoints for the development of drugs, devices and biological products for treatment. This table summarizes the aims, study population, primary endpoints and study duration recommendations from the EMA and the FDA. OA, osteoarthritis; JSN, joint space narrowing.

interventions that target symptoms, such as monoclonal antibodies that target nerve growth factor[19]. This slow progress is also reflected in the FDA recommendations[16] and underscores the unmet need for treatments to target disease progression and improve the outlook for patients with OA.

As the above discussion demonstrates, the current regulatory perspective of stratification is limited and could be developed using novel approaches.

Patient preferences for treatment

When deciding who to treat for OA, taking into account the perspective of the patient is vital[20]; it is particularly important to consider the preferences and expectations that each patient might have regarding OA treatment. This approach should ideally be performed in a patient-centred model of care.

Patient-centred care shifts the focus towards the individual patient, aiming to maximize overall health and well-being and tailoring the clinical approach accordingly. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defined patient-centred care "as an approach that facilitates engagement and partnership of patients in all stages of health-related care delivery to improve health care access and patient outcomes", which emphasizes the need to empower patients in decision making and respect their wants, needs and preferences[21]. Education is a cornerstone to achieving patient-centred care and clinicians should aim to 'expertize' patients in the conditions that affect them, promoting autonomy in care decisions through enhanced health literacy[22]. Guidelines and recommendations, therefore, should not be rigid and cast-iron, but flexible and accommodating of a personalized approach to each and every patient.

When clinicians consider the best management strategy for their patient, achieving a patient-centred approach means that they must take into account the preferences of that patient[20]. These preferences can include (but are not limited to) reduced pain, improved function, enhanced mobility, increased quality of life, the prevention of disease progression and an absence of serious or severe adverse effects[20,23]. In attempting to minimize adverse effects, clinicians must be aware that patients prioritize treatments with fewer adverse effects and tend to prefer non-surgical management initially, with operative intervention saved as a last resort.

Patient preferences should be integrated into treatment plans via shared-decision-making (whereby patients and health care providers collaborate to co-develop treatment strategies) and patient decision aids, which can improve understanding and engagement in this context[24]. When developing a treatment plan considering the following framework can be helpful: knowledge, values, support and certainty.

'Knowledge' refers to the importance of considering the baseline knowledge and educational needs of the patient, including the benefits, risks and unknowns of any interventions being considered. 'Values' highlight the need to identify which benefits and risks matter most to the patient. 'Support' emphasizes the necessity to ensure that they have credible, trusted advice (that is, from family or friends) and provide this advice if not available. 'Certainty' means clarifying which aspects of the decision-making process are particularly difficult. Promoting a healthy lifestyle is, of course, an appropriate aspiration, but providing a patient with the steps and social, employment and emotional support by which to achieve this lifestyle is far more effective[24]. These points should be emphasized when providing advice on weight management, exercise and on seeking further disease education.

Patient preferences in OA management are shaped by a complex interplay of factors, including prior treatment experiences, perceived treatment efficacy, comorbidity burden, cultural beliefs, health literacy and the quality of patient–provider communication. Recognizing and integrating these influencing factors into shared decision-making processes is crucial to optimizing adherence to management plans, improving outcomes and ensuring patient-centred care[20,22–24].

The preferences of patients, combined with an empathetically communicated clinical opinion is central to selecting and personalizing treatment approaches to OA. This includes ensuring that patients have a clear understanding of the particular aetiology, pathophysiology and phenotype of their OA.

Clinical features that predict progression

The pathogenesis of knee OA is heterogeneous, with systemic factors (including age, gender, ethnicity, genetics, bone density, obesity and oestrogen status) and local biomechanical factors (gravitational force, joint injury, joint deformity and muscle weakness) working in concert and leading to the development and progression of disease[25].

Pain tends to increase with increasing severity of radiographic grade; however, variable concordance between self-reported symptoms, clinical examination and radiographic disease can occur[26–28]. The activation of local nociceptors via non-neuronal tissue injury, which occurs as a result of damage to the somatosensory system, leads to neuropathic pain (including central sensitization) and nociplastic pain, which occurs owing to the activation of peripheral nociceptors despite the apparent absence of tissue damage or stimulus)[29,30]. Clinical history and examination relating to the joint might provide limited information as to the downstream progression of the condition except, possibly, if associated with inflammatory OA (with prominent joint effusions)[31].

Comorbidity might have an important role in the progression of OA. Strong associations between OA and sarcopenia (as an example

of a single 'comorbidity') have been reported[32,33], with Mendelian randomization demonstrating a potential causative relationship between sarcopenia biomarkers and knee and hip OA[34]. Clusters of comorbidity in OA have also been identified and related to mortality risk: 'low-morbidity' (with a low burden of comorbidity); 'back/neck pain plus mental health'; 'metabolic syndrome' and 'multimorbidity' (higher relative prevalence of all comorbidities)[35].

A variety of predictors of knee OA (including at least 16 that use regression models and 10 that use machine-learning approaches) have been developed and reviewed with broad variation in predictive capacity (area under the curve (AUC) ranging from 0.6 to 1.0 for the outcome of interest). Notably, the demographic parameters incorporated into these predictive models included age, sex, education, occupation and income; the clinical history parameters included knee symptoms (pain and stiffness), concomitantly affected joint, physical activity, history of knee injury and/or surgery, family history, pharmacological treatment and comorbidity[36].

Osteoarthritic endophenotypes for treatment stratification

Multiple (often overlapping) subtypes exist under the umbrella definition of OA, which can be divided according to the cause of disease, the presenting clinical phenotype and molecular endotype.

Phenotypes refer to the observable characteristics or outward expression of a disease, including clinical symptoms, signs and physical manifestations that result from the genotype–environment interaction. Endotypes refer to subtypes that are defined by distinct biological or molecular mechanisms identified via specific biomarkers drawn from imaging, biochemical investigations or '-omics' signatures (Fig. 2). For example, in chronic obstructive pulmonary disease (COPD), various clinical phenotypes have been identified, including those based on smoking history (smoking versus non-smoking COPD), predominant site of pathology (small-airway disease versus emphysema) and exacerbation profile (no exacerbation versus frequent exacerbation)[37]. Inflammatory endotypes of COPD are characterized by the predominant type of inflammatory cells (eosinophilic versus neutrophilic) and molecular endotypes have been recognized through genetic markers, such as α1-antitrypsin deficiency and telomerase polymorphisms[37]. These are complemented by emerging insights from transcriptomic, proteomic and other '-omics' technologies, which might offer further stratification strategies for patients[38].

Phenotyping and endotyping can be performed for intervention or prescriptive decision making via the identification of those who are more likely to experience benefit (or harm) from a particular treatment, for distilling mechanistic endotypes for the purposes of targeted therapy and drug development and for prognostic prediction, to guide the decision on who to treat and how to strategically stratify treatment[39]. Indeed, the term 'theratypes' has been attributed to the subtypes within a disease population who respond differentially to different therapies[40].

Numerous frameworks of OA subtypes have been proposed, including a chronic-pain phenotype with central sensitization, an inflammatory phenotype, a metabolic-syndrome phenotype, a bone- and cartilage-metabolism phenotype, a mechanical (malalignment) phenotype and a minimal joint-disease phenotype[39], or an alternative division of subtypes being senescent, genetic, inflammatory, metabolic, endocrine or 'other'[41].

One well-established phenotype (with a co-existent biochemical and molecular endotype) is that of inflammatory OA. This phenotype was first proposed in 1975 by George Ehrlich[42] and is characterized by joint swelling, early-morning stiffness and night pain driven by a low-grade pro-inflammatory cytokine milieu[43] and recognized by molecular endotypic features[44]. This inflammatory phenotype might be associated with metabolic syndrome, obesity, the innate immune

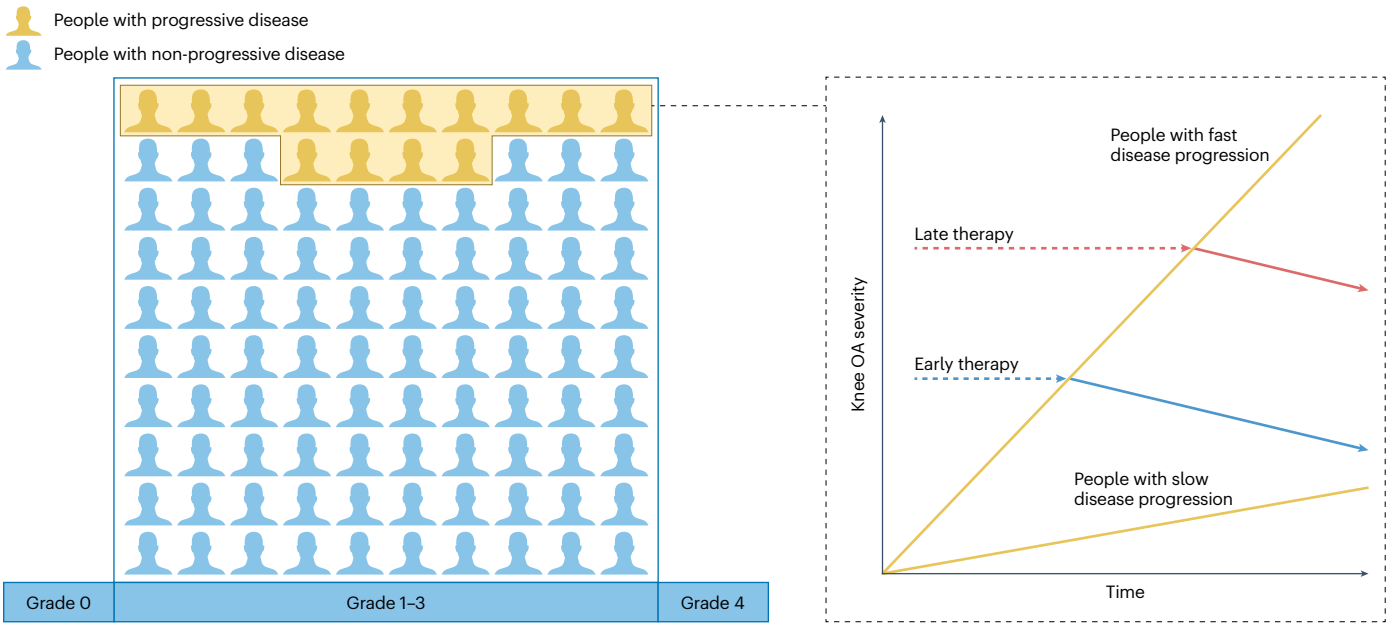

Fig. 1 | Progression and trajectory of knee osteoarthritis. Of patients with knee osteoarthritis (OA) who have a Kellgren–Lawrence grade between 1 and 3, 14% will probably have progressive disease (over 8 years)[49]. The trajectories of fast and slow disease progression differ, and early diagnosis and therapy can have beneficial outcomes in terms of disease severity.

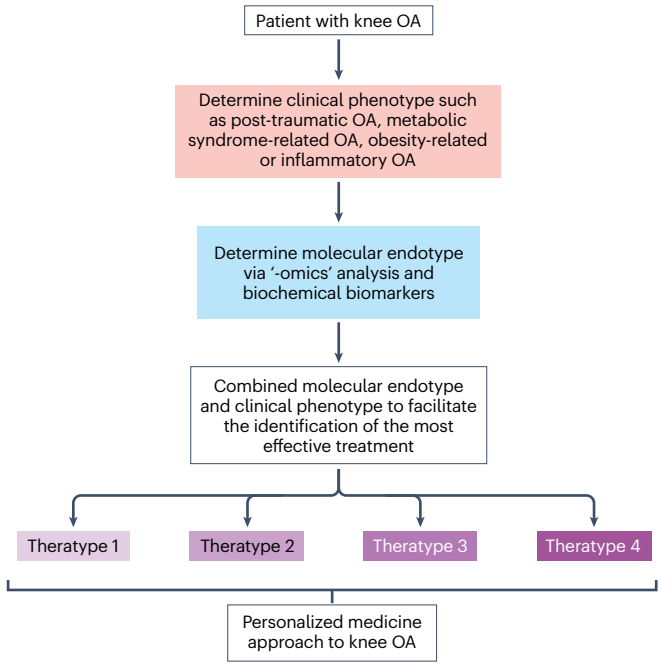

Fig. 2 | A personalized medicine approach to knee osteoarthritis. A patient with knee osteoarthritis (OA) presents and is assessed for clinical phenotype (including post-traumatic, metabolic syndrome-related, obesity-related, inflammatory), endotyped (via '-omics' analysis and biochemical biomarkers) and theratyped (to identify the most effective treatment option). Molecular medicine, imaging, biochemical biomarkers, clinical assessment and precision medicine techniques can all have a role in the subtyping and stratification of patients with OA.

system (via complement and pattern-recognition pathways) and/or inflammaging[43,45].

The Applied Public–Private Research enabling OsteoArthritis Clinical Headway (APPROACH) consortium investigated biomarkers of immune-cell activity, bone remodelling and inflammation, cartilage degradation and formation, and connective tissue sclerosis and thickening in a cohort of 297 people with OA[46] to define patient phenotypes, endotypes and disease progression rates and to improve the design of future OA clinical trials. Using machine learning, three biochemical endotypic clusters were identified: low tissue turnover, structural damage and systemic inflammation.

These endotypes might actually represent theratypes (or 'druggable endotypes') for DMOAD development. Patients could be stratified to receive anti-inflammatory drugs (such as anti-IL-1 therapy[47]) if synovitis biomarkers (either imaging, biochemical or molecular) predominate, to receive anti-resorptive agents if bone resorption and remodelling are predominant features, or to receive cartilage remodelling drugs (such as recombinant fibroblast growth factor-18 or recombinant growth differentiation factor 5) if cartilage remodelling is the overwhelming contributor to their endotype.

Although these clusters might be independent, there can be overlap in some patients and the tendency towards overlap increases in older adults[48]. In addition, longitudinal studies are required to confirm that the characteristics of endotypes are true subtypes of OA, rather than simply stages of the disease.

In summary, the terms phenotype and endotype refer to different features but both can be used to identify theratypes, which are amenable to different therapeutic strategies and have implications for stratification in clinical trials. Importantly, for validation purposes, serum samples should be collected in small aliquots (rather than large volumes) to enable the samples to be analysed in different institutions and the biomarkers of interest validated in different laboratories. This area holds great promise but is very much a research domain at present.

Imaging as a guide for knee osteoarthritis treatment

Imaging biomarkers include the established Kellgren–Lawrence grading system for knee radiographs but also incorporate other methods of analysing radiographs and more modern imaging modalities, including ultrasonography and MRI[49,50]. Medical imaging might be used in different ways to stratify those with symptomatic or structural disease.

When considering the context in which imaging might be used to stratify the treatment of patients with symptomatic disease, one possibility would be for those with high, unmet medical needs, such as patients with minimal structural disease and high symptom burden. In this group, DMOADs might be more effective if given early in the structural disease process.

For the stratification of patients with structural changes, biochemical biomarkers and MRI features can point towards early, or even preclinical, OA when the radiographic findings of established OA are not apparent[10]. Thus, MRI and biochemical biomarkers can be used to identify patients early, so that they might be treated and their trajectories of progression improved.

Using baseline radiographic grade to predict future outcomes has mixed results. The majority of patients with OA who have a Kellgren–Lawrence grade of 1–3 will not progress to OA with structural changes (in terms of JSN) over an 8 year period (86%). Of those who do progress, 8% have early disease progression and 6% have late disease progression[49]. The earlier patients are treated, then potentially the earlier their disease trajectory can be changed (Fig. 1). However, one of the predictors for both types of progression is a baseline Kellgren–Lawrence grade of 3 (more than for Kellgren–Lawrence grade 2), which has been demonstrated in the OA Initiative (OAI) cohort[49] and in a post hoc analysis of randomized trials of patients with symptomatic knee OA[51]. Thus, it certainly seems that lower grades of structural disease are less likely to structurally progress.

The MRI OA Knee Score (MOAKS) system is one of a number of scoring systems that assess severity of disease through semi-quantitative measurement of multiple OA pathologies, including cartilage damage (thickness and integrity across knee compartments), bone-marrow lesions (BMLs; location and size of lesions), meniscal damage (integrity of tissue), osteophytes, synovitis, ligamentous abnormalities (including anterior and posterior cruciate ligaments), subchondral bone cysts and other features (joint alignment and periarticular lesions such Baker's cysts). The association between 2-year progression of MOAKs and 4-year progression of radiographic (via JSN) and symptomatic progression (via a persistent, sustained progression at ≥2 timepoints and an increase of ≥9 on the WOMAC pain score (0–100)) was investigated in a nested case–control comparison of people with a Kellgren–Lawrence grade of 1–3 from the Foundation for the National Institutes of Health (FNIH) of OA Biomarkers Consortium Project[52]. The strongest MRI predictor of progression was cartilage-thickness score (odds ratio (OR) 2.8; 95% CI 1.3–5.9), followed by area of cartilage loss (OR 2.4; 95% CI 1.3–4.4), meniscal morphology (OR 2.2; 95% CI 1.3–3.8),

effusion-synovitis (OR 2.7; 95% CI 1.4–5.4) and Hoffa's synovitis (OR 2.0; 95% CI 1.1–3.9). These findings highlight the role of not only cartilage degradation but also synovitis in identifying OA progression. Indeed, data from a study of the OAI cohort that investigated the relationship between cartilage loss and pain indicated that a loss of 0.1 mm of cartilage thickness over 2 years was associated with a 1.6% increase in pain on the WOMAC pain score and that this increase was mediated by synovitis progression[53]. Thus, the slowing of cartilage loss alone might have minimal effects on concurrent symptoms.

The association of synovitis with progression of OA is also supported by a study of knee arthroscopy that investigated the relationship between synovitis and progression of OA (defined as change in Société Française d'Arthroscopie score of >4.5 and a VAS score of >8.0 mm after 1 year). Synovial inflammation was associated with greater progression of OA compared with normal or reactive synovium (OR 3.11; 95% CI 1.07–5.69)[54]. This discovery is supported by findings from the Multicenter Osteoarthritis Study (MOST) cohort (n = 514 knees with no cartilage damage at baseline) in which baseline effusion synovitis was strongly associated with cartilage loss at 30 months follow-up (OR 3.4; 95% CI 1.9–6.2)[55]. Synovitis is probably not simply present at baseline but is sustained throughout the disease course. This feature of persisting synovitis (assessed by MRI at baseline at 2 years' and 4 years' follow-up) was observed in the OAI cohort and was associated with a greater likelihood of structural degenerative disease than in those participants without synovitis[56]. This association of baseline synovitis with OA progression is also observed in progression to arthroplasty with the 12 month risk of total knee replacement increasing with increasing MRI synovitis grade (grade 1: OR 2.42, 95% CI 1.18–8.85; grade 2: OR 5.78, 95% CI 2.86–1.69; and grade 3: OR 7.80, 95% CI 3.56–17.1)[50]. Ultrasonography can also provide biomarkers of progression and assessment of knee effusion using this method demonstrated that effusions of ≥4 mm were associated with a greater hazard of total knee replacement over 3 years than effusions of <4 mm (hazard ratio (HR) 2.63; 95% CI 1.70–4.06)[57].

Early work that identified bone-marrow oedema from knee radiographs have highlighted this feature as predictive of OA progression[58]. Studies using MRI have identified BMLs within the knees of people with OA, which were associated with an increased risk of pain (2–5 times higher) compared with those without BMLs[59]; the size of the lesion is predictive of future pain and pain progression[60]. BMLs are substantially associated with knee OA progression; medially located BMLs are strongly associated with considerable reductions in medial cartilage thickness[61] and increasing size of medial BMLs is associated with progressive cartilage loss in the medial compartment[62].

With the advent of artificial intelligence in clinical practice, machine learning (and particularly neural networks) are being used on medical-imaging datasets to predict future outcomes via the developing field of 'radiomics'[63]. OA is no exception, with models developed to predict the development of knee OA from MRI, by integrating radiomic features of meniscus and femorotibial cartilage[64] or focusing on T2-weighted imaging of the cartilage[65].

Imaging provides numerous strong predictors for progression via the modalities of radiography, MRI and ultrasonography. Synovitis on MRI seems to be a particularly clear biomarker for structural progression and future need for arthroplasty. 3D statistical shape modelling based on MRI identified another structural biomarker (termed B-shape), which predicted both current and future symptoms and risk of joint replacement in the OAI cohort[66]. MRI is essential to identify those with early (pre-radiographic) disease to move towards the ultimate aim of identifying and treating people with 'early OA'. Synovitis on MRI should also be considered as at least part of a surrogate endpoint for accelerated clinical trials. It must also be considered that the joint is an organ containing multiple tissues, including bone, synovium and cartilage, and that MRI (and potentially ultrasonography) have the potential to delineate different disease subtypes.

Biochemical biomarkers as a guide for knee osteoarthritis treatment

Biochemical biomarkers have a particular role in the assessment of disease activity, including identifying 'early OA' and those in whom OA is likely to progress (Table 2). The breakdown products of cartilage degradation are often used as biochemical biomarkers as they might provide a measure of the extent of disease progression.

Type II collagen is a key component of cartilage and provides multiple opportunities to measure disease activity in OA, including the N-propeptide, the triple helix and the C-terminal telopeptide (CTX) of type II collagen and the C-propeptide and N-terminal telopeptide of type I collagen (NTX-I), which are often cleaved by enzymes, including cathepsin-K and matrix metalloproteinases (MMPs)[67]. The most common type II collagen biomarker used in the clinic is urinary CTX-II with high levels correlating with the level of cartilage breakdown, which makes it a useful marker of joint damage. Type III collagen provides more information about the synovium and synovitis via epitopes, including Pro-C3 (derived from the N-propeptide) and C3M (derived from the triple-helix structure)[67]. Aggrecan is a large proteoglycan that has a role in the maintenance of cartilage structure and constitutes a central protein core with surrounding glycosaminoglycan chains. Cleavage products of aggrecan that are released from cartilage include AGNx1 (which measures all breakdown of aggrecan) and AGNx2 (which focuses on MMP-mediated aggrecan cleavage)[68].

Clinical practice data from the FNIH OA Biomarkers Consortium provides some evidence for the use of baseline urinary and serum biomarkers to predict 24-month pain and structure progression, with the best model comprising urinary CTX-II, serum hyaluronic acid and serum NTX-I (AUC of 0.631). Urinary CTX-II alone and a serum-only biomarker model, including serum hyaluronic acid and NTX-I, performed marginally less well, with an AUC of 0.583 and 0.601 respectively[69]. These AUC values suggest that these biomarkers need to be further honed before they can be considered clinically useful. The exact threshold of AUC will vary depending on the context, although an AUC of 0.70–0.80 is generally considered to be acceptable[70].

Urinary CTX-II predicted the need for joint replacement in the OFELY cohort of pre-menopausal and post-menopausal women (a longitudinal cohort recruited randomly from the affiliates of a large health insurance company), with high urinary CTX-II associated with a greater risk of arthroplasty at 18 years of follow-up[71].

Cartilage acidic protein 1 (CRTAC-1) has a role in cartilage formation and maintenance via its communicatory role in the interaction between chondrocytes and the extracellular matrix (ECM). Plasma levels of CRTAC-1 have been associated with 18-year progression to joint replacement (OR 1.80; 95% CI 1.11–2.92, per standard deviation increase in CRTAC-1, adjusted for total hip-bone mineral density, baseline knee OA Kellgren–Lawrence grade, hip OA and WOMAC OA pain index)[72].

Periostin (also known as osteoblast-specific factor 2 (OSF-2), is an extracellular protein residing in the periosteum and cleaved by cathepsin-K, is associated with the development of knee OA, with lower levels of serum periostin associated with greater progression of Kellgren–Lawrence grade (although the discriminative AUC was only 0.66)[73].

Table 2 | Biochemical biomarkers for knee osteoarthritis (OA)

Biochemical biomarker	Description	Potential clinical use
Aggrecan	Large proteoglycan with a central protein core that is surrounded by glycosaminoglycan chains The presence of this biomarker reflects cartilage matrix degradation	Elevated levels of aggrecan can indicate cartilage damage
AGNx1 and AGNx2	Neoepitopes generated via aggrecanase activity AGNx1 reflects general aggrecan breakdown whereas AGNx2 reflects MMP-mediated aggrecan breakdown	AGNx1 and AGNx2 can be used as cartilage-degradation markers[68]; levels of these neoepitopes might correlate with cartilage loss and disease activity
C3M	Marker of type III collagen degradation An epitope derived from the triple helix structure of type III collagen	Levels of C3M reflect connective-tissue sclerosis and thickening C3M is cross-sectionally associated with the presence and size of bone-marrow lesions and the number of joint regions affected[75]
CRTAC-1	Facilitates communication between chondrocytes and the ECM	Associated with 18-year progression to joint replacement[90]
CTX-II	Marker of type II collagen degradation	High levels of CTX-II are associated with greater cartilage breakdown and thus can be used as a surrogate marker of joint damage Moderate performance when used alone but improved performance when trialled in consort with other biochemical biomarkers[76]
NTX-1	Marker of bone resorption derived from type I collagen	A constituent of a panel of serum and urinary biomarkers that moderately predicted 24-month pain and structural progression of knee OA[69]
Periostin	ECM protein that is cleaved by cathepsin-K and linked to tissue repair and inflammation	Low levels of periostin are associated with greater progression of KL grade in a limited discriminative model in women with knee OA[73]
miR-146a-5p and miR-186-5p	Circulating miRNAs	Associated with the prevalence and incidence of knee OA in women[74]
Pro-C3	Epitope of the N-terminal propeptide of collagen type III Marker of type III collagen formation	High levels of pro-C3 are associated with greater synovial inflammation Good discriminatory performance in psoriatic arthritis flare versus non-flare[91]

This table lists biochemical biomarkers for knee OA with descriptions of their origins and the potential clinical use. BMLs, bone-marrow lesions; CTX-II, C-terminal cross-linked telopeptides of type II collagen; ECM, extracellular matrix; KL, Kellgren–Lawrence; miRNAs, microRNAs; NTX-1, N-terminal telopeptide of type I collagen; OA, osteoarthritis; OSF-2, osteoblast-specific factor 2; Pro-C3, N-terminal propeptide of type III collagen.

The circulating microRNAs (miRNAs) miR-146a-5p and miR-186-5p were associated with prevalent knee OA (OR 4.62; 95% CI 1.85–11.5) and incident knee OA (OR 6.13; 95% CI 1.14–32.9) respectively[74], presenting potential biomarkers for OA progression.

Change in biomarkers can be used to predict particular aspects of OA, including the development of BMLs. This predictive capacity has been demonstrated using the OAI cohort data from the FNIH OA Biomarkers Consortium, which showed that the 12-month change in serum biomarkers of collagen type I, collagen type II and collagen type III degradation are associated with 24-month development of BMLs (with a maximum AUC of 0.75 for collagen type II MMP cleavage products)[75].

Omics technologies also hold great promise as predictive biomarkers, and a systematic, iterative and unbiased mass spectrometry approach has been used to create a multiple reaction monitoring proteomic panel of 99 proteins from serum that was highly indicative of radiographic OA[76]. The use of a subset of this panel (including 13 proteins) to predict progressive OA (comprising both radiographic and symptomatic progression) was then explored and compared with urinary CTX-II (as a 'best-in-class' biomarker) with the protein panel having a substantially better AUC of 0.75 (compared with 0.58 for urinary CTX-II)[77].

Elastic net regression (which is used to shrink the number of parameters used in a statistical model) was used to produce a panel of six proteins that could distinguish those who would develop OA before radiographic features were apparent, with an AUC of 0.77 (ref. 78).

Identifying those with incident OA, those who will probably progress and those requiring future joint replacement using biomarkers is possible. However, for these markers to be used in clinical practice, they need to be proven to perform well, to be adequately validated in clinical trials and need to complete the steps required to be acceptable for regulatory purposes. The use of these markers needs to be demonstrated at the level of the individual patient (rather than group level as in clinical trials) to be useful in clinical practice.

Using cartilage-on-a-chip models to personalize osteoarthritis treatment

The European Commission's definition of personalized medicine emphasizes that the crux of this field is "tailoring the right therapeutic strategy for the right person at the right time"[79]. The approach to personalized medicine is to create a model (in vitro or in silico) of a tissue, organ or patient, which can then be perturbed with therapeutic approaches and the resultant outcome measured. In this way, the treatment strategy for a patient can be experimentally honed and personalized to optimize the outcome in vivo.

In vitro cell culture dates back to the early 1900s[80], but these 2D models had limitations in terms of the authenticity of the modelled in vivo environment. Since then, microfluidic chip technologies have been developed. These chips enable 3D cell culture, and provide a method of studying cell–cell and cell–ECM interactions, the development of diffusion gradients via defined, unidirectional, microfluidic flow of nutrients and interventions (rather than fast diffusion across large volumes of stagnant media) and the option to apply mechanical stimulation[81,82]. This ability to simulate load-bearing force is important for the fidelity of the chondrocyte model, as in vivo, chondrocytes reside in a low-oxygen

environment, with nutrient diffusion via synovial fluid, and these cells are subjected to regular and substantial mechanical stimulation.

Cartilage-on-a-chip models enable chondrocytes to exist in a 3D framework, with the maintenance of spherical morphology, structural organization, low metabolic activity and differential gene expression compared with traditional 2D culture[83]. Such a system has been experimentally perturbed using hyaluronic acid, triamcinolone, platelet-derived growth-factor and diclofenac, demonstrating differential gene-expression responses to these medications for different individual patients[84].

Health economics as a guide for knee osteoarthritis treatment

Health-economics studies evaluate the cost-effectiveness, efficiency and value of health care technologies via economic evaluation (comparison of the relative costs and outcomes of health care technologies to optimize the allocation of resources) and budget-impact analysis (which estimates the financial implication of adopting novel interventions and approaches) and therefore guide the resource allocation (analysing how health care spending can maximize population health) and policy development (providing evidence of policy guidelines and intervention-reimbursement decisions). The key metric of economic evaluation is the incremental cost-effectiveness ratio (ICER), which is the ratio of the change in cost between the intervention and comparator, to the measured change in effectiveness (typically measured in quality-adjusted life years of the intervention). The cost-effectiveness threshold depends on the amount that a payer is willing to pay (such as £20,000–£30,000 per quality-adjusted life year gained in the UK[85]) and an intervention is cost-effective if the ICER is below that threshold (and more cost-effective the further below the threshold the ICER lies).

In OA, health-economics analyses of early surgical interventions have demonstrated conflicting findings, with early total knee arthroplasty shown to be cost effective, through the prevention of disease progression and reducing the need for costly treatments in a USA Medicare study of patients ≥65 years of age with end-stage knee OA[86]. Conversely, another study showed no clear cost–utility benefit of early versus late total knee arthroplasty in patients with knee OA in the French national health system[87]. The lack of cost effectiveness of early intervention might be because younger patients have early surgery and then require replacement surgery in the future.

Non-surgical and non-pharmacological interventions, including exercise and physiotherapy, are cost effective. These interventions might improve physical function and reduce the symptoms of disease progression (without incurring substantial costs)[88].

In terms of pharmacological treatments, a systematic review of 43 cost-effectiveness studies from across 18 countries demonstrated broad heterogeneity of ICERs for NSAIDs (US$44.40–307,013.56 per quality-adjusted life year), opioids (US$11,984.84–128,028.74 per quality-adjusted life year), symptomatic slow-acting drugs for OA (US$10,930.17–27,799.73 per quality-adjusted life year) and intra-articular injections (US$258.36–58,447.97 per quality-adjusted life year) ranging from marked cost-effective dominance, to very high, non-cost-effective ICERs[89].

Thus, a consensus on the health-economic benefits of treatments for OA is yet to be established. This lack of consensus is because of challenges (some of which are peculiar to OA), including fluctuating health care costs, the paucity of robust available data and variation in reimbursement barriers but also the endpoint of health-economic analyses. In osteoporosis, intervention is aimed at reducing the risk of fractures, which, in the case of hip fractures, are very costly to the health care system. For knee OA, the endpoint is often arthroplasty, which is well-established to improve quality of life; thus, novel OA interventions are often not considered as cost effective when compared with arthroplasty.

Therefore, further health-economics analysis is needed to inform the cost effectiveness of the 'who to treat for OA' approach, as the wrong approach could have severe implications for the wider health economy. Studies that enable targeted treatment allocation, assessment of personalized treatment strategies and the evaluation of cost-effectiveness are needed to guide policy makers in setting guidelines, recommendations and reimbursement policies.

Conclusions

By using a combination of potential approaches with novel developments (including biochemical biomarkers, imaging, cell-culture and '-omics' strategies) patients can be identified earlier and the best treatment option selected according to their preferences and the particular presentation of their OA. Clinical features, biomarkers and imaging features (particularly synovitis on MRI) have the potential to aid the identification of patients who are at risk of progression and therefore might be targeted for early intervention; however, the clinical and cost effectiveness of such approaches remains to be elucidated. Novel approaches, including cartilage-on-a-chip models, represent an exciting development for the targeted treatment of OA, but further hypothesis-generating studies and trials of novel approaches are needed to contribute to the substantial research agenda in this area.

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Competing interests

R.C., N.A-D., M.A., J.A.T., J.-J.B., N.B., E.C., M.M.R, C.C., G.I.I., A.K., N.L., S.M., R.M., S.O., M.C.P.Y., R.P.R., F.R., B.S., S.S., C.T., A.L. and E.B.I. declare no competing interests. N.R.F. has received speaker fees and honoraria from UCB and Viatris and travel bursaries from Pfizer and Eli Lilly. F.B. reports personal fees from 4P Pharma, 4Moving Biotech, Grunenthal, GSK, Heel, Nordic Bioscience, Novartis, Servier, TRB Chemedica and Viatris. O.B. has received consulting or lecture fees from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB and Viatris. P.G.C. has performed consultancies or speakers bureaus for Eli Lilly, Eupraxia, Formation Bio, Galapagos, Genascence, GSK, Grunenthal, Janssen, Kolon TissueGene, Levicept, Medipost, Moebius, Novartis, Pacira, Sandoz and Stryker & Takeda. E.M.D. reports honoraria from UCB, Viatris and Pfizer. M.E. reports consultancy for Grünenthal Sweden AB and Key2Compliance. I.K.H. reports personal fees from Novartis, AbbVie, Grünenthal and GSK during the past 36 months. M.H. reports in the past 36 months research grants (paid to institution) from Radius Heath and Angelini Pharma, as well as lecture or consulting fees (all paid to institution) from Grunenthal, Pfizer, Mylan Pharmaceuticals and IBSA. Leuven R&D and the valorization division of KU Leuven, and has received speaker fees and honoraria from AbbVie, Amgen, Galapagos, Biosplice (formerly Samumed), Biocon (formerly Viatris), Eli-Lilly, Novartis and UCB on behalf of R.L. A.M. has received speaker fees and honoraria from HALEON, Grünenthal, Kolon TissueGene, Kolon Life Science Cluster, Aptissen SA, California Institute for Regenerative Medicine (CIRM), Sanofi, Sanofi Consumer Healthcare, GSK, Novartis, Pfizer, Viatris, Contura, Enlivex, Orion Corporation, Pluri, Pacira Biosciences, Laboratoires Expanscience and Synartro Ampio Pharmaceuticals. N.V. reports personal fees from IBSA, Mylan, Viatris, Sanofi, Nestlè and Fidia outside of the submitted work. R.R. has received fees for advisory board or lectures from Abiogen, Effryx and Theramex. J-Y.R. reports consulting fees or paid advisory boards for IBSA-Genevrier, Mylan, Radius Health, Pierre Fabre, Faes Pharma, Rejuvenate Biomed, Samumed, Teva, Theramex, Pfizer and Mithra Pharmaceuticals, lecture fees when speaking at the invitation of sponsor for IBSA-Genevrier, Mylan, Cniel, Dairy Research Council, Nutricia, Danone and Agnovos, and grant support from IBSA-Genevrier, Mylan, Cniel, Radius Health and TRB. N.C.H reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, Theramex and Internis Pharma.

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