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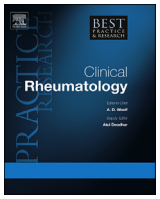

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Biomarkers for osteoarthritis: Current status and future prospects

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A B S T R A C T

Osteoarthritis (OA) is the most common form of arthritis globally and a major cause of pain, physical disability, and loss of economic productivity, with currently no causal treatment available. This review article focuses on current research on OA biomarkers and the potential for using biomarkers in future clinical practice and clinical trials of investigational drugs. We discuss how biomarkers, specifically soluble ones, have a long path to go before reaching clinical standards of care. We also discuss how biomarkers can help in phenotyping and subtyping to achieve enhanced stratification and move toward better-designed clinical trials. We also describe how biomarkers can be used for molecular endotyping and for determining the clinical outcomes of investigational cell-

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based therapies. Biomarkers have the potential to be developed as surrogate end points in clinical trials and help private-public consortia and the biotechnology and pharmaceutical industries develop more effective and targeted personalized treatments and enhance clinical care for patients with OA.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis [1], affecting more than 500 million people globally [2], potentially contributing to a "tsunami" of cases for healthcare systems by the year 2050. It affects 1 in 5 individuals in the general population and 1 in 3 people over the age of 50 [1,3,4]. OA can be broadly classified into 2 categories: primary OA and secondary OA [1]. Classically, OA presents with joint pain and loss of function; however, the disease is clinically highly variable, with considerable discordance between structural changes and symptoms [5]. OA can present merely as an asymptomatic incidental finding to a devastating and permanently disabling disorder [1]. For many years, OA was described as a non-inflammatory "wear and tear" disease because it was perceived as a slow-burning disease that typically develops over a long period of time due to the natural "wear and tear" in synovial joints. However, the "wear and tear" falls short in describing all inflammatory-driven disease mechanisms, and thus, the description is no longer used since it prevented the field from moving towards more innovative treatment options. The "wear and tear" disease concept is also antagonistic to data emerging from recent advances in our understanding of the crucially important role of inflammation, represented bycomplement cascades, innate and adaptive immunity, as well as the firmly established concept of chronic low-grade inflammation progressing OA [6–10]. Figs. 1 and 2 provide an overview of the structural features and molecular complexity of OA. For a modern definition of OA and the OARSI definition of OA, see Box 1.

The most common symptoms of OA include joint pain, stiffness, and swelling. Among the most frequently affected joints are the joints of the knees, hips, and hands [12]. OA symptoms are often worse in the morning or after periods of inactivity, and they may improve with movement, highlighting the important role of physical activity for optimal joint function and symptom management [1,13,14]. Risk factors for developing OA include age, obesity, previous incidence of joint injuries or joint

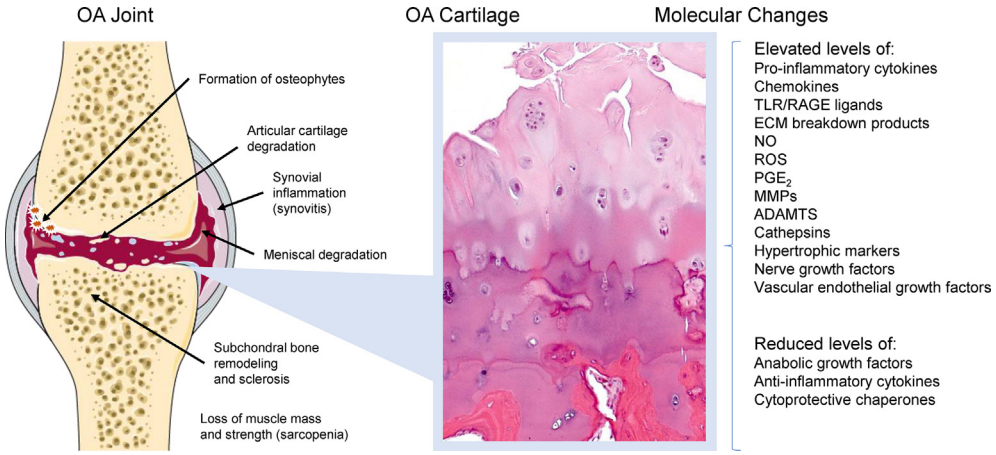

Fig. 1. Complexity of the molecular alterations in osteoarthritis, highlighting the need for biomarkers.

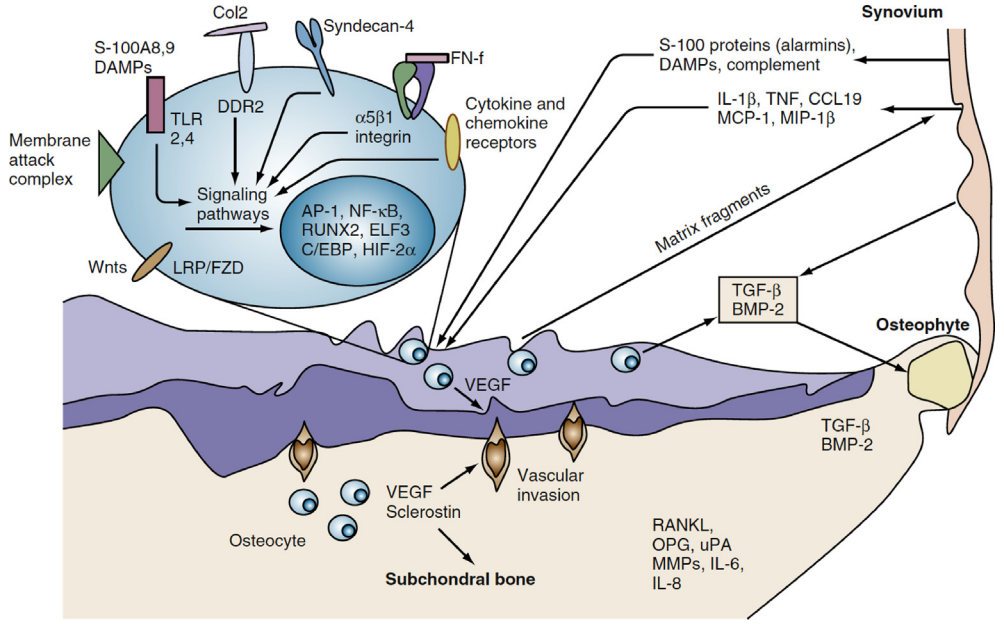

Fig. 2. Molecular cross-talk between articular cartilage, synovium, and subchondral bone in osteoarthritis. Figure adapted from Chapter 3. Cartilage and Chondrocytes, by Ali Mobasheri, Mary B. Goldring, and Richard F. Loeser in Kelley & Firestein's Textbook of Rheumatology 11th Edition, ISBN 9780323639200, Elsevier, 2020. Edited by Gary S. Firestein, MD, Ralph C. Budd, MD, Sherine E Gabriel, MD, MSc, Iain B McInnes, PhD, FRCP, FRSE, FMedSci, and James R O'Dell, MD; Edited by Gary Koretzky.

overuse, skeletal malalignment, and genetics [15–21]. At the present time, there are no approved disease-modifying OA drugs [22–25]. Recently published treatment guidelines developed by major international organizations recommend education, structured exercise, and weight loss as core treatments, topical non-steroidal anti-inflammatory drugs (NSAIDs) as first-line treatments, and oral NSAIDs and intra-articular injections for persistent pain management [26–32]. Therefore, current treatment options for OA are limited to prescribing pain medication, promoting exercise, physical therapy, and, in only some cases, joint surgery. The current goal of treatment is to manage symptoms, improve joint function, and prevent further joint damage [13,33,34]. The long-term but as of yet elusive goal is true disease modification.

Since OA is now understood to be a heterogeneous disease with multiple etiologies, clinical phenotypes, and molecular endotypes, this implies that we can potentially pave the way for treating it in a way similar to asthma [35], allergy, and other chronic and inflammatory diseases such as sarcoidosis, which are amenable to phenotyping and molecular endotyping [36]. Evidence still suggests that each of the different OA phenotypes and molecular endotypes of OA may be targeted differently, opening up multiple pathways for therapeutic intervention and creating new opportunities for rational prevention of OA and the development of effective disease-modifying OA drugs (DMOADs). This narrative review will focus on the current challenges in soluble OA biomarker (i.e., biochemical marker) research development and provides several examples of public-private partnerships that are working to incorporate biomarkers to understand OA pathology and provide the tools that are needed for successful future drug development.

Box 1

Various organizations have attempted to provide an updated and more "modern" definition of OA, describing it as a chronic degenerative joint disease that is characterized by the progressive breakdown of articular cartilage in the joints, along with changes to the underlying bone, synovial membrane, and joint capsule. The updated definitions have also highlighted the fact that OA is a multifactorial condition that can be caused by a combination of genetic, environmental, and lifestyle factors, including aging, obesity, joint injury or overuse, and genetic predisposition. The modern understanding of OA also recognizes that it is not simply a disease of articular cartilage but a whole joint as an organ and systemic manifestations, involving a complex interplay of various biological processes, including chronic low-grade inflammation, abnormal joint mechanics, and alterations in the extracellular matrix. As a result, modern approaches to OA management focus on a multimodal approach that includes lifestyle modifications, physical therapy, pharmacological interventions, and surgical interventions. The current goal of treatment is to manage symptoms, improve joint function, and prevent further joint damage. Future therapies are aimed at disease modification, promoting repair responses, and long-term joint preservation.

OARSI Definition of OA: "Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation, and loss of normal joint function), that can culminate in illness." [11].

Biomarker

A biomarker is a measurable indicator of a biological process, physiological, or pathophysiological state in an organism. The National Cancer Institute[1] at the National Institutes of Health[2] defines a biomarker as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition and may also be called a molecular marker or disease signature molecule". At the cellular level, biomarkers can be molecules, such as proteins, lipids, or nucleic acids, or they can be physical or physiological changes, such as changes in gene expression, cell structure, or metabolic activity. Clinical examples of biomarkers include blood glucose levels for diabetes, blood pressure for hypertension, and genetic mutations for certain types of cancer. Biomarkers can also be used in other areas, such as environmental monitoring, assessing food safety and authenticity, plus many applications in forensic science (see Box 2).

Box 2

Biomarkers are used in basic, translational, and clinical research and in clinical settings to facilitate medical product development and inform patient care decisions. Biomarkers even have applications in food safety, environmental science, veterinary medicine, and other fields. The scientific and medical communities, patients, providers, patient advocacy organizations, industry, and regulators all play important roles in the development, application, and continuous iterative evaluation and improvement of biomarkers.

[1] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biomarker#.
[2] https://www.nih.gov.

Biomarkers are valuable tools for disease diagnosis and drug development. The European Medicines Agency defines a biomarker as a biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals. The EMA has developed specific guidance on how biomarkers should be used under 'Qualification of novel methodologies for medicine development'.[3] The US Food and Drug Administration (FDA)[4] has proposed that biomarkers are a crucial drug development tools capable of facilitating the development of medical products and promoting new innovation. Therefore, if utilized in the correct scientific, clinical, and regulatory context, biomarkers have the potential to help expedite patient access to safe and effective treatments by reducing the time and cost of clinical trials while maintaining patient protection [37].

Although biomarkers are critical to the rational development of novel therapeutics, significant confusion has unfortunately crept into the published literature regarding fundamental definitions and the over-arching concepts involved in their use in research and clinical practice, particularly in the fields of chronic disease diagnosis and management [38]. Therefore, it has been proposed that clarification of the various definitions of different biomarkers and a better understanding of their appropriate application(s) could result in substantial scientific and healthcare benefits.

Biomarkers definition working group

The Biomarkers Definitions Working Group consisted of a group of experts in the field of biomarker research who came together in 2001 to develop standardized definitions and terminology for biomarkers and published a seminal first paper entitled: "Biomarkers and surrogate end points: preferred definitions and conceptual framework", focusing on a unified definition [39]. The group was formally endorsed by the National Institutes of Health (NIH) in 2006, and its primary goal is to facilitate the development and validation of biomarkers for use in clinical trials and other research studies. Over the last two decades, the Biomarkers Definitions Working Group has developed several key definitions related to biomarkers, including the definitions of a biomarker, a surrogate end point, and a clinical end point. These definitions are intended to provide clarity and consistency in the use of biomarker-related terminology across different fields of research. The group also established guidelines for the validation of biomarkers, which are intended to ensure that biomarkers are accurate, reliable, and clinically meaningful. These guidelines include recommendations for study design, analytical validation, and clinical validation. Overall, the Biomarkers Definitions Working Group has also played an important role in advancing biomarker research and promoting the use of biomarkers in clinical practice. By establishing standardized definitions and guidelines, the group also helped to ensure that biomarkers are used effectively and appropriately in research and clinical settings.

However, the Biomarkers, EndpointS, and other Tools (BEST) Resource glossary[5] made further efforts to clarify the confusing terminology in the published literature and contextualizes the applications of biomarkers and end points as they pertain to the progression from basic biomedical research to medical product development to clinical care. It was developed by FDA and NIH to promote the consistent use of biomarker terms and concepts and, thereby, advance biomarker science.

The definition of the term "biomarker" has evolved as a result of the efforts of the FDA-NIH Biomarker Working Group (see Box 3).

The NIH and FDA encourage all stakeholders to use BEST terms and definitions so that everyone speaks the same language when discussing biomarkers and end points. BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders. In addition, it includes examples of the various categories of biomarkers and their applications, and it distinguishes between biomarkers and clinical assessments. BEST was developed to address the linguistic confusion that has been hindering pharmaceutical and medical device product development, causing

[3] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/novel-methodologies-biomarkers/opinions-letters-support-qualification-novel-methodologies-medicine-development.

[4] https://www.fda.gov/science-research/about-science-research-fda/biomarkers-fda.

[5] https://www.ncbi.nlm.nih.gov/books/NBK326791/.

Box 3
Original and updated definition of biomarker.

Original definition of biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

BEST updated definition of biomarker: A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how a patient feels, functions, or survives. However, it may be used as a surrogate outcome measure to strategically guide investigators and sponsors of clinical trials.

misinterpretation of evidence, misunderstanding of evidentiary requirements, and even catastrophic failure in late-phase trials.

Biomarkers in osteoarthritis clinical practice and drug development

The diagnosis of OA is predominantly done clinically, without the requirement for biomarker utilization, either imaging or biochemical based. The clinical diagnosis is often confirmed by radiography but never with biochemical markers in a clinical primary healthcare setting. Biomarkers are already well-established in the OA research arena and also in relation to clinical trials of new and repositioned therapeutic agents [40–44]. However, there is considerable opportunity for using biomarkers for prognostic and disease monitoring purposes. Since biomarkers can also be used to diagnose OA, monitor disease progression and evaluate treatment response, and predict disease outcomes, various groups and organizations including the Osteoarthritis Research Society International (OARSI)[6] and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO)[7] have provided guidance on how they may be used in clinical studies to identify patients who are most likely to benefit from a particular treatment or to evaluate the safety and efficacy of new disease-modifying therapies [45–50].

In the context of OA, biomarkers are indicators of pathophysiological processes that are associated with the development and progression of the disease. In OA, as in other diseases, biochemical and immunological biomarkers may be used for monitoring disease progression and predicting response to pharmacological, non-pharmacological, and biological treatment. Some of the most commonly studied biomarkers of OA include.

1. Cartilage matrix breakdown products: These are the best-studied OA biomarkers that are released into the bloodstream as a result of the breakdown of cartilage in the joints. Examples include collagen type II C-telopeptide (CTX-II) and cartilage oligomeric matrix protein (COMP) [51–54].
2. Inflammatory biomarkers: OA involves a low-grade inflammation in the joints, and thus, several inflammatory biomarkers have been studied. Examples include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [55,56].
3. Metabolic biomarkers: OA is associated with metabolic dysregulation, including insulin resistance, glucose intolerance, and dyslipidemia. Putative biomarkers associated with metabolic processes include adiponectin, leptin, and insulin [57–60].
4. Biomarkers of bone remodeling: subchondral bone changes occur in OA, and biomarkers reflecting bone remodeling can be useful in the research and clinical trial contexts. The best examples include

[6] https://oarsi.org.
[7] https://www.esceo.org.

type I collagen cross-linked N-telopeptide (NTX) and bone-specific alkaline phosphatase (BSAP) [48,61,62].

Fig. 3 provides an overview of the different classes of soluble biomarkers, including those that were extensively studied in IMI APPROACH Consortium (see further below).

While these groups of biomarkers can be useful in a research context, for the routine diagnosis and management of OA, there are currently no approved biomarkers that can be used for earlier disease diagnosis or predicting the course of disease progression with absolute certainty. This is one of the main reasons for the cautious advice from regulatory agencies regarding their wider use and adoption. The use of multiple biomarkers in combination with clinical and imaging findings may provide a more comprehensive understanding of the disease state and therapeutic responses.

Current Efforts in OA Biomarker Development and Validation

There are a number of ongoing efforts to identify, characterize, and clinically validate OA biomarkers before placing them in the more challenging pipeline for regulatory qualification and approval. The following sections provide brief descriptions of the most relevant efforts including several public-private partnerships that the authors of this article have been involved in.

Osteoarthritis Biomarkers Consortium

The Osteoarthritis Biomarkers Consortium is a research initiative established by the Foundation for the National Institutes of Health (FNIH)[8] in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)[9] and the Osteoarthritis Research Society International (OARSI)[10]. The consortium was formed to facilitate the discovery and validation of OA biomarkers [63]. The Osteoarthritis Biomarkers Consortium comprises academic researchers, industry partners, patient advocates, and government representatives who collaborate on a variety of research projects related to osteoarthritis biomarkers. The consortium's research focuses on identifying and validating biomarkers for osteoarthritis diagnosis, prognosis, and treatment response. One of the key goals of the Osteoarthritis Biomarkers Consortium is to develop a set of standardized protocols and guidelines for biomarker validation, which will help to ensure that biomarkers are reliable, reproducible, and

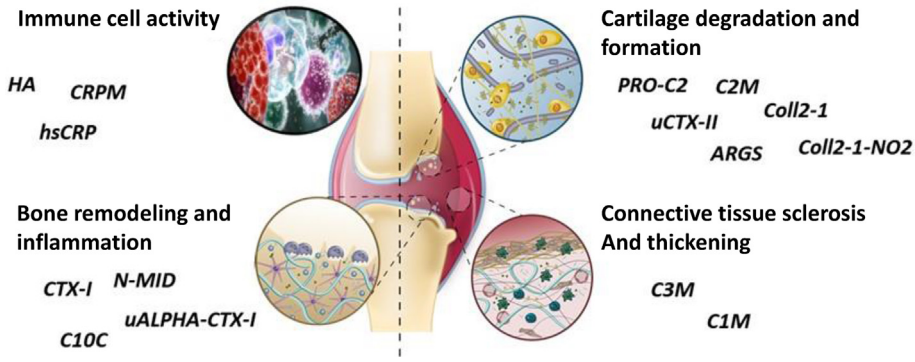

Fig. 3. Soluble biomarkers measured at baseline in serum or urine samples from participants in the APPROACH cohort. The biomarkers measured reflect four different processes: immune cell activity, cartilage degradation and formation, bone remodeling and inflammation, and connective tissue sclerosis and synovial thickening.

[8] https://www.fnih.org.
[9] https://www.niams.nih.gov.
[10] https://oarsi.org.

clinically relevant. The consortium also aims to promote the use of biomarkers in clinical trials and other research studies to facilitate the development of new therapies for OA. The work is ongoing, but a number of recent articles have highlighted the power of using this public-private partnership approach to advance the field [64–68] and validate biomarkers for clinical studies.

IMI APPROACH consortium

The Innovative Medicines Initiative (IMI) APPROACH consortium on OA is an ongoing collaborative public-private research initiative between the European Commission and the pharmaceutical industry

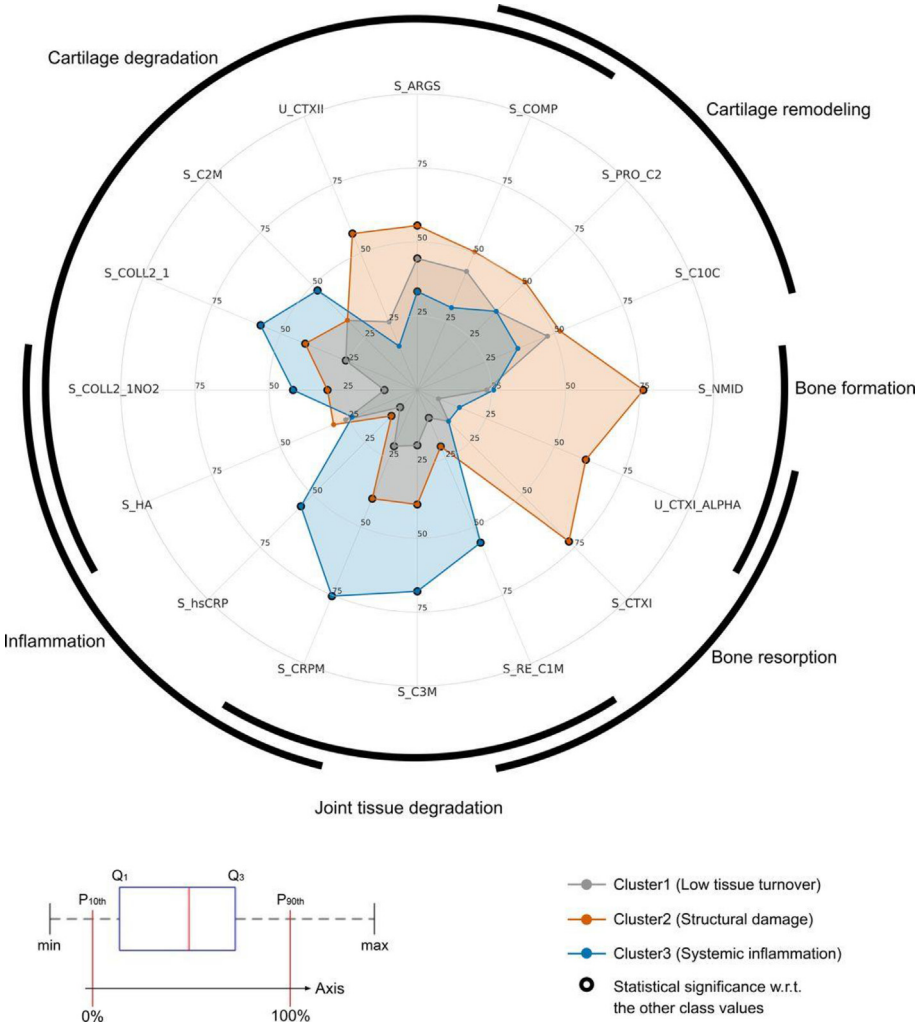

Fig. 4. Radar plot showing the median biomarker concentrations for each cluster. When the difference between the medians is statistically different, it is marked with a circle (instead of a dot). The axes show values between the 10% and 90% quantile and are expressed as percentages. The black arcs on the outside show the pathology associated with each biomarker. Reproduced from Angelini et al. Ann Rheum Dis 2022; 81:666–675, with the permission of BMJ Publishing Group Ltd and the European League Against Rheumatism.

aimed at developing new therapies. The consortium includes academic researchers, industry partners, patient advocates, and small and medium-sized enterprises that have worked together since 2015 to advance our understanding of OA subtypes and develop new and better-targeted treatments for the disease. The IMI APPROACH consortium also focuses on the identification and validation of biomarkers for osteoarthritis diagnosis, prognosis, and treatment response. One of the most important studies that emerged from this consortium was an OA endotype discovery study via clustering of biochemical marker data [69]. Biochemical markers reflecting joint tissue turnover were measured in the IMI APPROACH cohort at baseline and analyzed using a machine learning approach in order to study OA-dominant phenotypes driven by the endotype-related clusters and discover the driving features and their disease-context meaning. Methods used in this study included k-means clustering algorithm, which was used to find dominant subgroups of patients based on the biochemical markers data. Classification models were then trained to predict cluster membership, and Explainable AI techniques were used to interpret these to reveal the driving factors behind each cluster and identify phenotypes.

This study led to the development of three dominant clusters or diseases subtypes: C1), low tissue turnover (low repair and articular cartilage/subchondral bone turnover); C2), structural damage (high bone formation/resorption, cartilage degradation); and C3), systemic inflammation (joint tissue

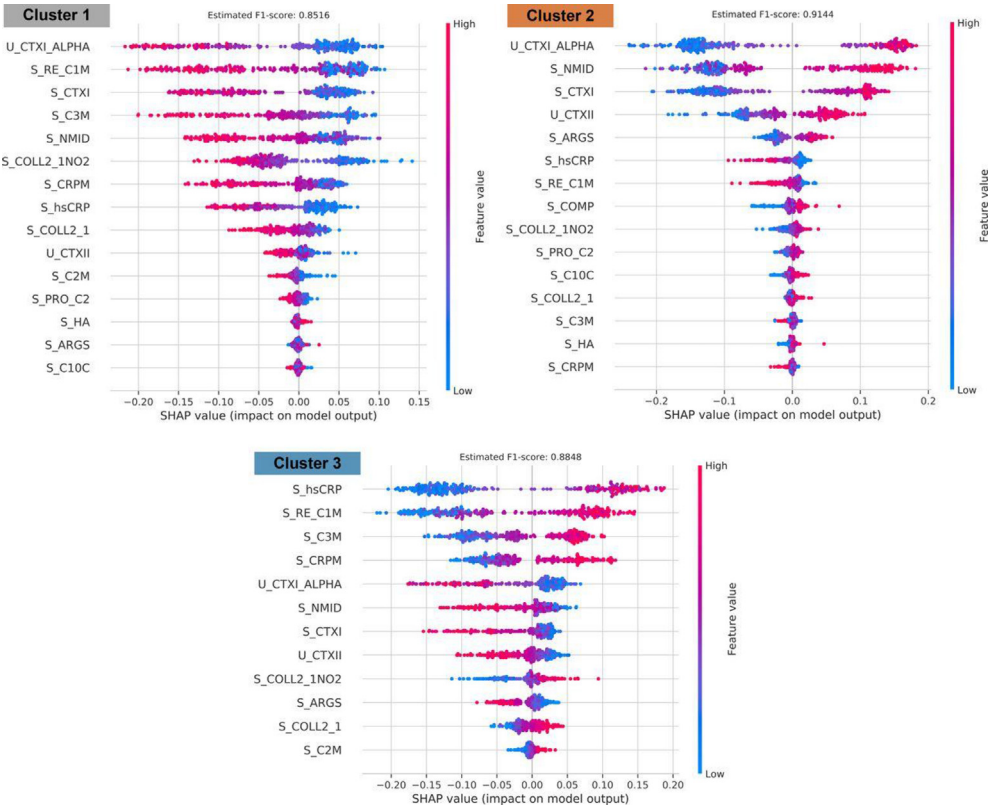

Fig. 5. Impact of biomarker values on classification models decisions. Biomarkers are ordered by importance (most important on top). The SHAP values on the x-axis represent strength and direction of impact (positive value indicates increased probability of belonging to the cluster) for each patient. The color represents the biomarker value (blue if low, red if high). Reproduced from Angelini et al. Ann Rheum Dis 2022; 81:666–675, with the permission of BMJ Publishing Group Ltd and the European League Against Rheumatism.

degradation, inflammation, cartilage degradation) (Figs. 4 and 5). Interestingly, the methodology employed also produced consistent results in the FNIH and Osteoarthritis Initiative (OAI) cohort.

This recent work supports the existence of differential subtypes in OA and provides an exemplar on how biomarker clustering approaches could potentially drive stratification for OA clinical trials (Fig. 6) and contribute to precision medicine strategies for OA progression in the future [46,69–71].

PROTO consortium

The PROTO consortium is a new research initiative funded by the European Commission aimed at developing new cell-based therapies for OA. One of the key objectives of the PROTO consortium is to develop a better understanding of the underlying biological mechanisms involved in the development and progression of OA also using new immunological biomarker strategies and functional patient stratification using biomechanical gait analyses [72,73]. This includes characterizing patient's status on low-grade inflammation, joint tissue remodeling, and metabolic dysregulation in the disease on the one side and functional joint loading on the other. The consortium also aims to develop new tools and technologies for the diagnosis and monitoring of osteoarthritis, such as advanced imaging techniques and wearable sensors to monitor real live mobility and functional status and recovery. Ultimately, the goal of the PROTO consortium is to improve patient personalized treatment by patient stratification, individualized management, and intervention based on an advanced understanding of the underlying inflammatory status and its molecular and cellular consequences. We believe such understanding is essential to develop effective advanced therapies targeting degenerative inflammation in OA-affected joints, for example, by an allogeneic cell-based therapy strategy.

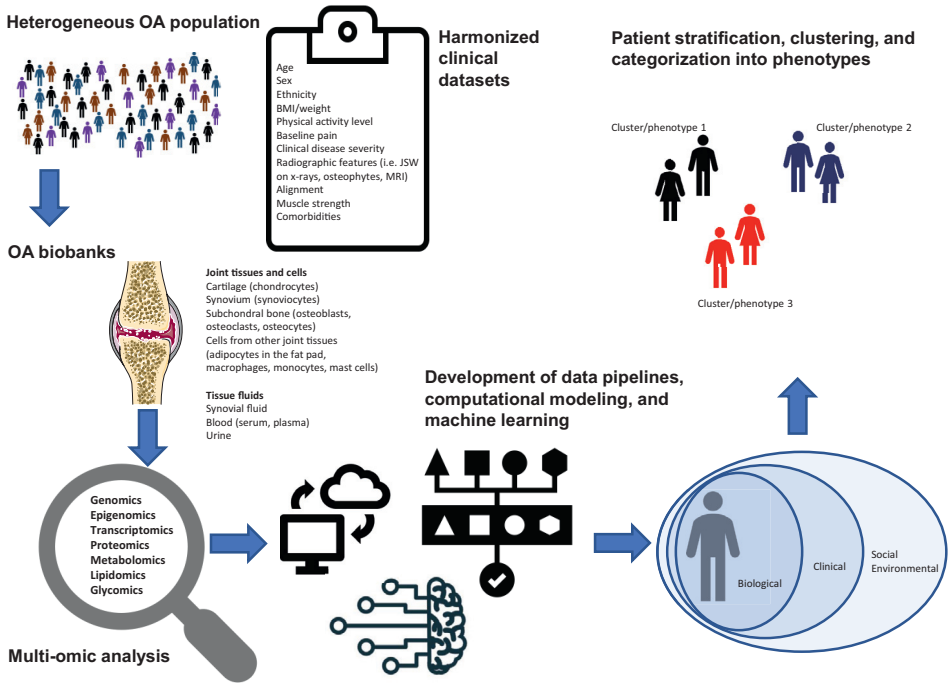

Fig. 6. Stratification of a heterogeneous population of osteoarthritis patients. Using this approach biological and high throughput multi-omics platforms may be used for patient stratification into different phenotypic categories that further refine the initial clinical classification criteria. Figure adapted from Ref. [89].

Future potential for biomarker innovations

The expectation of researchers, patients, and regulators is the establishment of pathways to develop innovative OA treatments that can modify the disease process in addition to having genuine impacts on the symptoms. Innovative biomarker discovery technologies and emerging platforms based on these technologies have been established to identify and characterize novel and exploratory OA biomarkers. Other platforms, such as organ-on-chip, and *in silico* models (using machine learning and/or artificial intelligence (AI) on big data) have already had a hugely positive impact in many other fields of medical research. Fortunately, in OA, things are picking up pace, and intersections between these innovations could potentially transform the way we conduct OA clinical trials and multi-disciplinary research to advance drug and biomarker development toward personalized medicine [74]. However, there are still no biomarkers that can serve as surrogate end points in OA clinical trials [75]. There are proposed study designs for potentially accelerated approval based on a surrogate end point and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease-modifying OA drugs [76] but no biomarkers have yet been able to pass this hurdle. Thus, there is a clear need to invest more time, intellectual effort, and financial resources and efforts to drive the development, validation, and qualification of OA biomarkers.

There is a clear medical need to couple a given disease activity with the optimal intervention for the right patient [77]. Therefore, more research is needed to integrate biomarkers in OA clinical studies and bring our expectations in alignment with the recent recommendations from the FDA guidance entitled, "Concept end points informing design considerations for confirmatory clinical trials in OA" [78,79].

Conclusions

OA remains a considerable challenge and a major burden to society. It is currently diagnosed clinically, and the clinical diagnosis is confirmed by imaging using radiograph, which remains the only available "gold standard" diagnostic technique used clinically and accepted by regulatory authorities. However, by the time the radiographic diagnosis of OA is made, the disease has progressed significantly and may be irreversible and unresponsive to any form of existing or experimental treatment. There is increasing emphasis on early detection of OA because early detection would allow more effective treatment of OA. This highlights a "window of opportunity" for using biomarkers to identify the disease earlier [80,81], thus improving clinical outcomes of current treatments, despite their inadequacies. However, it remains extremely challenging to use biomarkers, specifically biochemical markers in the asymptomatic stages of the disease. However, identifying biomarkers with the sensitivity and specificity to achieve this is a challenging problem in OA biomarker research. A systematic review published by van Spil and colleagues 10 years ago concluded that "None of the current biochemical markers are sufficiently discriminating to aid diagnosis and prognosis of OA in individuals or limited numbers of patients, or performs so consistently that they could function as an outcome in clinical trials." [82]. The conclusions of this study are still valid to date.

These challenges, along with the long-term futility of conventional radiography, bring into focus the crucial importance of combining biochemical markers with more sensitive imaging modalities such as magnetic resonance imaging (MRI) in early disease detection and progression monitoring as well as OA drug development [83]. The ongoing challenges also offer new and exciting opportunities for innovation and for the OA research community and pharmaceutical companies involved in developing DMOADs to develop better drugs.

In a previous review published in this journal [84], we questioned whether soluble biochemical markers of OA are close to being used in clinical practice. Our position has not changed, but we are increasingly optimistic that soluble OA biomarkers can be used for early disease diagnosis and DMOAD development. In the meantime, we need tools to integrate existing biomarkers into newer and more sensitive assays and biosensor platforms [85–88] and maintain a closer focus on the early disease diagnosis "window of opportunity". Biomarkers can still help us gain a better understanding of disease pathogenesis, and we still need new biomarker targets, monoclonal antibodies, and more sensitive biomarker assay platforms.

Practice Points

- Soluble biomarkers are not routinely used in clinical practice and are unlikely to be used in such settings for the foreseeable future
- Soluble biomarker assays are useful for the detection and monitoring of disease progression in osteoarthritis (OA) clinical trials
- Joint-derived soluble biomarkers are likely to be more sensitive than conventional radiography for the detection, diagnosis, classification, and monitoring of OA and its progression
- Currently, the majority of clinical studies routinely collect serum, plasma, and urine for soluble biomarker measurements
- Future clinical practice will benefit from the introduction of new combination biomarkers incorporating imaging and soluble biomarkers

Research Agenda

- Biomarkers have significant potential for use in basic, translational, and clinical research
- Biomarkers may be used for personalized medicine and enabling osteoarthritis (OA) drug development
- Many soluble biomarkers remain exploratory molecules and have yet to be validated clinically
- Soluble biomarkers are increasingly being expanded beyond proteins and peptides to include lipids and microRNAs
- Research on soluble biomarkers continues to provide insight into the pathogenesis of OA, thus enabling a better understanding of the underlying pathophysiological mechanisms
- Biomarkers that define molecular endotypes of OA will be great assets in OA research
- Artificial intelligence (AI) has the capacity to deliver new combination biomarkers from the analysis of large and complex datasets
- Future research should focus on developing biomarkers with the potential of being endorsed by the regulatory agencies as indispensable drug development tools

Authors' contributions

All authors have made substantial intellectual contributions to the conception and writing of this review. All authors contributed to manuscript preparation and approved the final version submitted.

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