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The next breakthrough in rheumatology will require prioritizing diversity

Progress has been astonishing, but the need for personalized care can only be addressed through a universal focus on diversity and equity in rheumatology research.

Nature Reviews Rheumatology celebrates its 20th anniversary this month, having witnessed in the past two decades the transformation of the field. Clinical practice has tremendously improved through several key advances: the introduction of a handful of tailored treatments, including Janus kinase inhibitors[1], B cell-targeting monoclonal antibodies[2] and CAR T cells[2,3]; the genetic characterization of previously unknown rare autoinflammatory diseases[4]; and the expansion of omics-based patient stratification[5].

While celebrating this progress, we also need to consider what is required for the next breakthrough to materialize. Prioritizing diversity in research will be crucial for establishing personalized care in rheumatology.

No matter what rheumatic disease or clinical stage is being reviewed, the converging message seems to be that to translate the progress made over the past 20 years into clinical benefits, "targeted therapeutic interventions … must be integrated with patient-centred evaluation methodologies", as put in a Comment in this issue by Francis Berenbaum and Emmanuel Maheu[6].

The obvious bottleneck in this proposed approach relates not to a lack of technologies but to a scarcity of data that reflect patient diversity, as well as the absence of concerted action to include patients from diverse backgrounds in clinical trials. Overcoming this bottleneck is crucial for personalized medicine to materialize in the field of rheumatology, in which varied and rare clinical manifestations are often observed even under the same diagnosis.

Actively involving patients in rheumatology research and care is a first step in the right direction. Patient priorities, such as those highlighted in a Viewpoint in this issue[7], need to be considered, for example, when deciding on future clinical trial endpoints. In addition, "the non-clinical and clinical rheumatology research community [should mirror] the diversity of patient populations through health equity initiatives", as Elizabeth Rosser and Lucy Wedderburn emphasize in their Comment[8].

The challenge will be to allocate resources for the inclusion of underrepresented areas of the world and socio-economically deprived individuals, who reportedly are most affected by delays in diagnosis and disease burden[9]. In addition, the obvious gap in timely diagnosis and positive disease outcomes between women and men — at the expense of women — can only be addressed through a multi-disciplinary approach involving several medical specialties as well as social scientists[9]. Encouragingly, Ashira Blazer and Grace Wright note that although the field of rheumatology was not initially shaped for or by women, "women have slowly changed this [field] to make space for diverse perspectives"[10]. Collaborative platforms that facilitate multidisciplinary assessment of rheumatic diseases also have the potential to improve patient experience.

> **"…the optimal path forward is to ensure diversity in every aspect of clinical practice…"**

In summary, the optimal path forward is to ensure diversity in every aspect of clinical practice, so that the breakthrough of early diagnosis and equitable care can be celebrated at the journal's next notable anniversary. To achieve this outcome, rheumatologists should remain vocal about the need for diversity, equity and inclusion in research and, more crucially, do so in the currently transforming science–policy interface. *Nature Reviews Rheumatology* will offer space for all these perspectives.

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20 years of *Nature Reviews Rheumatology*

Peter E. Lipsky

Both rheumatology and the publishing environment have seen tremendous changes over the past two decades. Here, the first Editor in-Chief reflects on the challenges faced by this journal and what it has taken to remain at the forefront of the field.

Time moves forward inexorably, and often we are so busy that we do not notice its passage. When there is an important anniversary, however, we get the chance to reconsider the designated event, but in the much richer tapestry of the elapsed time and what has transpired. So it is with the 20th anniversary of *Nature Reviews Rheumatology* (NRR). Twenty years after its first publication, it is worth reviewing the journal's challenges and the unique features that contributed to its success.

First published in November 2005 as *Nature Clinical Practice Rheumatology* (NCPR), the mission of the journal was to inform rheumatologists about the latest developments by "filtering the research and providing peer-reviewed discussion and analysis."[1] This aspiration was somewhat quixotic for a number of reasons. First, it was not clear that rheumatology needed a journal summarizing recent advances. A number of the existing journals published review articles, and the annual meetings of professional societies provided opportunities to review new developments. Moreover, at that time, physicians identified that they spent about 30 minutes per day reading the literature and mostly only the abstracts of articles, so it was not clear that a new journal could find an audience[2]. Also, the new journal was not affiliated with any professional society, so it lacked the imprimatur these groups afforded. Finally, there was no obvious way to gauge success. While the 'impact factor' is a widely used, if problematic, measure to score the academic value of a medical journal, it has little value in judging whether an article or journal influences clinical practice[3]. Despite these caveats, the journal was launched and rapidly gained acceptance in the rheumatology community. Much of the early success resulted from the amazing commitment of the founding editor, Jenny Buckland, and assistant publisher, Julie Solomon, along with a dedicated team of editors. They set a standard of quality, along with interaction with the rheumatology community, that has kept the journal at the forefront of the field and cemented its reputation as a source of accurate, objective and understandable information in a rapidly evolving field.

NCPR was launched a few years after the introduction of biologic therapies for rheumatoid arthritis (RA). The table of contents[4] of the first issue included Viewpoints on the 'window of opportunity' in RA and whether assaying autoantibodies might be useful in diagnosing early RA. Reviews included 'Optimum therapeutic approaches for lupus nephritis' and 'Cytokine networks—towards new therapies for [RA]'. Notably, a Practice Point asked 'Is combination therapy with methotrexate and intramuscular gold an efficacious method of treatment for RA?' The subjects were of contemporaneous importance, and some hinted at future developments. However, it was impossible in 2005 to predict the astonishing developments in rheumatology over the subsequent 20 years and the stress on rheumatologists to remain up to date. Moreover, it was unclear whether NCPR (re-launched as NRR in 2009) could continue to fulfill its mission in the rapidly changing environment.

Since the launch of this journal, biologic and targeted synthetic DMARDs have been developed for many rheumatic diseases; there is now focus on remission and prevention in some diseases, such as RA; conditions have been re-named (for example, axial spondyloarthritis and granulomatosis with polyangiitis) and expanded (for example, non-radiographic spondyloarthritis); disease spectra have been greatly expanded (for example, psoriatic arthritis); new nosology has been developed to aggregate previously diverse clinical syndromes into pathogenically defined entities (for example, IgG4-related disease) and entirely new diseases described (for example, autoinflammatory diseases and autoantibody-associated myopathies). This remarkably rapid growth has generated considerable stress on practitioners to remain current. However, it has also generated a new audience as sub-fields of rheumatology develop — namely, academic rheumatologists who desired to remain contemporary in areas upon which they may not focus or in diseases that they may not often encounter. The unique capacity of NRR to accommodate both audiences has been one key to its ongoing success.

A second challenge to the success of the journal has been the changing nature of the scientific and medical publishing arena. A number of major changes have altered scientific and medical publishing over the past 20 years, making the availability of objective information both more challenging and more competitive. The first is the expanding 'tyranny of the impact factor'[5]. The impact factor was developed by Eugene Garfield 70 years ago "to evaluate the significance of a particular work and its impact on the literature and thinking of the time," with the goal of eliminating "the uncritical citation of fraudulent, incomplete or obsolete data."[6] Despite its initial goal of evaluating the "significance" of individual papers, the impact factor has transformed into a means of ranking the 'quality' of scientific journals. Because it is believed that the impact factor has commercial and societal implications, many scientific and medical journals have altered their publication policies in the hope of elevating the impact factor; these changes include limiting the number of articles, and trying to focus on clinical trial results, reviews and guidelines that are anticipated to be highly cited. However, the goal of identifying articles with a high likelihood of being cited has tended to extend review times, foster 'desk rejections' by editors, and influence journals and reviewers to expect 'complete stories' told with multiple-part figures and extensive supplementary material but truncated text. The net effect has been that science articles in high-profile journals are even more difficult to read and understand. As a result, many journals now rely on 'graphical abstracts' and 'editor's summaries' to explain the science and to aid even the most sophisticated reader to understand the content. In this context, finding the nuggets of new information can be even a bigger challenge, and communicating that information effectively to persons not in the exact field can be more difficult.

An additional challenge has been the growth of open-access journals. NRR (then NCPR) was born just at the beginning of the 'open-access era'. Originally conceived as a means of rapidly communicating scientific information in a manner that permitted the investigator to retain the copyright, the commercial value of the open-access model was quickly recognized, and some publishers realized they could profit handsomely with very little investment. As a result, scientific publishing exploded, with the generation of a large number of new and often low-quality (but profitable) journals. This put additional strain on the field with an increased pressure on over-taxed reviewers and, more importantly, the requirement to sift through a larger and larger number of publications to find the few pearls. This task has been made even more difficult by the growth of 'paper mills' and associated enablers selling poor quality and/or fabricated research to those desperate to publish[7].

Finally, in 2005, it was difficult to anticipate the influence of the internet and social media on communication of scientific and medical information. More and more doctors have come to rely on information available on the internet or from 'trusted' sources on social media. Much of this information comes from personal experience or uncritical summaries of papers, press releases or company-sponsored marketing materials. Although certainly of less value and reliability than the interpretative Reviews available in NRR, when time is of essence, they provide a formidable challenge for a clinician's attention. Additionally, there is the new challenge of various artificial intelligence (AI) platforms that can provide detailed, on-demand, tailored summaries of nearly any topic, albeit with the risk of hallucinations and colored by sycophancy. The emerging ability of AI to serve as a sophisticated search engine with the capacity to carry out a 'dialogue' on a specific topic may evolve as an important means of identifying new information and interrogating the scientific literature in the future. However, AI platforms currently lack the point of view (POV) of the expert, an essential feature of NRR's Reviews.

Despite all of these changes in rheumatology, scientific and medical publishing and modes of communication, NRR has grown in prominence and maintained its relevance. Much of its success relates to the approach of its editorial staff, now led by Chief Editor Sarah Onuora. The editors are very much involved in the rheumatology community, attending meetings and interacting with many members of the rheumatology community. As a result, they are actively aware of current issues of interest to the community and are able to commission relevant articles. Moreover, they are actively engaged in the construction of articles. Rather than being passive copy editors worried about grammar and syntax, they are active collaborators in developing the articles. Although this can be trying for the academic author, all would agree that the input of the NRR editors makes the articles clearer, more focused and of greater value to the reader. Finally, the articles contain the POV of an expert. Many reviews or even AI can regurgitate the currently known 'facts', but an NRR article interprets them in the context of the experience and knowledge of an expert, adding additional perspective. Although 'eminence' is not graded as highly as evidence, it can be extremely important when trying to evaluate new and complex information. Finally, the graphics are great, summarizing complex points in a simple but nuanced manner, and are excellent teaching tools. All of these features serve to distinguish NRR content from that of other journals and make it likely that the journal will continue its prominence over the next years, regardless of future changes in rheumatology or the communication environment.

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Looking to the new horizon in rheumatology research

Elizabeth C. Rosser & Lucy R. Wedderburn

The future of rheumatology research will be defined by the growing era of personalized and stratified medicine, with a focus on establishing drug-free remission. In the face of substantial global upheaval, now is the time to ensure no patient group is left behind by prioritizing research equity and inclusion.

Since the establishment of *Nature Reviews Rheumatology* in 2005, treatment of rheumatic diseases has changed beyond recognition. Alongside the anti-TNF inhibitor etanercept, there are now an additional nine biologic DMARDs (bDMARDs) and a new class of targeted synthetic DMARDs that have been approved for the treatment of rheumatoid arthritis[1]. Most rheumatic diseases also now have at least one bDMARD approved for disease management in adults. Although these treatments have improved outcomes for many people, 20–40% of patients do not respond to first-line bDMARDs; efficacy can wane over time, and the field lacks reliable tools to predict treatment response or disease trajectory. Emerging technologies and large-scale multi-omic enterprises have provided unprecedented insights into the molecular pathways that drive disease pathology. While the categorization of patients by clinical presentation is informative, it is becoming clear that overlapping molecular pathways that drive tissue damage, such as type I interferon signatures, or the roles for TNF and IL-6, span multiple rheumatic diseases regardless of clinical manifestation. A considerable conceptual shift is that the application of stratified biologic therapies based on molecular pathologies, rather than clinical phenotypes, might improve therapeutic outcomes[2,3]. In the next 20 years, building on this platform is vital, as moving rheumatology research forward will be defined by growing stratified and personalized medicine initiatives.

This new era will require accessibility to new and existing datasets, both clinical and biological, and transparency around clinical metadata. Untold millions of pounds have been invested in profiling immune cells within the blood and inflammatory tissue sites in rheumatic diseases using large-scale omics analyses. This large-scale investment makes it imperative to democratize these data by making them widely available and enabling researchers from different disciplines to assess rheumatic disease trajectories alongside immunological signatures. These existing datasets are complemented by new efforts to enable bio-sampling and the measurement of biomarkers within clinical trials. Collecting samples from inflamed tissues and matched blood samples before and after treatment with immunomodulatory drugs should improve understanding of the biological pathways underpinning treatment response. Studying individuals who do not respond to treatment within clinical trials is also necessary to provide insights into how the modulation of molecules targeted by different medications can influence downstream pathways associated with vastly disparate disease outcomes. Innovative approaches to data integration and interrogation, such as machine learning and artificial intelligence, are needed to maximize the potential of these new and existing big datasets, which includes not only omics data but the increasing data available from electronic health records[4].

Despite these exciting initiatives, many questions remain unanswered. Current therapeutic strategies are based on immunosuppression, but the new goal is to move towards drug-free remission for most patients, which essentially amounts to a functional cure of many disorders. Accordingly, understanding how to 'reset' the immune system and, in particular, how to restore homeostasis in affected inflammatory tissue sites is key. Further areas of clarification include why distinct rheumatic diseases are associated with distinct comorbidities, such as the strong association of juvenile idiopathic arthritis with eye inflammation and spondyloarthritis with gut inflammation. A substantial knowledge gap regarding the pathways that control tissue tropism in autoimmunity persists, including whether immune cells recirculate between different inflammatory sites in the same individual. Finally, despite detecting changes in the gut microbiota in many rheumatic diseases, it is still unknown whether these observed changes are important mechanistically, if they precede the onset of disease, and if targeting the gut microbiota therapeutically through dietary changes, pre- or probiotics or other strategies will have a place in the future of clinical practice.

Even with ongoing progress in these research areas, certain patient groups remain underserved, especially those with rare phenotypes. Thus, ensuring a comparable pace of research innovation occurs for these patients as that for those with more common diseases is crucial. The combined prevalence of rare rheumatic diseases exceeds the prevalence of some more common disease subtypes, and studies should assign them equal importance. Much can be learned from rare diseases regarding pathways driving inflammation. A noteworthy example is the inclusion of children and young people in research studies as, thus far, most research studies have focused on adult phenotypes. Innovations that address this gap include the application of multi-omics techniques to biopsy-obtained synovial tissue samples collected from children and young people with arthritis for the first time, which shows that unique cellular niches are associated with severity and age-of-onset[5], and the identification of blood biomarkers that predict treatment response to first-line therapies in childhood arthritis[6]. In the future, we hope that the often-ten-year delay in new therapies for adults being available for children and young people is reduced[7] and that there will be examples in which child-led research leads to the development of therapies with broader applicability across the age-spectrum.

When considering diversity within the understanding of rheumatic disease pathology, there is an emerging focus on considering sex and gender in immunological research studies. The next stage of ensuring gender parity in rheumatology research is to consider

biology unique to women's health including the large fluctuation in sex hormone levels associated with first menarche, the menstrual cycle, pregnancy, breastfeeding and menopause alongside the effect of exogenous hormones taken in the form of the contraceptive pill or in menopausal hormone therapy. Importantly, women often report changes in rheumatic disease symptoms during transitional stages in their life and yet, mechanistic evidence as to why these changes might occur remains limited. Inclusion of gender-diverse and transgender people with matched data regarding hormone therapy is also imperative[8]. In addition, and incredibly starkly, marked health inequalities in disease outcomes remain associated with socio-economic deprivation. Despite this obvious need, studies often do not reflect the true diversity of patient populations. The field of rheumatology should also strive towards a situation in which the non-clinical and clinical rheumatology research community mirrors the diversity of patient populations through health equity initiatives[9].

In addition to challenges regarding research inclusion and equity, assessing how the ever-changing geopolitical and academic landscape will affect the future of rheumatology research is essential. For example, in the UK, a complex array of factors, including student debt, financial pressures in institutions and changes in training programmes, has led to a decline in clinically trained academic research staff[10]. An urgent co-ordinated effort is needed to stop this decline, or the future of rheumatology research will be severely affected. Clinical academics currently function as a linchpin in our field, integrating basic science with clinically relevant questions that have been fundamental for driving therapeutic innovation to this date. Another example is the increasing infringement on freedom of movement between countries. Without support across all stages of research and clinical careers, from undergraduate to professor, from trainee to consultant, to support relocation to pursue research questions and/or travel to attend conferences and training courses, rheumatology research innovation will be curtailed. Facilitating free flow of ideas between individuals and reducing administrative barriers are necessary to ensure research moves forward in a timely fashion. This period in history in which academic institutions and hospitals are under immense financial and political pressures has made them and other stakeholders inherently risk adverse, and risk is necessary for true research innovation. These challenges are not specific to rheumatology research alone, but rather affect the global environment of scientific research.

The ultimate dream of any basic scientist, clinical researcher or patient within the rheumatology discipline is the discovery of a cure for these conditions with return to tissue homeostasis and drug-free remission. The field is moving in this direction. In the meantime, what is perhaps a more achievable goal, is a situation in which at time of diagnosis, rheumatologists can provide personally tailored information around stratified therapeutics, disease trajectory, safety of drug tapering and, ultimately, disease resolution. Despite challenges, the opportunities are immense, and this new horizon is an exciting time for rheumatology researchers. Consequently, an improved quality of life for all current and future patients living with the burden of a rheumatic disease should be our priority.

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A firm grip on hand OA: 20 years of progress and prospects

Francis Berenbaum & Emmanuel Maheu

In the past two decades the field of hand osteoarthritis (OA) has moved from resignation to action. Despite progress, such as the recognition of the phenotypic heterogeneity of hand OA (including inflammation- and/or metabolic syndrome-associated hand OA) and the standardization of imaging and treatment outcomes, challenges remain in achieving truly disease-modifying therapies.

In 2009, we published an article in *Nature Reviews Rheumatology* (formerly *Nature Clinical Practice Rheumatology*), titled 'Time for new outcome measures in hand osteoarthritis?', that called for a transformation in the assessment and management of hand osteoarthritis (OA)[1]. Despite its longstanding portrayal as a natural consequence of ageing rather than a disease, and its frequent perception as inevitable, this prevalent disease (the hand is the second most common site of OA, after the knee) affects the quality of life of the patient to an extent similar to that of RA, and pain associated with hand OA is a substantial burden, owing to a lack of efficacious treatments. In 2009, hand OA was often considered a 'second-class' discipline within rheumatology, lacking effective disease-modifying treatments and appropriate assessment tools. In the 16 years since our call to action[1], what advances have been made? In this Comment, we summarize the scientific, clinical and methodological advances that have shaped research on hand OA and highlight the remaining challenges in this field.

Diagnostic criteria

Since 2009, there have been advances in the diagnosis and assessment of hand OA, largely attributable to the analysis of data collected from hand OA cohorts (such as the HOSTAS, DIGICOD and NOR-HAND cohorts). In 2024, EULAR published new classification criteria in the form of a 15-point clinical-radiological score[2], with two main objectives: first, to enable earlier diagnoses; and second, to improve patient stratification. The aim of the criteria was to distinguish hand OA that affects the thumb base or the interphalangeal joints from OA of both the thumb and interphalangeal joints.

Clinical assessment

Concurrently, core disease-assessment tools have been refined. Nevertheless, the most widely used conventional pain and function scales (such as the visual analogue scale, the Australian/Canadian Hand OA Index, and the functional index for hand OA) are limited in their capacity to encompass pivotal clinical dimensions of patient impairment and subjective experience. Despite its importance, grip strength has received scant attention from the scientific community. Loss of grip strength can impair a wide range of professional, domestic and recreational activities.

Inflammatory activity, as indicated by the presence of soft tissue swelling, joint stiffness and the duration of such symptoms, is now widely acknowledged as a hallmark of hand OA. Its evaluation is mandatory in both ambulatory clinical practice and clinical research. Assessing synovitis (soft tissue swelling), pain flare and ultrasonography Doppler signals is pivotal for evaluating inflammation. Patients with hand OA who have synovitis in at least one joint exhibit more-severe structural damage and symptoms. Inflammation has been shown to predict worse clinical and radiographic outcomes[3,4].

Aesthetic discomfort has emerged as another important domain to assess in hand OA. A 2012 study emphasized the need for a specific tool for quantifying aesthetic discomfort[5]. Indeed, the use of specific assessments for this feature (for example, using a visual scale) has now become common, confirming the considerable impact of this domain on quality of life. Efforts have focused on standardizing objective endpoints for aesthetic damage to develop a validated tool.

Imaging

Substantial advances have been made in imaging hand OA. MRI has emerged as a pivotal tool for musculoskeletal imaging that enables the visualization of all joint structures and the detection of lesions, such as synovitis, early erosions and bone oedema, that are not visible on conventional radiographs. MRI images are scored with a validated quantitative scoring system, ensuring standardized assessments across readers[6]. Similarly, ultrasonography has been developed that can accurately identify osteophytes and synovial inflammation and assess synovitis[3]. The presence of synovitis or bone oedema in imaging studies has been associated with painful flare-ups and accelerated radiographic progression[4]. Artificial intelligence can also be used to analyse radiographic images and facilitate the automatic differentiation between OA hands and healthy hands, which could lead to more-objective screening and monitoring. Nevertheless, contemporary practice still relies on radiographic scores as the main instruments for evaluating disease severity and progression[6].

Hand OA phenotypes and personalized medicine

Hand OA is not a homogeneous entity; research has refined its classification into subgroups. For example, the erosive form of hand OA, which is diagnosed by central erosions in the interphalangeal joints on radiography, is associated with a more-severe phenotype[2,7] and is predictive of faster and more-severe structural progression[3,4]. This phenotype is also called 'inflammatory hand OA', owing to the occurrence of local inflammatory flare-ups (redness, swelling and pain in the fingers), although not all instances of erosive hand OA are accompanied by such symptoms. Inflammatory phases are characteristic of disease progression for a considerable number of patients; however,

clinical trials of systemic DMARDs (such as anti-TNF, anti-IL-6 or anti-IL-1 antibodies) have not demonstrated clear efficacy, which suggests a pathophysiology distinct from that of chronic inflammatory arthritis[8].

Personalized medicine approaches have also underscored the heterogeneity of clinical presentations. A multifactorial analysis of symptoms within the DIGICOD cohort identified five patient profiles, from those exhibiting mild symptoms to those experiencing considerable pain and aesthetic discomfort[7]. This study confirms that negative aesthetic perception is higher in patients with erosive damage and nodular deformities. Furthermore, systemic factors seem to influence symptoms; metabolic syndrome has been associated with high pain intensity in hand OA, irrespective of the location of the affected joint[9]. In addition, an inflammatory gut phenotype has also been associated with erosive hand OA and increased pain severity[10]. These findings suggest a metabolic phenotype, consistent with the concept of 'metabolic OA', in which low-grade inflammation associated with adiposity exacerbates pain. Several comorbidities have been associated with hand OA; coronary heart disease has been associated with worse clinical outcomes[11], and a greater incidence of hand OA has been reported in patients with HIV, especially in cases of metabolic syndrome[12].

Treatments

In the absence of curative treatments, the management of hand OA has long been limited to providing symptomatic relief through analgesics, topical and oral NSAIDs, orthoses and physical therapy, as stated in the 2019 EULAR recommendations[13]. According to the objective of these recommendations, the methodology for conducting clinical trials in hand OA has been refined, and assessment tools and outcomes have been better specified. Since 2009, a few pharmacological avenues have emerged; for example, a multicentre randomized controlled trial demonstrated that 6 months of methotrexate (20 mg weekly) significantly reduced pain compared with placebo in patients with hand OA with synovitis[8]. This result provides proof of concept that disease-modifying treatments, such as methotrexate, might have a role in inflammatory hand OA. By contrast, in another trial of patients with erosive hand OA, 10 mg of methotrexate weekly showed no superiority over placebo for pain relief[8]. Nevertheless, methotrexate could be a promising treatment for hand OA with synovitis and inflammation. Inflammation should be a target for hand OA; however, anti-inflammatory therapeutics, such as colchicine and hydroxychloroquine, have shown minimal efficacy when compared with placebo[8]. Despite these setbacks, the field of therapeutic research remains open to novel avenues. Results from a 2024 study indicated that targeting osteoclasts with denosumab might slow radiographic progression of erosive hand OA, but with no substantial pain reduction[14]. This result underlines the potential of bone-protection strategies for destructive forms of hand OA. A 2024 review of nonpharmacological and pharmacological treatments identified 65 published randomized trials on hand OA between June 2017 and December 2023, compared with 25 studies between 1994 and 2000, indicative of a growing number of studies performed[15].

Conclusion

The conceptualization of hand OA has undergone a substantial transformation. The severity of hand OA is now more widely recognized, new diagnostic and assessment tools have emerged, and the diversity of phenotypes is better understood. Concurrently, considerable progress has been made in the domain of outcome measures, including the development of standardized imaging scores, improvement in the reliability of functional tests, and the consideration of morning stiffness, synovitis assessments, aesthetic concerns and quality of life. Nevertheless, more-reliable, validated and sensitive assessment tools are urgently needed in clinical research. A set of common endpoints for hand OA is currently being developed by international initiatives (such as OMERACT). Given these challenges, the rheumatology community needs to intensify efforts across several domains, including a reorientation of research agendas to study not only the development of new therapeutics but also the improvement of tools for assessing hand OA (Supplementary Box 1).

The rheumatology community should also translate the progress made over the past 20 years into tangible clinical benefits for patients, building on that progress. To achieve this objective, targeted therapeutic interventions based on comprehensive assessments of inflammatory, erosive or metabolic phenotypes must be integrated with patient-centred evaluation methodologies. This integrated research approach is mandatory to identify effective treatment strategies that improve outcomes for people with hand OA.

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A 20-year reflection on women in rheumatology

Ashira D. Blazer & Grace C. Wright

The collective priorities of the rheumatology field represent the lived experience, and therefore diversity of its members. The 'mould' of rheumatology, that is, its culture, structures and expectations, was not created for or by women, but women have slowly changed this mould to make space for diverse perspectives.

For decades, women have been underrepresented in rheumatology; in 2000, women made up only around 20% of clinically active rheumatologists[1]. Today, women remain underrepresented in academic leadership, editorial boards, grant review panels and decision-making positions. In this Comment, we explore how women have shaped rheumatology and the ways in which the field can in turn better support, retain and elevate women.

Sex differences in autoimmune pathogenesis

Systemic autoimmune rheumatic diseases (SARDs) disproportionately affect women. Researchers such as Betty Diamond have helped to identify key molecular mechanisms that underlie the immunomodulatory effects of oestrogen. Her lab found that downstream signalling through oestrogen receptors on the cell surface of B cells impairs B cell receptor-mediated apoptosis[2]. Later, epigeneticists such as Claire Rougeulle expanded the understanding of the X chromosome and its role in autoimmunity. Her work has shown that X-linked immune genes, such as *TLR7*, *TLR8* and *FOXP3*, escape X inactivation by *Xist* non-coding RNA[2]. The resulting accessible chromatin leads to a gene dosage effect that increases autoimmune susceptibility with each additional X chromosome. These discoveries, along with those of other female scientists, have clarified fundamental aspects of disease pathogenesis and identified new therapeutic targets that could lead to more precise and effective treatments.

Reproductive health

For decades, little was known about risk stratification for pregnant people with SARDs. Female rheumatologists Jane Salmon, Jill Buyon and Lisa Sammaritano transformed reproductive care by publishing the landmark PROMISSE (predictors of pregnancy outcome: biomarkers in SLE and APS) study[3]. This study was the first to define risk factors for adverse pregnancy outcomes in systemic lupus erythematosus (SLE) including high disease activity, hypertension and the presence of antiphospholipid antibodies[3], which established the foundation for informed family planning in SLE. To fill an important knowledge gap in rheumatoid arthritis (RA) treatment during pregnancy, clinical epidemiologist Kimme Hyrich leveraged The British Society for Rheumatology biologics register to collect prospective data on pregnancy outcomes in women treated with TNF inhibitors[4]. Reproductive health advocates such as rheumatologists Megan Clowse and Mehret Talabi have developed innovative clinical support tools that integrate reproductive health planning into routine clinical care through counselling frameworks to facilitate shared decision making[5]. These same women exhibited leadership beyond the clinic following the repeal of Roe versus Wade. They acted as powerful voices speaking on the safety and necessity of abortion access for individuals with SARDs and advocated for wider access to DMARDs when these medications were being limited owing to their abortifacient properties[6].

Equity in clinical trials

Women have also led the way in addressing gender and racial equity in clinical trials. Despite their risk of severe disease, women of colour remain systematically underrepresented in clinical research. Epidemiologist Titilola Falasinnu found that African Americans represented 43% of people with SLE but just 14% of participants enrolled in clinical trials[7]. Her team identified systemic factors including socioeconomic inequities, geographic barriers and bias in healthcare provider (HCP) decision-making that drive this phenomenon[7]. Other female researchers have implemented initiatives to address these disparities. Rheumatologist Saira Sheikh, in collaboration with the American College of Rheumatology (ACR), developed an innovative program to train both HCPs and community health workers to increase knowledge, self-efficacy and intention to enrol diverse patients in clinical research[8]. These efforts demonstrate that both discovery and implementation can help to promote diversity and therefore the generalizability of findings from rheumatology clinical trials.

Pain research

Female researchers have elevated pain research as a legitimate and complex area of scientific inquiry. Rheumatologists Patty Katz and Lindsey Criswell showed that women with RA were more likely to report severe pain, have higher rates of depressive symptoms and experience more functional limitations than men[9]. Falasinnu's group found that organ damage and disease activity in SLE explained only one-third of pain severity[10]. The main contributory factors were psychosocial and sociodemographic in nature. Individuals who experienced depression, sleep disturbance, substance use, self-blame, lower educational attainment or household income and single marital status reported higher levels of pain and lower quality of life[10]. This body of work underscores the importance of adopting a biopsychosocial model of pain in rheumatology that accounts for lived experience, structural inequities and intersecting vulnerabilities, shifting the pain discussion beyond inflammation and antibodies towards a multimodal, patient-centred approach. By challenging the narrative around pain, these women have brought clarity, legitimacy and urgency to an area long relegated to the margins of rheumatological care.

Advocacy

Women in rheumatology, as in other medical disciplines, have been instrumental in advancing structural reforms that promote work–life integration. Birthing parents face disproportionate financial burdens, from unpaid parental leave to reduced productivity associated with lactation. Acknowledging the effects of these barriers, organizations such as the American Medical Association have endorsed 12 weeks of paid family and medical leave for HCPs. Female leaders have expanded the scope of medical leave to include pregnancy, abortion, stillbirth, adoption, caregiving for ill family members and even safe leave in the context of intimate partner violence. At institutions such as the University of California, San Francisco, female leaders have pioneered clinical scheduling innovations that support lactating HCPs, such as reserving one 30-minute lactation break per half-day clinic session. These efforts enable women to thrive as both parents and professionals, while helping close the gender wage gap in medicine.

Extending care

Female rheumatologists in countries with workforce shortages face additional challenges but continually strive to improve patient care. In Accra, Ghana, rheumatologist Dzifa Dey founded the Rheumatology Initiative to expand rheumatology care capacity. She trains non-specialist HCPs and patient advocates to recognize, manage and educate on SARDs, while lobbying the Ghanaian government for improved access to DMARDs[11]. Her work has secured funding, political support and community empowerment for patients across the region. In the Caribbean, rheumatologists Amanda King and Cindy Flower have led similar efforts through the Caribbean Association of Rheumatology. By training primary HCPs to recognize and manage SLE earlier, they have substantially lowered the time to referral for individuals with SARDs, which has reduced morbidity and improved quality of life in regions where access to specialist care is limited[11].

Call to action

As the proportion of women in rheumatology grows, so too does their collective influence on the field's priorities and innovations. This demographic shift will continue to drive discovery and advance health equity; however, women in rheumatology face substantial challenges in retention and promotion. The demanding nature of medical practice can lead to extended work hours, leaving little time for personal life and self-care. Many female physicians also have responsibilities as caregivers, making it difficult to balance professional obligations with family duties. In addition, female physicians might receive inadequate institutional support for initiatives that promote work–life integration. The field must therefore increase awareness about specific challenges that affect the recruitment and retention of women rheumatologists.

Professional networking, mentorship and sponsorship tailored specifically for women are key to building these supportive spaces. Women such as Puja Mehta, former chair of The Early Career Research Network, have supported trainees through mentorship and programming that highlight issues such as authorship, power dynamics and academic disagreement[12]. Equally important is democratizing the promotion process to value the service work women provide within institutions. The Association of Women in Rheumatology (AWIR) was founded to address these exact needs. With a mission to promote gender equity, AWIR has built a robust infrastructure that provides tools, mentorship and leadership training tailored to women in the field. Over the past decade, it has empowered women to navigate the dual demands of personal and professional life. Women are a powerful force for change, discovery and health equity in rheumatology. By actively supporting their retention and advancement, the field not only honours their contributions but also embraces the inclusive change necessary to serve our patients.

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Competing interests

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Autoinflammatory disease

DADA2 as an autosomal dominant disease

Mutations in the *ADA2* gene (which encodes the ADA2 enzyme) cause deficiency of adenosine deaminase 2 (DADA2). DADA2 is described as a monogenic, autosomal recessive autoinflammatory disease, as individuals who carry a single pathogenic variant of *ADA2* are generally defined as asymptomatic carriers. However, some individuals present with clinical symptoms of DADA2 despite being heterozygous carriers of pathogenic *ADA2* variants, albeit with no clear disease mechanism.

A study now provides insights into how specific *ADA2* variants might cause disease in heterozygous carriers. Corresponding author of the study, Isabelle Meyts, explains "we encountered ten patients from seven kindreds with a typical and often severe DADA2 phenotype, yet they all carried a single pathogenic variant in the *ADA2* gene. More interestingly, in two pedigrees there was an autosomal dominant inheritance pattern, albeit with incomplete penetrance. This finding convinced us to pursue this study."

The authors investigated the effects of *ADA2* missense variants on the secretion of the wild-type ADA2 protein. Four variants considerably reduced wild-type protein secretion: G47A, G47R, G47V and Y453C. Assessing the effects of each variant on wild-type ADA2 enzymatic activity revealed that the variants G47A, G47R, G47V, R169Q, E328K, H424N and Y453C had a dominant-negative effect on both intracellular and extracellular enzymatic activity.

Enzymatic activity was then measured in the sera of the ten heterozygous carriers compared with healthy DADA2 carriers and non-carriers. Both healthy DADA2 carriers and individuals with DADA2 had reduced levels of enzymatic activity compared with healthy individuals. However, serum levels of enzymatic activity could not be used to identify those variants with autosomal dominant-negative effects.

When assessing the prevalence of the identified variants in the general population, the authors found that the R169Q variant was the most common. Analyses of two databases (the UK Biobank and FinnGen) indicated that the R169Q variant was associated with clinical presentation of DADA2. "These findings imply that the incidence of DADA2 is higher than the published 1 in 222,146 individuals," notes Meyts.

"Our study has multiple leads for future research. First, we want to understand the incomplete penetrance — we will investigate monoallelic expression of the *ADA2* allele but also explore polygenic risk scores. Second, as a dominant-negative effect of some variants was not reflected in ADA2 enzymatic activity in the serum, we aim to identify a more sensitive measure to detect ADA2 deficiency. Third, this study highlights the importance of pathogenic validation of variants in *ADA2*, research into the dominant-negative effect of *ADA2* variants is required to improve diagnosis and optimise treatment. Finally, the population genetics analysis gave us interesting leads to further study the role of ADA2 in other conditions" concludes Meyts.

Holly Webster

Original article: Wouters, M. et al. Dominant negative *ADA2* mutations cause ADA2 deficiency in heterozygous carriers. *J. Exp. Med.* **222**, e20250499 (2025)

Immunopathogensis

STING-driven necroptosis linked to autoinflammatory disease

Research reveals that the cellular sensor protein STING induces necroptotic inflammation, and that this mechanism underlies inflammatory disease in a mouse model of STING-associated vasculopathy with onset in infancy (SAVI). The findings also suggest a potential therapeutic approach for STING-driven autoinflammatory diseases.

"By establishing that STING-driven necroptosis causes pathological inflammation in SAVI, our work provides the first direct evidence that necroptosis can act as a pathogenic mechanism in its own right, not merely as a fail-safe in the absence of apoptosis," notes Gianmaria Liccardi, corresponding author of the paper published in *Nature*.

The researchers showed that deficiency of caspase 8 in mouse keratinocytes leads to activation of STING, which drives interferon-dependent upregulation of ZBP1 and MLKL, thereby sensitizing the cells to necroptosis. Further investigations revealed that the necroptosis induced by STING activation is mediated via a FADD–RIPK1–RIPK3 complex independently of the TNFR1 receptor, and that STING signalling contributes to TNF–TNFR1-driven necroptosis and inflammation, potentially through autocrine TNF production and activation of NF-κB.

In SAVI, gain-of-function mutations lead to chronic activation of STING. Transcriptomic analysis of samples from individuals with SAVI and from mice with caspase 8 deficiency in keratinocytes revealed an overlap in upregulated genes, including genes related to the interferon response, nucleic acid sensing and necroptosis. In a mouse model of SAVI, deletion of RIPK3 rescued mice from the immune abnormalities, tissue pathology and reduced survival induced by STING gain-of-function.

"Our findings suggest that inhibition of necroptosis, and of programmed inflammatory cell death more broadly, could become a therapeutic strategy for STING-driven autoinflammatory diseases," remarks Liccardi. Given that STING activation is implicated in several other interferonopathies and autoinflammatory conditions in addition to SAVI, targeting these cell death pathways could have broad therapeutic implications, although further research is needed to confirm the translational value of this approach in human disease.

Sarah Onuora

Original article: Kelepouras, K. et al. STING induces ZBP1-mediated necroptosis independently of TNFR1 and FADD. *Nature* https://doi.org/10.1038/s41586-025-09536-4 (2025)

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The role of the patient in rheumatology

Jeanette Andersen, Janet Church, Seth Durrant, Sue Farrington, Noriko Okochi & Natasha Trehan

In this Viewpoint article, six patients and patient advocates discuss the role of the patient in rheumatology, the current unmet needs of patients and promising advances. By reflecting on their own lived experiences, the authors emphasize the integral role of patients for progress in the field.

How do patients influence policy, research and healthcare in rheumatology?

Jeanette Andersen: As chair of Lupus Europe, I see patients as having a vital role in shaping policy, research and healthcare in rheumatology, particularly for conditions such as systemic lupus erythematosus (SLE). Patients influence these areas through active advocacy and participation in organizations such as Lupus Europe that conduct surveys, host patient panels and collaborate with clinicians to highlight real-world experiences. For instance, Lupus Europe's involvement in European Reference Networks (ERNs), such as Connective Tissue and Musculoskeletal Diseases (ReCONNET), enables patient representatives to contribute to clinical guidelines[1] and research priorities. I'm personally engaged as a European Patients' Academy-trained patient expert, leading the Lupus Europe Patient Advisory Network, which matches trained patient experts with research projects from academia, the pharmaceutical industry and the EMA. In addition, committees such as European Alliance of Associations for Rheumatology (EULAR) and People with Arthritis/Rheumatism in Europe (PARE) push for patient-centred education and research. Patients also influence policy by lobbying for better access to care; Lupus Europe has made efforts to reform referral pathways to reduce diagnostic delays. Surveys, such as the 2020 (ref. 2) and 2024 (ref. 3) Lupus Europe studies, which provide data that inform policymakers and researchers, ensure that patient voices drive change in healthcare delivery and funding.

Janet Church: It is crucial that policymakers, researchers and healthcare industry stakeholders listen to patients, so they can truly understand the lived experience and impact of having a chronic illness. Because of the complexities and heterogeneity that autoimmune diseases present, symptoms can vary widely, so the only way to develop the most effective policies and programmes is to listen to a multitude of patient stories.

For advocacy and policy change, policymakers must gain an understanding of the barriers faced by patients in their country. In the USA, between 23.5 million and 50 million people have an autoimmune disease and the prevalence is rising[4]; quality of life can be so profoundly impacted that people might be unable to work, socialize and support a family. These diseases cause a substantial burden on the healthcare system and on the patient, as the high cost of treatment and care can be extreme. Telling patient stories to educate policymakers on the impact of these diseases on the lives of patients is the only way to enlighten them about the positive impact that policy can have, not only on the individual but also on the economy.

The patient voice is also crucial for research; patients communicating to researchers which areas are most important to them enables researchers to focus on the most impactful projects. For example, although dryness is an issue for almost all individuals with Sjögren's disease (SjD), fatigue or neurological complications often have the greatest impact on quality of life. Historically, research has mostly focused on dry eyes and dry mouth, but SjD also affects other organs, the nervous system and can cause fatigue and pain. Patient stories can also motivate researchers to look beyond the science and see the very human impact of what they do. I have been frequently heartened when told that patient stories led to a researcher's choice to focus on a particular autoimmune disease or diseases.

If researchers and healthcare providers (HCPs) assume that a disease such as SjD looks the same in everyone, then they will miss correct diagnoses, leading to a lack of optimal care and treatment. Also, laboratory results do not always tell the whole story, so HCPs should listen to a patient's concerns and trust that the patient knows their body best. To clearly convey the patient experience, The Sjögren's Foundation conducted the 'Living with Sjögren's'[5] patient survey to learn about disease impact from thousands of patients. In fact, this study of 3,600 patients determined the neurological impact on people with SjD and led The Sjögren's Foundation to invest in neurological research.

Seth Durrant: Patients can affect policy and research by raising awareness for diseases through open dialogue with HCPs, researchers and others. This dialogue can be enhanced by patients actively learning and engaging with scientific literature and research. Autoinflammatory diseases, as an example, are considered incredibly rare, and many HCPs are unfamiliar with them. As a result, patients must actively engage with the current research to best advocate for their health to their HCP or others. For me, I was too young to do the advocacy myself, but my parents had to dig into the science and determine possible diagnoses, and the related genetic tests and clinical trials available. This effort and communication with my doctors led to my early diagnosis and faster initiation of treatment. The capacity of a patient to raise awareness for themselves and others and tell their story is greatly enhanced by being informed about the science of their disease.

For example, I taught scientific literacy to an audience of patients attending a research conference a few years ago. This presentation prepared them for the daunting world of scientific jargon and was met with a great response from both patients and researchers. The patients were delighted to be welcomed into the scientific world as a vital and inspiring component of research. By being equipped with scientifically sound knowledge, a patient becomes not just a passive part of research but can be an active advocate for their health, especially when their disease is a daunting enigma. This example emphasizes why the patient needs to be vocal and, most of all, knowledgeable. The more patients share about their disease and life, the more the world will learn about these diseases and their diverse traits. As this knowledge spreads, more people will become aware, more diagnoses will occur and more lives will be improved.

Sue Farrington: Patient advocates, whether individuals, organizations or alliances, have an important role in driving change. In the context of rare diseases, collective action is essential;

for example, Scleroderma and Raynaud's UK (SRUK) collaborates with Rare Auto-Immune Rheumatic Disease Alliance (RAIRDA) UK and Federation of European Scleroderma Associations (FESCA) Europe. Both of these alliances have conducted patient surveys to gather data and insights into the lived experience of those with rare rheumatic diseases. These findings have been used to inform policy, highlight gaps in care and propose actionable solutions to decision-makers.

Patients also influence healthcare directly. SRUK contributed to the updated British Society for Rheumatology and EULAR guidelines for systemic sclerosis (SSc)[6,7], ensuring that they reflect real-world challenges and treatment preferences. Another example is the patient-led initiative to develop a quality standard for rare diseases, which filled a critical gap in the UK rare diseases framework[8]. Through rigorous scoping, stakeholder engagement and alignment with National Institute for Health and Care Excellence standards, a multistakeholder group of patients, clinicians and others created measurable benchmarks for diagnosis, mental health and patient experience.

Noriko Okochi: In the past 10 years, the role of patients in rheumatology has undergone a substantial transformation. Patients are now positioned as partners across a range of areas including research, health policy and clinical practice. Their participation in research is encouraged, not only in clinical trials and the development of clinical practice guidelines but also in all types of research, including basic science. Patients are increasingly recognized as collaborators throughout the entire research process, from identifying research questions and designing studies to disseminating and implementing results. Systematic training programmes for patients are also being developed to support their meaningful involvement in shared decision making[9].

In the field of health policy, patient organizations have influenced reforms through advocacy, such as making recommendations regarding healthcare funding and criteria for disability certification. In Japan, patient representatives also participate in the development of clinical practice guidelines[10] and policy review meetings organized by the Ministry of Health, Labour and Welfare, which enables patient voices to be reflected in both health care and policy-making processes.

Natasha Trehan: Young patient engagement is crucial, as their voices shape the future of advocacy, healthcare delivery and research. As a young person living with juvenile idiopathic arthritis (JIA), I have witnessed and contributed to this shift firsthand. I founded Take a Pain Check Foundation (TAPC), a youth-led non-profit that elevates young voices in rheumatology through peer support networks, leadership programmes, events and lived experience storytelling. TAPC initiatives include a podcast, educational initiatives and partnerships with clinicians, patient advocacy groups and researchers to integrate youth perspectives into healthcare systems. In addition to leading TAPC, I serve on national advisory committees (such as Pain Canada and Arthritis Research Canada) and research teams (such as the Choice Research Lab) as a patient partner, co-authoring peer-reviewed publications on health care transitions, neurodevelopmental disabilities and inclusive research practices. Patients like me are influencing policy by advocating at Parliament on critical healthcare issues that affect over 6 million Canadians with arthritis, presenting at international and national conferences, such as the American College of Rheumatology Convergence, the Canadian Rheumatology Association's Annual Scientific Meeting and the EULAR Congress, as well as co-developing tools and resources that genuinely reflect community needs.

What are the unmet needs of patients?

JA: From my experience and the insights that I have gathered through work at Lupus Europe, the unmet needs of individuals with SLE and other rheumatic diseases are multifaceted. Key issues include delayed diagnosis, which often takes years owing to non-specific symptoms such as fatigue and joint pain, with 45% of patients initially misdiagnosed[2]. Fatigue affects 85% of patients and remains poorly managed, alongside muscle pain (63%) and frequent flares[2]. Access disparities are substantial and include geographical barriers in rural areas, shortages of specialized rheumatologists, high medication costs and unequal reimbursement across Europe, all of which limit care. Quality-of-life and emotional impacts are profound, with high disease burden scores that affect the careers (58%), studies (51%) and emotional life (38%) of patients[2]. Communication gaps with clinicians persist, whereby patients feel that their holistic needs — beyond disease activity — are overlooked, and the use of non-pharmacological therapies or digital tools (only 14% adoption) are limited[3].

JC: Individuals with rheumatic diseases face many unmet needs owing to the complexity of these diseases. The heterogeneity of SjD is not yet fully understood, nor are the mechanisms that underlie the diverse clinical presentations of this disease. These limitations in current knowledge have prevented timely diagnosis and disease management for patients. Fatigue, brain fog, neurological symptoms and joint and muscle pain are areas that desperately need more research and targeted therapies. Additionally, the scientific and medical community needs to look beyond a single disease to common symptoms and biological pathways across rheumatic diseases. Understanding clinical phenotypes and endotypes

The contributors

Jeanette Andersen is 46 years old, lives in Denmark and was diagnosed with SLE in 2011. She is the chair of Lupus Europe, leader of the Lupus Europe Patient Advisory Network, an ERN ReCONNET patient representative and a steering committee member. She is also a leader for the Danish Lupus group, a EULAR PARE committee member and chair of the EULAR PARE education and research sub-committee.

Janet Church is the president and chief executive officer of The Sjögren's Foundation and lives with SjD. She leads the foundation with a focus on supporting the four million individuals in the USA with SjD, educating HCPs in many specialties, investing in innovative research and advocating for all patients.

Seth Durrant is a patient advocate for the Autoinflammatory Alliance, and has been diagnosed with CAPS. He supports patients through online community activities and advocacy work. He is a PhD candidate at the University of California, Merced, where he studies innate immune proteins in the de Alba Lab.

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is crucial for patient stratification, especially in SjD. Without better information on these signatures, getting a timely diagnosis and selecting the best treatment plan for each patient will remain challenging.

SD: Patients have many unmet needs, but a major one is a general awareness and knowledge of these diseases. Both patients and HCPs are unfamiliar with or dismissive of autoinflammatory diseases, owing to their rarity, and as a result, a patient might remain uninformed and untreated. When left untreated, these autoinflammatory diseases cause systemic damage and have a major impact on quality of life. Without proper awareness, an HCP might not diagnose a patient until much later in life, leading to permanent damage. Even after diagnosis, most treatments are not curative and can be associated with adverse effects that diminish the patient's quality of life.

Beyond the physical struggles caused by these diseases are the poorly considered psychological and social aspects. Autoinflammatory diseases are commonly diagnosed in childhood but as several of these diseases were only defined recently, many patients are just starting to transition to adulthood, which presents new pressures and challenges. I, and others, have experienced that adult-focused rheumatologists and other HCPs create a very different environment of care from paediatric HCPs, and there is little support for this transition. Many HCPs expect that the patient, having lived with the disease since childhood, understands and knows how to manage the disease well enough, without much additional input. However, these diseases continue to affect the patient's quality of life into adulthood, and the patient's management methods only go so far, as adult life brings new and different challenges. Adding to this lonely health-balancing act is the isolating mental strain caused by trying to meet the demands of busy everyday life and keeping up with peers. These autoinflammatory diseases are often invisible, and few fully understand or believe the pains and challenges that a patient might have. The high costs of diagnosis and treatment further exacerbate the financial, psychological and social strain on patients. Overall, individuals with autoinflammatory diseases who are transitioning to adulthood face many unmet needs, particularly in terms of social and psychological impacts.

SF: Despite advances, unmet needs remain stark. Delayed diagnosis is a persistent issue, particularly for rare conditions such as SSc; lack of awareness among HCPs leads to missed or late referrals. The complexity and variability of this disease further complicate diagnosis and treatment. Quality of life is another overlooked area. Patients report that simple daily activities become major challenges, and the disease can be disabling or even fatal. These impacts are often invisible to the healthcare system. Social and economic burdens — such as employment loss, financial strain and isolation — are also under-recognized. Surveys conducted by RAIRDA and FESCA have highlighted inefficiencies, gaps and limitations in care. The Rare Care Matters report (2025)[11] and the FESCA report (2023)[12] underscore the urgent need for better support, earlier intervention and more holistic care approaches.

NO: Although the importance of patient engagement is increasingly emphasized globally, substantial regional disparities remain in the conception and implementation of such engagement. In particular, the perspective of considering patients as equal partners in research and medical decision making is substantially behind in countries in Asia compared with countries in Europe and the USA. This delay is not limited to rheumatology but is observed across various disease areas[13].

In major academic rheumatology societies, such as EULAR and the American College of Rheumatology, systems are being developed to incorporate patient perspectives, including sessions specifically dedicated to patients in scientific meetings; however, such sessions are rarely found in academic meetings in countries within Asia. Educational programmes and training opportunities that facilitate genuine collaboration between patients and researchers are lacking in many of these countries. The role of patients in research remains unclear, except for a few selected studies, and patient involvement is often limited to 'advice' rather than true 'co-creation'. The majority of patients in many Asian countries are unaware that their lived experiences can contribute considerably to research, and there is no existing framework in these regions to connect patients who wish to collaborate with researchers. As a result, in some regions, research is being conducted without incorporating patient experiences and perspectives at all, thereby undermining the objectivity and inclusivity of scientific inquiry and representing a substantial loss of valuable insight for the global community.

In the field of rheumatology, mental-health support remains a major unresolved issue. Although certain conditions, such as neuropsychiatric lupus and glucocorticoid-induced psychosis, require specialized treatments by rheumatologists, psychological intervention by trained mental-health professionals remains extremely limited, despite the high prevalence of psychiatric comorbidities[14].

Furthermore, support for individuals with childhood-onset rheumatic diseases remains insufficient. Transitional care and preconception counselling are often designed from an adult perspective, and the specific needs of paediatric patients are not adequately captured or addressed. Identity crises, medical trauma from repeated procedures and challenges in education and social participation remain unresolved both in research and in practice.

NT: Despite progress, many teenagers and young adults living with rheumatic conditions still face isolation, delayed diagnoses and inconsistent care. When I transitioned from paediatric to adult rheumatology, I felt lost navigating fragmented systems, which reflects the challenges that occur with this transition and inconsistent care between paediatric and adult rheumatology. Many peers in our community report similar challenges, especially those managing multiple diagnoses such as SLE, vasculitis or rare comorbidities. Mental-health support is limited, and pain is often neglected because it is invisible. Culturally inclusive care and accessible tools for decision making are also lacking. Systemically, rural and marginalized communities continue to struggle with long wait times and limited specialist access.

How can unmet needs be addressed?

JA: Addressing these unmet needs requires a collaborative, patient-centred approach, as outlined in initiatives such as the Global Patient Charter for SLE, which I helped to develop. This initiative proposes four principles. First, improving recognition of early symptoms through awareness campaigns, clinician education and standardized referral pathways to speed-up diagnosis. Second, enhancing access to reliable information via self-management tools and multilingual resources to empower patients and reduce flares. Third, ensuring coordinated multidisciplinary care teams, including psychologists and physiotherapists, regardless of location, supported by telemedicine to bridge geographical gaps. Fourth, providing appropriate pharmacological and non-pharmacological treatments, minimizing

long-term steroid use and encouraging clinical trial participation. Opportunities such as ERNs for knowledge sharing, patient organizations lobbying for equitable funding and training for primary-care physicians can drive these changes. The Charter emphasizes better patient–physician communication and integration of patient-reported outcomes to tailor care effectively.

JC: Unmet needs can be addressed through better and more consistent clinical care, increased access to needed treatments and clinical and basic scientific research. To make progress through increased research, the scientific and patient communities must work collaboratively across the globe and identify new approaches.

SF: The most effective way to address unmet needs is to involve patients in shaping research and care strategies. SRUK co-produced their research strategy with the community and clinical leaders, with an independent scientific advisory group ensuring that patient benefit and scientific feasibility were central. Four core themes emerged: precision medicine, early detection and diagnosis, quality of life and understanding disease causes. These now guide SRUK funding calls and research priorities.

Engagement with industry is also key. Meaningful collaboration, beyond tokenism, has increased over the past 10 years. Patients now contribute to early-stage research, clinical-trial design and even practical aspects such as tablet size and packaging. These seemingly minor details can considerably impact adherence and trial integrity. Pharmaceutical companies are increasingly committing to patient-centric approaches, recognizing that those who live with the disease are best placed to identify what works and what doesn't.

NO: The delay in establishing systems that position patients as equal partners in research and healthcare stems from a complex interplay of factors, including language differences, cultural values, healthcare and social systems, political environments and economic disparities. The structure, history and mission of patient organizations are shaped by the region in which they are located and differ accordingly, which in turn substantially affects how patients are involved in research and healthcare.

One practical solution gaining attention is the advancement of digital technologies, such as the widespread use of online meetings and the development of artificial intelligence (AI) tools. These technological innovations have made it easier for patient leaders across borders to share information and collaborate[15], enabling cross-regional learning. International advocacy is now achievable at an unprecedented level.

The high degree of variability in symptoms and disease progression has made it difficult to establish standardized forms of psychosocial support; however, comprehensive psychological assessments can enable a multifaceted understanding of each patient. Now that treatments have advanced to prevent acute exacerbations and maintain good conditions in many rheumatic diseases, greater attention should be given to psychological assessments that help patients to live better lives.

Clinical psychologists can provide individualized psychological support based on comprehensive evaluations of the cognitive and intellectual abilities, emotional states, personality traits, developmental history and behavioural characteristics of a patient. When rheumatologists are aware of the existence, scope and needs of such assessments, it can enhance their understanding of challenges faced by patients and contribute to more appropriate treatment and support.

For children with systemic rheumatic diseases, comprehensive support that encompasses both medical care and social aspects of daily life is essential. Although the term 'multidisciplinary collaboration' often refers to coordination among HCPs, it is important to propose a broader approach, which includes cooperation among education professionals, school counsellors and social workers to establish a comprehensive support system that goes beyond the medical framework.

NT: To truly address unmet needs, systems should be designed with patients, not for them. TAPC has taken a co-creation approach by co-developing programmes such as the Teen Backpack Program (in partnership with the Arthritis Society Canada), which equips newly diagnosed young people with ergonomic backpacks and essential resources to support their healthcare journey in Canada. The Young Scholars Program at TAPC awards scholarships to students with rheumatic diseases and pairs them with mentorship to help them navigate both academic and workplace challenges. I have also co-developed and evaluated digital tools such as the JIA Option Map[16], which is a web-based decision aid that supports shared decision-making for young people and caregivers, currently being adapted for French-speaking communities in Canada. These patient-driven solutions empower self-advocacy, education and informed decision making. On a broader scale, sustained investment in multidisciplinary care models, digital health integration and accessible transition clinics that prioritize continuity of care, cultural safety and mental health are needed.

In your view, what are the most exciting advances in the field?

JA: In my view, the most exciting advances in rheumatology, especially for SLE, include the shift toward targeted therapies such as biologic drugs (for example, obinutuzumab for lupus nephritis) and tyrosine kinase inhibitors, which promise better disease control with fewer adverse effects. Ongoing research into chimeric antigen receptor (CAR) T cell therapies also holds potential for long-term remission or even cures. The rapid adoption of telemedicine post-COVID-19 has improved access for remote patients, whereas ERNs such as ReCONNET foster collaborative research and patient pathways. Patient involvement in trials, such as the TRM-SLE taskforce for new outcome measures[17,18], is groundbreaking, ensuring that treatments address what matters most to the patient.

JC: In SjD, new research has provided important insights into the neuro-immune connections that might drive disease manifestations; however, more research is needed on neurological involvement and its role in SjD. I suspect that future research will profoundly improve understanding of the pathogenesis of SjD, how this disease is diagnosed and what the best treatment is for each patient.

SD: As a biochemist and as a patient, I enjoy research that unifies the genetics or symptoms of these rare autoinflammatory diseases with the biochemistry of protein function. At the core of cryopyrin-associated periodic syndrome (CAPS), the disease I have been diagnosed with, is the NLRP3 protein, and in 2024, the full active structure of this protein was reported using cryo-electron microscopy[19]. Studies on the structure and function of NLRP3 are exciting and might help to shed light onto conditions such as CAPS. The structure of the protein has been combined with studies on NLRP3 mutations to decipher its function in depth. In one study[20], the authors report how known disease-causing mutations can activate NLRP3 and how these mutations vary in their

response to current NLRP3 inhibition methods. This work suggests that each mutation requires an informed analysis of protein function to develop personalized treatment for individual patients. The wealth of data from biochemical research and autoinflammatory disease studies continues to enhance understanding of the role of the immune system in driving these conditions and will ultimately improve patient care. I am excited to see further progress in the field.

SF: The past decade has seen major advances in the SSc field. The complex pathogenesis of SSc — immune dysregulation, vasculopathy and fibrosis — is now better understood, which is leading to more targeted therapies for complications such as interstitial lung disease and pulmonary arterial hypertension. Emerging treatments such as CAR T cell therapy and agents that target fibrotic and interferon pathways offer new hope.

Research into disease mechanisms is also progressing. Studies are exploring the interplay between genetic predisposition and environmental triggers, such as silica exposure and viral infections. One of the most exciting developments is the focus on very early diagnosis. Raynaud phenomenon, puffy fingers and acid reflux have been identified as potential early indicators of SSc; early diagnosis is crucial for timely management and improved outcomes.

NT: Some of the most exciting advances in rheumatology today centre around personalized medicine, digital health innovation and patient-centred care models. For example, researchers are developing biomarkers and genomic tools that can help to predict treatment response, enabling more targeted and effective therapies. The growing emphasis on the lived experience and the engagement of young people in research represents a major shift. Young people are no longer just subjects to study. We are collaborators, co-designers and advocates. This evolution is not only exciting but essential to driving innovation that reflects real-world needs.

How will technological advances impact patients?

JA: Technological advances, including AI, will profoundly impact patients by enhancing access to information and care, but they must be implemented thoughtfully. LupusGPT, which was developed by Lupus Europe, is a prime example; it is a multilingual AI chatbot providing scientifically reliable, patient-centric answers based on validated sources, helping to bridge knowledge gaps when patients cannot wait for appointments. With proper supervision, AI chatbots such as LupusGPT can empower self-management, reduce misinformation (as many turn to 'Dr Google') and support physicians. However, risks such as biased data or over-reliance need to be addressed through human oversight. Overall, AI and digital tools could personalize care, monitor symptoms remotely and democratize access across Europe, ultimately improving quality of life for people with SLE.

JC: AI and the capabilities it will bring for data analysis will lead to considerable advances in understanding autoimmune diseases. The ability to look at large data sets within a disease and, just as importantly, across the autoimmune spectrum with speed and different permutations, engenders new opportunities to understand these diseases. These advances could lead to refinement of disease signatures, discovery of disease progression and new biomarkers to aid in precision medicine. Ultimately, AI can serve to improve science and the patient experience. The challenge here will be to protect the patient so that their data are used only to support them rather than against them; for example, avoiding compiling patient data in such a way that a third party might justify limiting access to or payment for treatment.

SF: Technological innovation is poised to transform rheumatology. For SSc, AI models are being developed to assess skin fibrosis, offering earlier and more objective measurements of disease progression, which is particularly valuable in clinical trials, in which skin thickening is a key endpoint.

Advanced technologies such as single-cell RNA sequencing, spatial transcriptomics and imaging mass cytometry are revolutionizing the understanding of SSc at the cellular level. AI can quantify disease severity — skin involvement, inflammation and vascular abnormalities — and analyse nailfold capillaroscopy images to detect microangiopathic changes.

Perhaps most promising is the potential of AI to personalize treatment. By analysing genetic profiles and patient-specific data, AI can predict responses to therapies and recommend optimal treatment plans, which moves the field closer to a precision-medicine paradigm, whereby care is tailored to the unique needs of each patient.

NT: AI and digital tools have the potential to radically improve early diagnosis, personalized treatment plans and system navigation. Apps, wearable devices and web-based decision aids such as the JIA Option Map[16] are empowering patients to track symptoms, provide treatment options to make informed choices and engage in shared decision making with their care teams. AI can also aid in the analysis of imaging data to detect inflammatory changes before symptoms worsen, and predictive models can help to flag individuals at risk of flares. I have been involved in a European research collaboration called STRATA-FIT, exploring computational models to personalize treatment plans for people with difficult-to-treat rheumatoid arthritis, which holds great promise for improving outcomes. For young patients like me, apps integrated with electronic health records could offer real-time insights, appointment reminders and medication tracking; however, we must ensure that these tools are developed ethically with diverse data sets and patient oversight to avoid reproducing bias or excluding marginalized voices. If designed inclusively, AI could become a powerful force for accessibility, personalization and equity in rheumatology.

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Competing interests

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Additional information

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Related links

Global Patient Charter for SLE: https://worldlupusfederation.org/a-charter-to-improve-care-for-sle-systemic-lupus-erythematosus/
LupusGTP: https://lupusgpt.org/
STRATA-FIT: https://strata-fit.eu

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Review article

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Immune-cell profiling to guide stratification and treatment of patients with rheumatic diseases

Deepak A. Rao

Abstract

Methods for high-dimensional immune-cell profiling have advanced dramatically in the past decade. Studies of tissue and blood samples from patients with rheumatic diseases have revealed stereotyped features of immune dysregulation in individual diseases and in subsets of patients who share diagnosis of a heterogeneous disease. Translating immunological patterns into clinically implementable, actionable biomarkers has the potential to improve detection and quantification of pathological immune activity and selection of appropriate treatments for autoimmune rheumatic diseases. For example, cytometric features can be used to distinguish the various forms of inflammatory arthritis, stratify subsets of patients with rheumatoid arthritis or subsets of patients with systemic lupus erythematosus and predict treatment responses. Cellular immune profiling also enables the identification of specific features of immune dysregulation in individuals with rare, undiagnosed, inflammatory diseases. Several paths might lead to translation of discoveries from broad immune profiling into clinical tests to interrogate immune activation in people with rheumatic diseases.

Sections

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Key points

- Profiling of immune cells in blood and tissue from patients with rheumatic diseases has helped to define populations of activated immune cells that are characteristically expanded in specific diseases, highlighting both unique and shared features across diseases.
- Immune profiling of patients with SLE has identified specific axes of immune dysregulation, including activation of type I IFN pathways, proliferation of lymphocytes, expression of cytotoxic molecules on T cells and upregulation of myeloid cell- and neutrophil-associated signatures; these features vary across patients and help to delineate subgroups of patients that differ in immune activity.
- Longitudinal evaluation of cellular profiles of patients receiving treatments targeting rheumatic disease helps to associate immunological features with treatment effects and predict response to treatment.
- Incorporation of immune profiling into clinical evaluation of patients with rheumatic diseases might enable improved patient stratification, assessment of disease activity and prediction of treatment response.

Introduction

Individuals who seek rheumatological evaluation for a possible autoimmune rheumatic disease commonly describe that they feel 'inflamed' and often wonder whether their immune system is 'overactive'. A major challenge for the evaluating physician is to determine whether the immune system has become pathologically activated, driving an autoimmune or inflammatory condition, or whether symptoms are caused by non-immune mechanisms. These decisions are impactful, as they might dictate whether immunosuppressive therapies will be used. Yet, currently available laboratory tests provide rheumatologists with a quite limited assessment of an individual's immune status at any given time.

Routine immunological tests include a complete blood count to determine if the major blood-cell lineages (neutrophils, monocytes, lymphocytes) are present at normal levels. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests provide measures of systemic inflammation[1]. Total immunoglobulin levels determine whether the immune system has made antibodies at normal levels, and autoantibody tests demonstrate the presence of antibodies that are, for example, specific to double-stranded DNA or antibodies to citrullinated proteins. Tests of serum complement levels evaluate whether the complement cascade has been activated, for example, by antibody–antigen immune complexes[2]. However, this set of widely used tests provides limited insight into the level of activity of the immune system. In contrast to the range of functional tests to assess cardiac, pulmonary, renal and hepatic function, we currently lack functional tests to assess normal versus aberrant activity of the immune system.

Serum protein profiling, bulk RNA sequencing (RNA-seq) of whole blood or specific cell populations and cytometric profiling — which is the focus of this Review — have been used to interrogate the activity of the immune system in a research setting. Over the past 10 years, the advent of high-dimensional cellular-profiling technologies, including spectral flow cytometry, mass cytometry and single-cell RNA-seq (scRNA-seq), have provided a powerful set of tools for analysing the composition and functional states of immune cells in human blood and tissues. Studies using these methods are providing a new set of metrics for assessing normal and aberrant immune profiles, emphasizing abnormalities in the abundance or activation states of immune-cell populations. These metrics have the potential to complement the current clinical evaluation of rheumatic diseases, including evaluation of rheumatoid arthritis (RA) (Box 1).

This Review discusses insights from selected immune-profiling studies that have highlighted specific features of immune-cell dysregulation across rheumatic diseases, across subgroups of patients with the same rheumatic disease or in individuals with very unusual clinical presentations. This discussion covers only a subset of the wide range of immune-profiling studies that have been performed in past years, with an emphasis on studies of RA and systemic lupus erythematosus (SLE) that involve broad cytometric profiling approaches, including approaches with single-cell resolution; studies using serum proteomics or bulk transcriptomics are noted in some cases to provide context or complement interpretation of cellular-profiling studies.

High-dimensional cellular profiling

Cytometric profiling with flow cytometry, mass cytometry or single-cell transcriptomics enables the quantification of the various cell populations and activation states within a complex mixture of cells. Flow cytometry methods have been well established for decades, using antibodies tagged with fluorophores to quantify the expression of cell-surface or intracellular proteins with single-cell resolution. Advances in 'spectral' flow cytometry have dramatically improved the ability to discriminate signals from different fluorophores, expanding the number of proteins one can detect simultaneously to >30 (ref. 3). Mass cytometry captures even more protein markers on individual cells than flow cytometry, and it is based on a similar approach, although using antibodies tagged not with fluorophores but with heavy metals[4]. When attached to cells, heavy metals are quantified by a mass spectrometer at single-cell resolution, providing high-dimensional single-cell analyses. scRNA-seq captures RNA from individual cells[5], typically using individual lipid droplets, yet the analysis is often conceptually similar to other cytometry approaches, characterizing individual cell identities based on expression of cellular markers. The addition of oligo-DNA-tagged antibodies to the single-cell RNA-seq workflow enables the quantification of both transcription and cell-surface protein expression[6,7]. Data from each of these analyses is often visualized in two-dimensional UMAP plots, and clustering approaches have been the go-to method of quantifying the abundance of the various cell populations within a sample[8,9]. Several methods have been developed to evaluate high-dimensional cellular profiling data to identify differences between two or more patient groups or to associate these data with clinical or serological parameters[10–12].

Distinct immune-cell features across rheumatic diseases

Although standard laboratory tests currently used in clinical practice provide limited insight into immune activation, they already indicate some clear patterns of immune abnormalities across rheumatic diseases. The serum CRP level is characteristically elevated in giant cell arteritis and polymyalgia rheumatica (PMR), reflecting an important role for IL-6, which induces CRP expression, in these diseases[13,14], yet CRP levels are often normal during SLE flares[15,16]. By contrast, serum complement levels are reduced in active SLE but not in giant-cell arteritis or PMR, reflecting the immune complex formation and complement

Box 1 | Features that reveal heterogeneity in patients with rheumatoid arthritis

Clinical heterogeneity
- Demographic characteristics
- Joint distribution
- Extra-articular disease manifestations
- Erosion extent[150]
- Imaging heterogeneity (in ultrasonography)[151]

Serological and transcriptomic heterogeneity
- Erythrocyte sedimentation rate and levels of C-reactive protein
- Seropositivity for autoantibodies such as anti-CCP and rheumatoid factor
- Multi-analyte immunoassays
- Cytokine signatures
- Additional autoantibodies

Genetic heterogeneity
- HLA alleles[152]
- Non-HLA risk alleles[153]
- Polygenic risk scores[154,155]

Histological heterogeneity
- Krenn histological scores[156]
- Cellular density
- Immune-cell aggregates
- Pathotype: lympho-myeloid, diffuse-myeloid, or fibroid[64]
- Ectopic lymphoid structures

Cellular heterogeneity in the synovium[39,113]
- Cell-type abundance phenotypes: T cells+B cells (T+B); T cells+myeloid cells (T+M); T cells+fibroblasts (T+F); myeloid cells (M); fibroblasts (F); endothelial cells+fibroblasts+myeloid cells (E+F+M)[39]
- T cell phenotypes: T peripheral helper and T follicular helper cells, granzyme K^+ T cells, granzyme B^+ T cells, regulatory T cells[39,42,50]
- B cell infiltrates: age-associated B cells, plasma cells[39]
- Myeloid phenotypes: $HBEGF^+IL1B^+$, $SLAMF7^+$, $MERTK^+$ macrophages[39,113,157], conventional type 2 dendritic cells, and inflammatory dendritic type 3 cells[114]
- Fibroblast phenotypes: lining fibroblasts, sublining fibroblasts, perivascular fibroblasts[39,158,159]

Cellular heterogeneity in the blood
- T cell phenotypes: T peripheral helper or T follicular helper cells, effector-memory T cells that re-express the naive-cell marker CD45RA, regulatory T cells, T helper 17 cells[42,69]
- B cell phenotypes: age-associated B cells, plasmablasts[160]
- Myeloid phenotypes: monocytes, dendritic cells[161]
- Pre-inflammatory mesenchymal cells[108]

cascade activation in SLE[2]. Early microarray studies highlighted a prominent upregulation of interferon (IFN)-stimulated genes in blood cells of patients with SLE, far exceeding levels seen in patients with inflammatory arthritis[17]. This recognition of a prominent activation of a type I IFN response in SLE fuelled the evaluation and ultimate approval of type I IFN receptor (IFNAR) blockade with anifrolumab to treat SLE[18]. SLE provides a benchmark for strong activation of a type I IFN response against which other diseases can be compared[19]. Although type I IFN signatures are not routinely measured, commercial tests that quantify these signatures are becoming available[20].

Moving beyond cytokine signatures, immune-cell profiling studies are now identifying some of the major axes of immune activation that distinguish autoimmune rheumatic diseases or disease groups with cellular resolution. Flow-cytometry profiling of blood cells from almost 1,000 individuals, representing 11 autoimmune rheumatic diseases, revealed characteristic patterns of activation in immune-cell subsets across diseases. SLE and mixed connective tissue disease (MCTD) showed shared patterns, as expected given their clinical and serological similarities, whereas RA and spondyloarthropathies (SpA), including psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), shared a distinct set of immune features, perhaps reflecting the shared responsiveness of RA and SpA to inhibitors of TNF[21]. SLE and MCTD were associated with a particularly prominent expansion of activated ($HLA\text{-}DR^+ CD38^+$) $CD4^+$ and $CD8^+$ T cells in circulation, consistent with observations from other studies[22–24]. Additional studies have highlighted a T cell–B cell axis, involving expansion of both B cell-helper T cells, such as T follicular helper (T_{FH}) cells and T peripheral helper (T_{PH}) cells, as well as activated B cells, as a core immunological feature of SLE[25–31]. This T cell–B cell axis stands out in blood immune profiles of patients with SLE when these are compared with patients with other rheumatic diseases; blood profiles of patients with RA do not show the same extent of adaptive immune-cell dysregulation on average as seen with patients with SLE[25,32,33].

Combining cellular and transcriptomic profiling, the ImmunoNexUT consortium reported bulk RNA-seq transcriptomes of 28 sorted immune-cell populations from the blood of 337 individuals with ten rheumatic diseases[34]. With this broad approach, diseases segregated into two major groups: immune profiles of SLE, MCTD, RA and systemic sclerosis (SSc) segregated from those of the autoinflammatory conditions Behcet disease and adult-onset Still's disease. Correspondingly, IFN signatures were enriched in SLE and MCTD, as well as in some SSc, idiopathic inflammatory myopathy and Sjögren disease, whereas IL-18 or IL-1 signatures were enriched in Behcet disease and adult-onset Still's disease[34].

Rheumatoid arthritis versus spondyloarthritis

RA and PsA represent similar, but distinct, forms of inflammatory arthritis, with distinguishable patterns of joint involvement, risk factors, demographics and genetics. Clinical trials have highlighted differences in the efficacy of various immunological therapies for these conditions, with IL-17A blockade being more efficacious in SpA than in RA, despite similar total levels of expression of IL-17A in synovial samples[35]. By contrast, B cell depletion with rituximab is commonly used to treat RA but has not shown clear efficacy in SpA[36,37]. These treatment response differences illustrate that immunological drivers differ between these conditions; immune-cell profiling studies are now providing a clearer view of the cellular immunology that underlies these therapeutic differences.

Immune cells in synovial tissue or synovial fluid have been evaluated by scRNA-seq and mass cytometry in both RA and PsA[24,38–41].

T_{PH} cells were markedly expanded in joints of patients with seropositive RA but had comparatively lower abundance in patients with seronegative RA or SpA[24,42,43]. T_{PH} cells are a subset of CD4 T helper cells specialized to provide help to B cells, much like T_{FH} cells; T_{PH} cell expansion in seropositive RA is aligned with the roles of T_{PH} cells in B cell recruitment and stimulation[44]. By contrast, IL-17A$^+$ CD8 T cells[45,46] are enriched in the joints of patients with PsA, and this finding is consistent with the responsiveness of these patients to IL-17A blockade[47,48]. In addition, profiling of T cells from synovial fluid of patients with axSpA showed increased abundance of an integrin-expressing CD103$^+$ CD49a$^+$ CD8 T cell population that expressed both IL-17A and cytotoxic molecules[49]. The distinct patterns of expanded T_{PH} cells in seropositive RA versus IL-17A$^+$ CD8 T cells in SpA seem to align well with the differential efficacy of B cell depletion versus IL-17A blockade in these two diseases. Nevertheless, other features, including accumulation of granzyme K (GZMK)$^+$ CD8 T cells, granzyme B (GZMB)$^+$ cytotoxic T cells, and regulatory T (T_{Reg}) cells within joints, are shared between RA and SpA[38,50]. Further studies are needed to associate lymphocyte features with differences in synovial pathology between RA and PsA, including differences in the patterns of vascular remodelling and immune–stromal interactions[51–53].

Immune-cell profiling studies using blood samples have also indicated distinct circulating immune-cell patterns in RA and PsA. Consistent with results from synovial tissue and synovial fluid, T_{PH} cells are increased in the circulation of patients with seropositive RA, but not seronegative RA or PsA[42,43]. Broad mass cytometry profiling comparing peripheral blood mononuclear cells (PBMCs) from patients with RA or PsA highlighted increased frequencies of terminally differentiated (CD27$^-$ CD28$^-$) effector CD8 T cells in seropositive RA but not in seronegative RA or PsA[54]. Interestingly, the blood-immune profiles of seronegative RA and PsA had no clear differences[54,55]. The large-scale effort of the 'Accelerating Medicines Partnership (AMP) on Autoimmune and Immune-Mediated diseases' (AMP-AIM) network, which includes a comparison of blood and tissue immune profiles between RA and PsA, will provide substantial power to define robust immunological differences distinguishing these diseases, also with spatial resolution within tissues[56]. Although the presence or absence of autoantibodies provides a foundational tool helping to distinguish clinically overlapping entities of seropositive RA, seronegative RA and SpA, one can imagine that immunological assessment of T_{PH}, T_{FH} or T_H17 cell pathways in patients might help to further distinguish subsets of patients with undifferentiated arthritis or patients with seronegative RA to guide selection of an RA- versus an SpA-aligned treatment framework.

Immune checkpoint inhibitor-induced arthritis

Cellular profiling of the active immune response in patient samples has proven valuable in assessing a form of inflammatory arthritis that has emerged with the advent of immunotherapies for the treatment of cancers — immune checkpoint inhibitor (ICI)-induced arthritis. ICI therapy using an antibody that blocks the inhibitory receptor PD-1 induces a range of immune-related adverse events, including ICI-induced inflammatory arthritis, which occurs in ~4% of treated patients[57,58]. ICI-induced arthritis can involve RA-, PsA-, or PMR-like manifestations, usually without generation of anti-cyclic citrullinated peptide (anti-CCP) or rheumatoid factor autoantibodies[58,59]. Similar to RA and PsA, ICI-induced arthritis involves an active, presumably autoreactive, T cell response, yet the specific features of this response differ starkly across the three conditions[24,60]. Mass cytometry-based comparison of T cells from synovial fluid of patients with ICI-induced arthritis, RA or PsA showed clear expansion of a population of CD38^{hi} CD8 T cells specifically in ICI-induced arthritis[24]. CD38^{hi} CD8 T cells were also expanded in the circulation of patients with ICI-induced arthritis, and broadly among patients treated with ICIs, yet these cells were not highly expanded in patients with RA or PsA[24]. Transcriptomic comparisons of synovial fluid T cells demonstrated a higher type I IFN response signature in T cells from patients with ICI-induced arthritis than synovial T cells from patients with RA or PsA, and in vitro treatment of synovial fluid CD8 T cells from patients with RA or PsA with type I IFN promoted acquisition of the CD38^{hi} T cell phenotype seen in patients with ICI-induced arthritis. The type I IFN signature in ICI-induced arthritis samples provided an unexpected immunological link between ICI-induced arthritis and SLE, a disease marked by high type I IFN production that also features expanded CD38^{hi} CD8 T cells[19,23].

Defining such immunological benchmarks across diseases is likely to provide a deeper understanding of why certain therapies work well in one condition versus another and might help to identify therapies that are likely to work in newly emerging conditions, such as those induced by immunotherapies. Cross-disease comparisons integrating data across different forms of inflammatory arthritis, including juvenile idiopathic arthritis and others[61], should demonstrate the relative prominence of specific features of the active immune response in inflamed joints, including the abundance of proliferating, exhausted or stem cell-like lymphocytes, the expansion of T_{PH} and T_{FH} cells, the presence of GZMK$^+$ T cells versus GZMB$^+$ T cells, and the frequencies of T_{Reg} cells, infiltrating monocytes versus tissue-resident macrophages, dendritic-cell (DC) populations, age-associated B cells (ABCs) and plasmablasts, to amass a clearer taxonomy of inflammatory arthritides according to features of immune activation[62].

Immune-cell heterogeneity within a disease

Immune-cell heterogeneity in rheumatoid arthritis

In addition to highlighting differences across diseases, immune-cell profiling is a valuable tool for dissecting immunological heterogeneity among patients who share a diagnosis. Patients with RA display substantial variability in clinical course, the likelihood of developing erosions and response to treatments. Correspondingly, studies of synovial tissues have highlighted differences in synovial immune infiltrates among patients with RA, even when they share comparable imaging and clinical features of synovitis[63,64]. Patients with seropositive RA frequently show a 'lympho-myeloid' pattern of immune infiltration in the inflamed synovium, with aggregates of synovial B cells and T cells that range from loose, disorganized clusters to well-organized follicular structures[65]. In other patients with RA, the synovium either shows a diffuse myeloid-cell infiltrate without lymphoid follicles or a 'fibroid' or 'pauci-immune' synovial pattern with few immune-cell infiltrates. Patients with a lympho-myeloid pathotype are the most likely to develop erosions and joint damage progression, whereas patients with a fibroid pathotype show the lowest disease activity, yet also the weakest response to DMARD treatment[66]. Detailed cellular analyses have defined the composition of immune cells in synovial-tissue samples across the various pathotypes. scRNA-seq of RA synovial biopsies delineated six 'cell-type abundance phenotypes' (CTAPs), representing six types of synovial inflammation, that differ in the relative abundance of each of the following cell types: fibroblasts; T cells and NK cells; B cells; endothelial cells; and myeloid cells[39] (Box 1). These CTAPs roughly correspond to histological patterns, with the CTAP containing both T cells and B cells (CTAP-TB) showing the highest histological scores of synovitis (according to the histological score developed by Krenn) and aggregate density. However, immunological information captured by

CTAPs largely seems to be orthogonal to clinical or serological assessments, suggesting that these tissue analyses will be complementary, and not redundant, with current clinical assessment of RA.

Given the difficulties of sampling synovial tissue from patients with RA, there has been substantial interest in identifying signatures in blood that capture immune activity in the joints. Direct parallels between synovial infiltrates and immune-cell phenotypes in blood are challenging to identify, although some shared features of the adaptive immune response have been demonstrated, such as shared T cell receptors (TCRs) and, occasionally, shared T cell clone phenotypes in synovium and blood of patients with RA, PsA and ICI-induced arthritis[24,50,67,68]. Analyses of paired blood and tissue samples from large numbers of patients, such as those profiled in the AMP RA/SLE Network, should help to clarify the extent to which features of immune cells in blood can reflect specific immune processes occurring within synovium.

Independently of synovial analyses, flow cytometry profiling of blood cells from over 500 patients with RA has highlighted substantial variability in immune-cell profiles that were non-redundant with clinical and serological phenotypes[69]. These blood immune profiles were used to stratify patients into peripheral blood-cell abundance phenotypes (PCAPs, analogous to synovial CTAPs). Patients with distinct PCAPs showed distinct patterns of cell abnormalities, including one group of patients with expanded activated CD4 T cells, CD8 T cells and plasmablasts (PCAP-TB), a separate group with increased effector-memory T cells that re-express the naive-cell marker CD45RA (T_{EMRA} cells) or T_{EMRA} and T_H1 cells (PCAP-T1/T1T4), and two more patient subgroups (PCAP-LD and PCAP-SD) that cytometrically resembled healthy individuals[69]. The frequency of anti-CCP antibody or rheumatoid factor did not differ across these groups, yet patients in the PCAP-TB group showed the highest disease activity and ESR, as well as the least frequent use of methotrexate. Inclusion of additional immune-cell subsets with an emerging role in disease pathogenesis, including T_{PH} cells, T_HA cells – a $CXCR3^{mid}$ cytotoxic CD4 T cell population expanded with age[70] – and $GZMK^+$ T cells[50], might enhance the utility of blood-cell profiling in RA. In addition, the identification and quantification of immune-cell subsets are aided by high-resolution scRNA-seq and mass cytometry analyses that precisely define the phenotypes of activated cells in the circulation[71,72]. In total, cellular profiling of blood and tissue samples from patients with RA is providing an additional set of informative variables with which to understand immunopathology in individual patients (Box 1).

Immune-cell heterogeneity in systemic lupus erythematosus

Patients with SLE display stark variability in terms of organs affected, disease severity and response to immunosuppressive therapy, potentially reflecting substantial immunological heterogeneity. Serum proteomics, gene-expression profiling and flow-cytometry analyses have illustrated key features of immune activation in SLE that are consistently observed across cohorts. Expression of IFN-stimulated genes has reproducibly been found to be increased across many SLE studies, with the majority of patients showing a type I IFN signature[17,19]. scRNA-seq profiling has further refined immune-cell populations with the highest expression of an IFN response signature in the blood, including monocyte and lymphocyte subsets[73,74], and has demonstrated a clear IFN response signature across many tissues, including skin and kidney, in SLE[75–78]. In both kidney and skin samples, a subset of T cells and B cells shows a very high IFN signature, above the basally elevated IFN signature seen broadly in cells from patients with SLE compared with healthy individuals[75–77]. What distinguishes the IFN signature-high cells from other cells in the tissue remains unclear. It will be interesting to integrate these observations with emerging spatial transcriptomics data, which suggest that cells with the highest IFN signatures are enriched in the glomeruli in the kidneys of patients with lupus nephritis (LN)[79].

In addition to the IFN signature, other immune signatures extracted from whole-blood transcriptomic analyses have enabled patient stratification into subgroups, particularly when analyses were run on longitudinal samples. Longitudinal whole-blood profiling of patients with childhood-onset SLE stratified patients into seven groups that vary in transcriptomic signatures associated with erythropoiesis, IFN response, myeloid cells and neutrophils, plasmablasts and lymphocytes. Among these patient subgroups, a plasmablast-associated signature was strongly associated with disease activity over time[80]. Studies using blood-transcriptomic profiling of adult patients with SLE have stratified patients into 3–7 subgroups based on similar but not identical features to those used for the stratification of paediatric patients[81–83]. In the adult cohorts, increased expression of inflammation, myeloid/neutrophil and plasmablast transcriptomic signatures have been associated with increased disease activity, as defined based on SLE Disease Activity Index scores[81–83].

The cellular resolution of cytometric profiling studies has in some cases extended understanding of the immune pathways previously implicated by bulk RNA-seq in SLE, for example, the plasmablast-associated signature. Cytometric studies evaluating B cell phenotypes in SLE have extended the understanding of the activated B cell response, which includes expansion of both plasmablasts and ABCs (also known as DN2 B cells), which are characterized by high expression of CD11c and TBET and low CXCR5 and CD21 (refs. 29–31,84). The expansion of $CD21^{low}$ ABCs is perhaps the most prominent cytometric abnormality among circulating B cells in patients with SLE and is highest in patients with active disease, including patients with LN[25,29,30,71,85].

Cytometric profiling can also capture immunological features that are difficult to detect in whole-blood-transcriptomic analyses, for example, the abundance of specific T cell subsets or T cell functional states. Flow cytometry-based profiling of PBMCs stratified patients with SLE into three subgroups based on T cell profiles, with one group marked by expanded T_{FH} cells and activated T_H1 cells (that probably included T_{PH} cells) and a second group marked by expanded T_{Reg} cells[86]. Disease activity or duration did not differ across the three groups, yet the T_{FH} cell-associated group had the highest total immunoglobulin levels, consistent with amplified T cell–B cell interactions. Mass cytometry-based profiling of T cells from patients with SLE highlighted a prominent expansion of T_{PH} cells in patients with LN, with the expansion of circulating T_{PH} cells exceeding that of T_{FH} cells[25]. Both T_{PH} cells and T_{FH} cells have been identified as expanded in multiple cohorts of patients with SLE and associated with the clinical and serological measures of disease activity[26–28,71,87,88]. T_{FH} cell expansion seems to be clearer among patients with shorter disease duration compared with those with longer disease duration[87]. The abundance of T_{PH} cells correlates positively with that of ABCs in patients with SLE, probably reflecting an ongoing extrafollicular response[25,89,90].

The AMP RA/SLE network used mass cytometry of PBMCs to stratify patients with LN into three immunologically distinct subgroups[71]. Among patients with biopsy-demonstrated class III, VI or V nephritis, more than half of whom had established disease with prior treatment for LN and prior kidney biopsies, cytometric profiling identified one subgroup that was immunologically indistinguishable from healthy

individuals, a second subgroup had a very high type I IFN response signature, and a third subgroup had an intermediate type I IFN response signature but a distinctive expansion of GZMB$^+$ T cells, suggesting activation of a 'cytotoxic lymphocyte' axis. Both the type I IFN response-high and GZMB$^+$ subgroups had expansion of proliferating B cells and T_{PH} cells, indicating a shared activation of a B cell–T cell axis. These patient subgroups had distinct features in terms of both kidney histopathology and clinical course; the GZMB$^+$ subgroup had patients with the highest disease activity in the kidney based on the histological NIH activity index and the highest likelihood of a good renal response to standard-of-care therapy at 1 year[71]. By contrast, the immunologically quiet subgroup showed the highest degree of chronic kidney damage histologically, which perhaps reflects prior immunological injury. The poor response to treatment in this subgroup suggests that these patients might have chronic kidney disease without ongoing immune activation and might not benefit from escalated immunosuppressive therapy. Notably, kidney biopsies shared the specific features of blood-immune profiles; patients with a high proportion of GZMB$^+$ T cells in blood also had an increased proportion of GZMB$^+$ CD8 T cells in kidney tissue, and patients with the highest type I IFN signatures in blood also showed the highest IFN signatures in cells from the kidney[71]. Further validation of these signatures and additional prospective studies are needed to determine if a very high type I IFN response signature enriches for patients most likely to respond to IFN blockade, or if cytotoxic T cell activation is differentially susceptible to the various SLE therapies.

Given the observations from studies on RA and SLE discussed above, cytometric immune profiling has the potential to identify immunologically distinct subgroups of patients in other rheumatic diseases as well. In PsA, blood-cell profiling by flow cytometry highlighted four subgroups of patients through principal components analysis, with a subgroup that was characterized by increased frequencies of T_H17 cells, memory T_{Reg} cells, DCs and monocytes being associated with increased disease duration and activity[91]. Moreover, scRNA-seq analysis of blood segregated patients with Sjögren disease into two major subgroups, corresponding to the presence or absence of anti-SSA antibodies; a strong type I IFN signature was associated with anti-SSA seropositivity[92]. Integrating large datasets, especially scRNA-seq datasets, across diseases might provide the ability to identify immunologically similar patients across clinical-disease presentations.

Immune profiling of treatment responses

In both RA and SLE, the expanded armamentarium of immunosuppressive drugs poses new challenges for patients and physicians in selecting which therapy is most likely to be beneficial for an individual patient. In RA, at least five mechanistically distinct classes of biologic therapies are available: TNF blockade; IL-6 blockade; JAK inhibition; B cell depletion; and T cell costimulation blockade[93]. However, there is little guidance on the decision about which therapy to use for an individual patient. In SLE, the expanded range of treatment options, now including B cell inhibition or depletion[94], IFNAR blockade[18] and calcineurin inhibition[95], similarly poses questions about which drug to use for which patient. Longitudinal studies of pre- and post-treatment samples provide crucial insights into the major pathways affected by each DMARD and potentially identify cellular features at baseline that are associated with a good response to treatment. This review will not attempt to broadly summarize the wide range of cellular treatment response biomarker studies in RA and SLE, but will, rather, highlight specific examples of promising approaches or consistently observed signals.

Profiling treatment responses in rheumatoid arthritis

Blood-cell-based profiling of treatment responses. Identifying predictors of patient responses to DMARDs remains an area of active research in RA. Tremendous effort has been focused on identifying biomarkers of response to TNF inhibitors, but analyses of standard laboratory markers, antibodies, serum proteins, whole-blood transcriptomes and cell phenotypes have not yet led to the identification of any robust predictors of treatment responses[96,97]. The advent of broad profiling methodologies has yielded some successes: whole-blood-transcriptomic analyses combined with advanced computational approaches have led to the commercial development of a test to predict the likelihood of a non-response to TNF inhibitor therapy[98,99].

The search for treatment response biomarkers has been importantly advanced by applying immune-profiling studies within the context of clinical trials, especially those involving randomization. This approach leverages the standardized clinical assessment of disease activity within a trial infrastructure, and the randomization minimizes concerns about confounding by indication and unaccounted bias. Such studies have highlighted a reproducible relationship between the frequency of circulating T_{FH} cells in the blood and response to abatacept, a drug that blocks T cell costimulation. In a cohort of patients analysed by flow cytometry in the NORD-STAR trial, which randomized patients with early RA to methotrexate plus one of four biologics, cytometric quantification of 12 T cell populations demonstrated a specific association between elevated baseline PD1$^+$ T_{FH} cell frequency and achieving remission following treatment with abatacept[100]. Similarly, in a prospective observational study of patients with RA and an inadequate response to methotrexate, patients who achieved remission after treatment with abatacept had higher frequencies of PD1$^+$ T_{FH} cells in the blood at baseline than patients who did not achieve remission[101]. Consistently, elevated frequencies of activated T_{FH} and T_{FH} cells in the blood of patients with early type 1 diabetes were associated with a good clinical response to abatacept[102]. Abatacept robustly reduces the frequency of circulating T_{FH} and T_{PH} cells, supporting the biologic plausibility of the cellular association with treatment response[101,102].

Studies looking for cytometric features predictive of response to rituximab have highlighted an association with circulating B cell populations. In the SMART trial of rituximab in patients with RA, flow cytometric analysis of B cells indicated that a low proportion of circulating CD27$^+$ memory B cells was associated with a good response to treatment at 24 weeks by EULAR criteria[103]. Independently, the FIRST study, which evaluated 154 patients with RA who were treated with rituximab using flow cytometry, associated a high proportion of circulating CD27$^-$ IgD$^-$ B cells with a good response to rituximab, especially when considered in combination with rheumatoid factor positivity. Combined with additional studies[104,105], these observations strongly associate features of B cell activation or B cell memory with likelihood of response to rituximab. Irrespective of B cell phenotype, a randomized study of 25 patients with RA associated the detection of residual circulating B cells after two doses of rituximab with significantly improved response rates to a third dose of rituximab[106].

Applying standardized profiling methods across patients treated with various DMARDs has the potential to identify specific cellular patterns that are associated with an improved response to a specific treatment. Exploratory studies using flow-cytometry profiling, applied longitudinally to over 500 patients with RA as described above, identified subgroups of patients with a differing likelihood of response to the various DMARD classes[69]. Using PCAPs to stratify patients as

described above and prospective longitudinal evaluation indicated that patients in the PCAP-TB group, who are marked by an active B cell response, were the least likely to achieve remission overall after treatment with one of four biologic DMARDs interrogated: abatacept, JAK inhibitors, TNF inhibitors and IL-6 inhibitors. By contrast, patients in the PCAP-SD or PCAP-LD groups, who collectively showed relatively few cellular changes compared with healthy individuals, were more likely to achieve remission following treatment with JAK inhibitors than were patients in other PCAPs.

To define operational links between PCAPs and treatment assignments, the authors then assigned each of the four specific DMARDs as associated or not associated with a good response for each PCAP-based patient subgroup. Patients were then assigned a status of 'expected' or 'non-expected', reflecting whether the patient received a DMARD associated with a good response in their identified PCAP. Promisingly, in a validation cohort of 183 patients, patients with an 'expected' designation, indicating that the patient received a DMARD expected to produce a good response in their identified PCAP, were more likely to achieve remission than patients with a 'non-expected' treatment assignment (33% versus 18%). These treatment-response associations need to be validated further, and a substantial challenge remains to identify stratification parameters that can be reproduced and adopted widely. Nonetheless, the impressive scale of the study and the ability to reproduce signatures in a validation cohort provide hope for extension of this approach. A broader immune profiling approach that captures activated T_{FH} and T_{PH} cells or other cell populations with a key role in RA might improve treatment assignment to specific patient subgroups.

Using a clever, alternative strategy, the BioRRA study investigated how circulating immune-cell profiles change during arthritic flares that occur in patients with RA after withdrawal of synthetic DMARD treatment[107]. The analyses associated expansion of activated T cell and B cell populations, including $PD1^+$ $CD38^+$ CD8 T cells and $PD1^+$ $ICOS^+$ $CD38^+$ CD4 T cells, with disease flares after DMARD withdrawal. This finding suggests that synthetic DMARDs hold these T cell populations in check, such that treatment withdrawal allows for $PD1^+$ $CD38^+$ CD8 T cell and $PD1^+$ $ICOS^+$ $CD38^+$ CD4 T cell activation and expansion. Frequencies of these cell populations at baseline (pre-drug withdrawal) did not differ between patients who remained in remission and patients who experienced disease flares after drug withdrawal; thus, it is unclear whether such signals can help predict disease relapse prior to drug withdrawal. Nonetheless, the above cellular correlates might provide a valuable readout to confirm re-activation of the disease-associated immune response, if symptoms emerge following treatment cessation. Immune-cell profiles that are potentially associated with disease flares were also identified by a separate study using frequent, serial assessment of whole-blood samples by RNA-seq; in this study, disease flares were associated with preceding changes in B cell signatures and a concurrent increase in rare, circulating mesenchymal cells potentially related to synovial fibroblasts, called PRIME cells, during the flare[108].

Synovial cell-based profiling of treatment responses. There is major interest in understanding the associations between immunological features in synovium and response to the various treatments. Results from the pioneering R4RA trial provided encouraging initial observations, indicating that patients with a diffuse myeloid infiltrate were more likely to respond to tocilizumab than to rituximab[109]. Extending these observations using CTAP designations further supported the idea that patients with a fibroid (CTAP-F) phenotype, generally lacking large lymphocyte or myeloid infiltrates, were the least likely to respond to biologic treatment[39,110]. One tangible prediction in connecting synovial infiltrates to treatment response would be that patients with a B cell-enriched synovium are more likely to respond to B cell depletion with rituximab than patients without B cells in synovium; however, this has not been consistently observed in the clinical trials that have assessed synovium[109,111,112]. Among synovial myeloid cells, an increased proportion of $MerTK^+$ tissue macrophages is associated with a state of treatment-induced remission in RA, and an increased proportion of $MerTK^+$ tissue macrophages in synovium at baseline is associated with maintenance of remission after TNF inhibitor withdrawal[113]. Spatial transcriptomic analyses have further associated synovial DC populations with disease activity and treatment response, reporting on a tolerogenic AXL^+ cDC2 population that is present in healthy synovium but absent in RA synovium, even when remission is achieved, suggesting a lasting remodelling of the DC populations due to synovitis[114].

With these early observations guiding new study design and analysis approaches, there remains substantial enthusiasm that cellular features within synovium will provide crucial insights into the variable treatment responses of patients with RA. Detailed single-cell analyses, including spatial transcriptomic analyses, comparing pre-treatment and post-treatment samples, as reported in inflammatory bowel disease, should aid in identifying specific cell populations associated with response and non-response to treatment[115]. Indicatively, spatial transcriptomic analyses of longitudinal synovial tissue biopsies from patients with RA demonstrated a $COMP^{hi}$ fibrogenic fibroblast population that is enriched in pre-treatment samples of patients who do not achieve remission and that persists in synovium despite effective reduction of immune cells by DMARD therapy[56].

Profiling treatment responses in systemic lupus erythematosus

Cellular or molecular signals that are associated with treatment effects and treatment responses have been identified in several clinical trials in SLE. Correlative transcriptomic and serum-profiling studies of patients treated with anifrolumab have illustrated a clear reduction in IFN responses at both transcriptomic and proteomic levels in treated patients in both clinical trials and observational studies[116–118]. Profiling of blood samples from patients with SLE before and after treatment with anifrolumab in the MUSE trial demonstrated that anifrolumab alters several measures of immune activation in SLE, with a high IFN signature at baseline; anifrolumab treatment increased numbers of circulating neutrophils, platelets and lymphocytes, especially naïve CD4 and CD8 T cells[118]. Anifrolumab treatment also reduces circulating levels of several chemokines, including CXCL13, a potent B cell chemoattractant produced by T_{PH} and T_{FH} cells[118,119]. Longitudinal scRNA-seq profiling of blood samples from a small cohort of patients that received anifrolumab demonstrated that IFNAR blockade reduces the abundance of circulating T_{PH} cells, and concurrently expands a counter-regulated population of IL-22-producing CD4 T cells (T_H22 cells), which are reduced in patients with active SLE[119]. This reduction in circulating T_{PH} cells following type I IFN blockade functionally links IFN signalling to enhanced T cell–B cell interactions and B cell activation in SLE[119]. Understanding the effects of type I IFN blockade on other components of the pathological adaptive immune response in SLE is of major interest. Thus far, it has not been evident from available data that patients with a low IFN signature have a substantially weaker clinical response to

Table 1 | Immune profiling of response to treatment

Type of treatment	Engagement of primary target	Pre-treatment vs post-treatment comparisons	Predictors of treatment response	Assessment of treatment duration
Synthetic DMARDS	Unclear	What cell populations or pathways are most altered by treatment?	What cellular features at baseline (pre-treatment) predict a good response to treatment?	For how long can therapy continue to suppress signs or markers of immune dysregulation?
Biologic DMARDs	Inhibition of targeted pathway (for example, TNF, IL-6, IFN)			
CAR T cells or depleting antibodies	Depletion of targeted cell population (for example, B cells, plasma cells, $PD1^{hi}$ T cells)			For how long does cell depletion last? For how long do signs or markers of immune dysregulation remain absent after a single dose of the respective treatment?
BiTEs	Depletion of targeted cell population Extent and nature of T cell activation			

BiTEs, bispecific T cell engagers; CAR T cells, chimeric antigen receptor T cells; IFN, interferon; PD1, programmed cell death protein 1.

anifrolumab than those with a prominent IFN signature at baseline[120]; further immunological assessments might help to dissect whether specific features of the IFN response, such as very prominent and distinctive IFN activation[71] or expansion of IFN-associated immune-cell populations, predict a better response to anifrolumab.

Longitudinal profiling of blood samples from patients treated with B cell-directed therapies have also identified cellular correlates of treatment effect and response. Treatment with belimumab, an FDA-approved agent for SLE that blocks B cell activating factor (BAFF), reduced whole-blood-transcriptomic signatures associated with B cells, as well as signatures associated with IFN and IL-6 signalling and neutrophils, especially in responders[121]. Similarly, patients treated with tabalumab, an IgG4 antibody that blocks BAFF, also demonstrated a reduction in B cell-associated transcripts in whole-blood transcriptomics, consistent with a reduction in circulating B cell counts[122]. Transcriptomic analyses of sorted leukocyte subsets from blood collected before and after treatment with belimumab demonstrated clear effects of belimumab on the transcriptomic features of B cell subsets, with few effects on transcriptomes of circulating T cell or myeloid cell subsets, consistent with the direct effects of belimumab on B cell activation[123]. Further, the number of differentially expressed genes, comparing pre-treatment and post-treatment B cell subset transcriptomes, was higher in good responders to belimumab treatment than in poor responders. A separate study reported reductions in both $CD19^{+}$ B cells and activated $PD1^{+}$ T cells after treatment with belimumab[124]. Interestingly, a longitudinal flow-cytometry assessment of T cell subsets from the blood of patients treated with belimumab demonstrated an increase in the ratio of T_{Reg}–T_H17 cells following treatment, an effect that was reproduced in an independent, broader mass-cytometry profiling study[125,126]. These observations associate specific immune alterations with BAFF blockade, with both direct effects on B cells and secondary effects on T cells.

The use of molecular profiling in studies evaluating new therapeutic agents might also facilitate the identification of molecular predictors of treatment response in SLE. In a phase II trial of obexelimab, a bifunctional antibody that binds CD19 and the inhibitory receptor FcγRIIB, given after initial high-dose steroid treatment, whole-blood transcriptomics were used to classify patients into subgroups: patients with increased expression of lymphocyte modules and cell-proliferation modules but without high expression of inflammation-associated modules were more likely to respond to obexelimab than patients from other subgroups, as assessed by maintenance of disease improvement[127]. In a phase IIb study with iberdomide, a cereblon ligand that promotes degradation of the B cell transcription factors Ikaros and Aiolos, which are important for lymphocyte development and function and which both have polymorphisms associated with SLE[128], blood-cell profiling demonstrated that treatment resulted in dose-dependent decreases in the number of circulating B cells and memory B cells, as well as in plasmacytoid DCs and myeloid DCs[20]. Concurrently, the number of T_{Reg} cells increased in a dose-dependent fashion, paralleling an increase in circulating IL-2 levels. Transcriptomic analyses also highlighted clear reductions in IFN response signature with treatment, and patients with the highest IFN response signature at baseline were the mostly likely to have reduced disease activity after treatment, as assessed by SLE responder index 4 (SRI4)[20].

Following these examples, it is of substantial interest to define the effects of the commonly used synthetic DMARDs, such as azathioprine and mycophenolate, given their widespread use and their difficult-to-predict effects on cellular immunology. The effects of these drugs have not yet been revisited in detail using high-dimensional cellular profiling approaches. Looking forward, understanding the broad scope of immunological changes induced by cell-depletion strategies, such as CD19 CAR T cells and bispecific T cell engagers (BiTEs), will be crucial[129–131]. Deep B cell depletion with these methods has the potential to correct multiple immune abnormalities in patients with SLE, including normalization of complement levels and reduction in type I IFN response[129,132], but the extent to which B cell depletion also corrects T cell and myeloid-cell abnormalities in patients with SLE remains to be defined. The extent and nature of CD8 and CD4 T cell activation induced by BiTEs that target B cells can also be assessed using broad immune-profiling approaches (Table 1).

Immune profiles of individuals with undiagnosed disease

Cellular profiling studies typically utilize a grouped comparison analysis strategy, comparing patients with healthy individuals, pre-treatment with post-treatment, or responders with non-responders. However, cellular profiling also has the potential to identify individual patients with very abnormal features of immune activation compared with a reference population. A pilot study evaluating this approach was performed on samples from 16 patients seen in the Undiagnosed Diseases Network

programme, an NIH-funded programme that focuses on patients with very rare or unusual disease presentations[133,134]. These 16 patients, who all have unusual disease presentations thought to be potentially immune associated, underwent whole-exome or -genome sequencing that did not reveal a clear monogenic cause of disease. This cohort therefore underwent mass cytometry immune profiling of blood cells, and immune profiles were assessed against ~140 reference datasets that included healthy individuals, patients with RA and patients with SLE[134]. Immune profiles from 5 of the 16 patients from the Undiagnosed Diseases Network programme were identified as 'outliers' based on the presence of at least one immune-cell population that was extremely expanded compared with the overall cohort, but no outliers were identified among the reference datasets. Of these patients, one had a dramatic expansion of $CD25^{hi}$ T_{Reg} cells, which comprised 50% of the circulating CD4 T cells, one was identified as having B cell leukaemia, one had an aberrant expansion of a gamma delta T cell population, and one had a very abnormal myeloid-cell phenotype. This exploratory work suggests that immune profiling can be used to identify specific immunological abnormalities in individuals with rare or unusual disease presentations and enable individualized treatment strategies.

Such an immune profiling approach can complement interrogation for rare monogenic causes of immune-mediated disease using whole-genome or whole-exome sequencing[135] or bulk RNA-seq and scRNA-seq analyses reporting outlier gene- or splice-variant expression profiles[136,137]. In both cases, immune profiling has the potential to delineate pathways of immune activation that are activated in the context of a monogenic disease and potentially relevant for treatment. In addition, deep analyses using scRNA-seq might be able to identify immunological abnormalities missed by the cytometric approach, as scRNA-seq captures cytokine response signatures more readily than protein cytometry. As scRNA-seq analyses of PBMCs from healthy donors, individuals at risk of disease (for example, individuals at risk of RA[138,139]) or individuals with defined diseases, including SLE[73], RA, Sjögren disease[92], SSc[140] and others, are becoming increasingly available, they enable mapping of any individual scRNA-seq profile to these reference datasets to identify aberrant cell populations, phenotypes, or states in an individual.

Translation into clinical practice

Cellular profiling studies have yielded several robust features of immune activation or dysregulation that capture clinically relevant information. Assessment of such features in clinical practice might be complementary to and non-redundant with serological tests. Translation of findings from cellular profiling studies into clinical practice could follow multiple paths, but two paths will be considered here: the implementation of flow cytometry-based assessment of pathological immune activation and the introduction of scRNA-seq analysis in a clinical setting.

Cytometric assessment of pathological immune activation

A straightforward path to clinical implementation might involve distilling down the most informative features from high-dimensional profiling studies and then developing targeted, cost-effective tests for these features. In SLE, a disease with prominent immune abnormalities in blood, several informative features from transcriptomic and cytometric studies can be captured in straightforward ways. An IFN signature can be captured by flow cytometric screening for the cell surface marker Siglec-1, a protein strongly upregulated on monocytes by type I IFN[141,142]. The additional four features (proliferating lymphocytes, cytotoxic T cells, $CD21^{low}$ B cells, low-density neutrophils) that stratified subgroups of patients with LN as discussed above could be distilled down to simple parameters that can be measured by flow cytometry[71]. Similarly, the major defining features of synovial CTAPs in RA can be captured by standard flow cytometry[39]. Although, thus far, flow cytometry has little regular use in patients with rheumatic diseases, save for quantifying $CD19^{+}$ B cells in patients treated with anti-CD20 antibodies, this method is routinely used in oncology to aid in the search for haematological malignancies[143]. Further, in clinical immunology, flow cytometry is used routinely to quantify lymphocyte subsets in patients with suspected immunodeficiencies, and also to detect features of immune dysregulation in these diseases, such as expansions of activated B cells and T cells[144].

The development of a flow cytometric test to quantify T_{FH} cell frequency in children with immune dysregulation provides a valuable example of how these tests can be implemented clinically for evaluation of immune activity[145]. Building on established flow-cytometry protocols, an assay to quantify $PD1^{+}$ $CXCR5^{+}$ T_{FH} cells was developed with robust reproducibility across instruments and sample storage times of up to 24 h. Interrogation of cohorts of healthy individuals and individuals with relevant diseases using this assay defined normal ranges and indicated a sensitivity of 88% and specificity of 94% in discriminating autoimmune disease from autoinflammatory conditions[145]. With an estimated cost of <$200 per test, this approach provides a practical, feasible strategy for detection of features of immune activation that are currently missed by routine tests such as ESR, CRP, complement

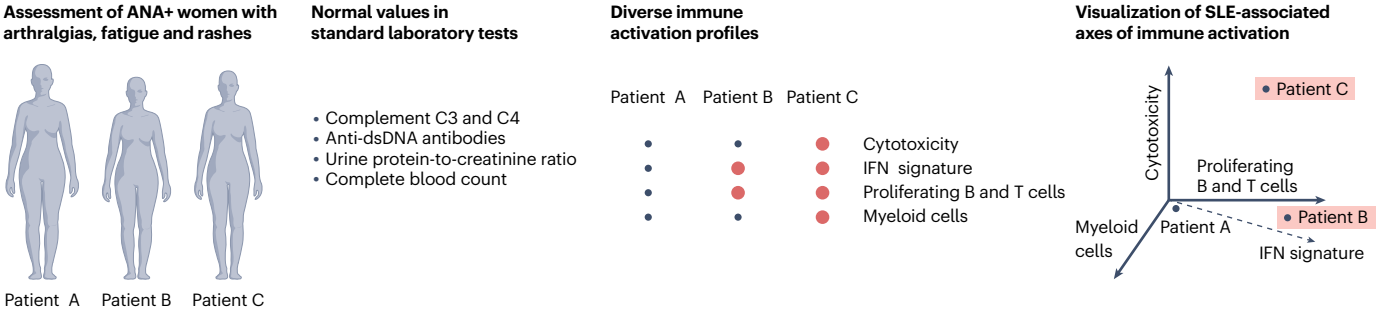

Fig. 1 | Focused immune assessments to identify immune dysregulation in patients with suspected systemic lupus erythematosus. Evaluation of individuals who are seropositive for anti-nuclear antibodies (ANAs) for possible systemic lupus erythematosus (SLE) with standard laboratory tests, followed by immune profiling for specific SLE-associated features of immune dysregulation. In individuals with normal results of standard laboratory tests, immune profiling might reveal SLE-associated immune activity to aid in the diagnosis of SLE. Individual patient profiles can be visualized on axes of immune dysregulation[71]. C3, complement C3; C4, complement C4; dsDNA, double-stranded DNA.

factors and autoantibodies. Although broad adoption of such tests will require standardization of cytometry markers and analysis methods across laboratories, potential value seems clear. For example, for individuals who present at rheumatology clinics with a positive anti-nuclear antibody (ANA), arthralgias, rashes and fatigue but have otherwise normal laboratory tests, a flow-cytometric quantification of circulating T_{FH} cells, T_{PH} cells, ABCs and plasmablasts might help to distinguish between SLE-associated pathological immune activity and immunological quiescence (Fig. 1).

Single-cell RNA sequencing as a clinical tool

Broad profiling approaches such as scRNA-seq of blood samples are likely to be translated into clinical practice in the next decade, following the example of whole-genome sequencing. The rapid advancement of clinical genome sequencing was aided by technological advances that made DNA sequencing feasible at reasonable costs, as well as by the establishment of a reference genome. In this context, immune profiling has struggled with myriad variations in cytometric definitions for the quantification of cell populations, complicating comparison of results

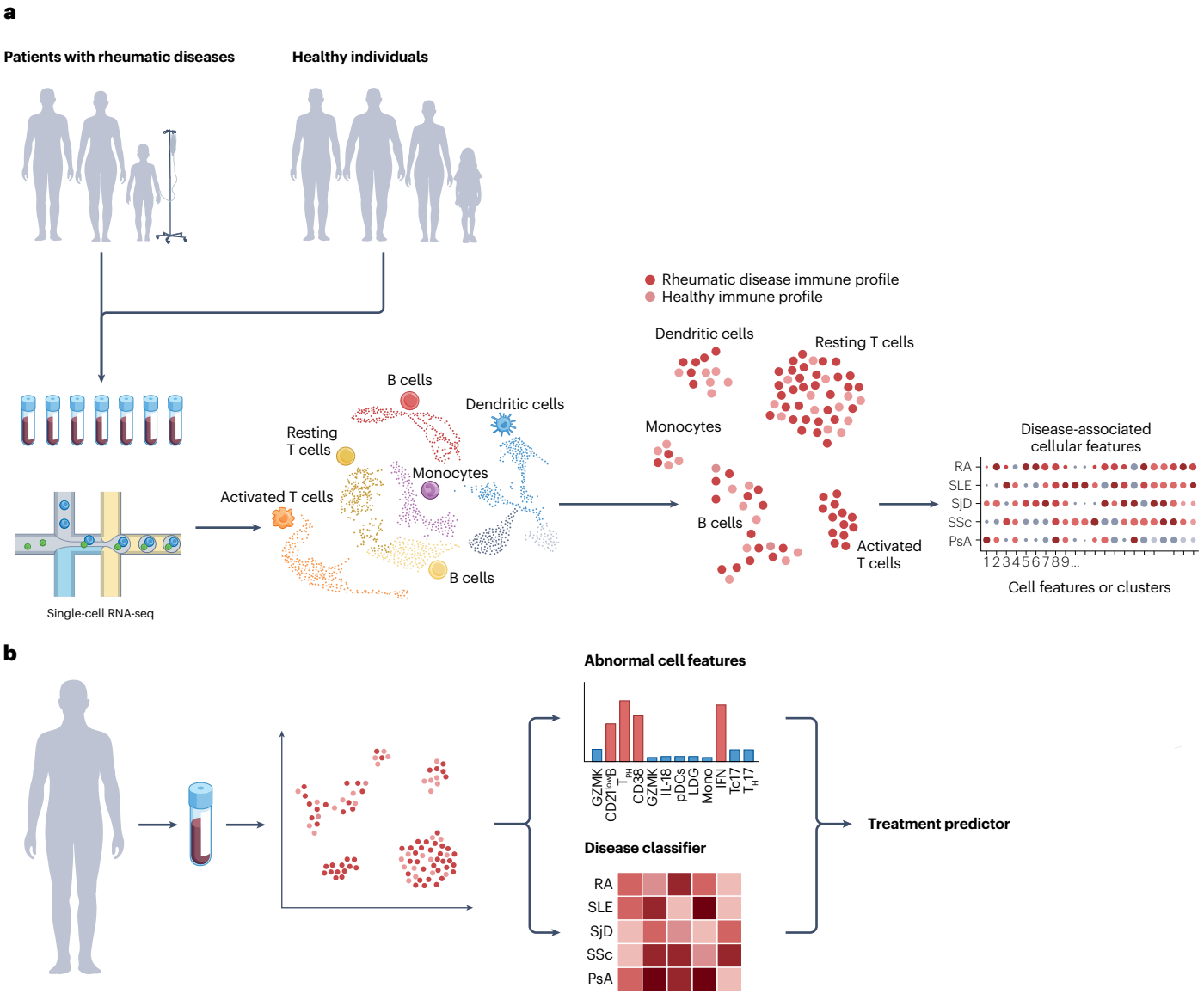

Fig. 2 | Broad immune profiling to identify immune abnormalities in rheumatic diseases. a, Broad immune profiling by single-cell RNA sequencing (RNA-seq) is able to define cell types (for example, monocytes, dendritic cells, B cells, T cells) or cell-activation states (for example, among resting T cells or activated T cells) that are characteristically altered in specific diseases and to generate healthy- and rheumatic-disease-associated reference datasets. These rheumatic-disease-associated cell types or cell states can be considered globally in a multi-dimensional fashion and then delineated further as specific cellular parameters. **b**, The immune profile of an individual sample is mapped against reference profiles to identify cellular features that differ from the healthy control-associated reference. Comparison with rheumatic disease-associated references matches individual profiles of undiagnosed individuals to the most fitting rheumatic-disease reference profile. A combination of these analyses has the potential to identify treatments that are the most suitable to modulate the pathologically activated pathways. LDG, low density granulocyte; Mono, monocyte; pDCs, plasmacytoid dendritic cells; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SjD, Sjögren disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

across studies and samples. The widespread use of droplet-based scRNA-seq now provides an opportunity to establish generalizable health- and disease-associated reference datasets. Moreover, advancing computational approaches will enable integration of scRNA-seq results from many diverse datasets, enabling cross-disease comparisons across studies, despite technical and methodological differences[146,147].

Leveraging a common language for scRNA-seq-based immune profiling will enable the mapping of scRNA-seq profiles of individual patient samples against a reference database of health- and disease-defined scRNA-seq profiles (Fig. 2), indicatively, screening for a strong type I IFN signature, as seen in patients with SLE, an expansion of ABCs, plasmablasts, T_{PH} and T_{FH} cells, as seen in SLE, ongoing T cell–B cell interactions, expansion of T_H17 cells, activation of IL-1β or TNF pathways in myeloid cells or abnormal T_{Reg} cell profiles. Unbiased approaches should be able to define SLE-like, RA-like, PsA-like, and other disease-associated immune profiles, enabling an immunophenotypic definition of immune health or disease-like status with any sample. Comparison with other states of immune activation, such as protective anti-viral and antibacterial responses as well as vaccine responses, will also be valuable.

Currently, technical and logistical challenges remain to be overcome for this kind of approach. RNA transcriptomes change with incubation time, such that improved methods are needed that limit artefactual changes in transcriptomic profiles after sample acquisition that may obscure biological signals. Costs of scRNA-seq remain considerable (typically >US$1,000 per sample), slowing the generation of foundational datasets that can demonstrate the utility of such immune profiling, yet newer scRNA-seq profiling methods using probe capture are substantially reducing sequencing costs and broadening the ability to analyse fixed samples[148]. Incorporation of scRNA-seq profiling into the protocols of ongoing industry-sponsored clinical trials, as has been done previously using whole-blood RNA-seq, would be immensely valuable to generate urgently needed scRNA-seq biomarkers of treatment effect and treatment response. As with more focused assays, standardization of methods across laboratories, and agreement on standard reference datasets, will be required to implement these approaches broadly.

Multi-modal immune profiling

A set of cellular profiling assays has the potential to complement other modalities that assess immune or inflammatory features, such as serum proteomic profiling or metabolomic profiling. In some cases, the different modalities might converge on the same fundamental observations; for example, a type I IFN signature can be detected by bulk RNA-seq, PCR, serum proteomic, or cytometric assays in SLE; in this case, the simplest and most cost-effective method should be used. Some modalities might, however, measure a given pathway more efficiently than others; for example, the enzyme-linked immunosorbent assay may be most suitable for detecting a circulating cytokine, mass spectrometry for a key metabolite and cytometry for a relevant cell population. Given the rapid advances in tissue-biopsy profiling with high-dimensional imaging and spatial transcriptomics, specific features of tissue architecture or cell infiltrates, or features of stromal or parenchymal cells, might also provide unique, non-redundant measures of disease-relevant immunopathology. Key informative inputs from any of these modalities can be incorporated as components of a broad assessment of immune dysregulation in patients, adding to the current assessments of CRP, complement components and autoantibodies. Machine-learning approaches that incorporate both molecular and clinical data also have the potential to establish robust diagnostic markers, as in a study that improved identification of patients with PsA using this approach[149].

Conclusion

In total, the rapidly expanding universe of immune-profiling data on blood and tissue samples from patients with rheumatic diseases is providing an increasingly well-defined set of parameters of immune dysregulation that is typical for these diseases, highlighting similarities and differences across diseases and among patients sharing a diagnosis. Immune profiling has so far highlighted several straightforward parameters of immune dysregulation that are ready for clinical implementation. In the near future, broad tests that assess the current activity level of the immune system, with an ability to detect pathological immune activation or deviation from homeostasis, might become as available as blood tests currently used to interrogate the functioning of other organs, such as the kidney and the liver. These methods have the potential to dramatically improve assessment of immune-mediated disease and guide therapeutic decisions for patients with rheumatic diseases.

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Review article

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Glucagon-like peptide-1 receptor agonists in arthritis: current insights and future directions

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Abstract

Obesity affects nearly one in six adults worldwide. Excess adiposity is a pro-inflammatory state associated with increased risk of several types of arthritis, increased arthritis disease activity and/or severity, and poorer response to certain treatments. Obesity is a major risk factor for cardiovascular disease, the leading cause of death in people with common arthritides such as osteoarthritis (OA), gout, rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a promising therapeutic option for people with arthritis and obesity or type 2 diabetes mellitus owing to their pleiotropic effects, including weight loss, improved survival and reduced risk of major cardiovascular and renal events. In vitro and preclinical in vivo experiments in arthritis have uncovered weight-loss-independent anti-inflammatory and chondroprotective properties of GLP-1RAs. In knee OA, clinical data suggest that GLP-1RAs improve pain and function and reduce the risk of surgical intervention; however, their effects on OA incidence remain incompletely understood. Evidence suggests that GLP-1RAs do not directly prevent gout attacks, but are effective in managing cardiometabolic conditions commonly associated with gout and other arthritides. More research is needed to clarify the effects of GLP-1RAs on incidence, disease activity, and progression of rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.

Sections

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Key points

- Obesity is a risk factor for developing osteoarthritis (OA), gout, rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), and is associated with higher disease activity and/or severity, and worse response to common treatments.
- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve glycaemic control, facilitate clinically meaningful weight loss, improve survival, and reduce the risk of renal failure and major adverse cardiovascular events.
- In vitro and in vivo experiments in OA, RA and psoriasis models have demonstrated weight-loss-independent anti-inflammatory and chondroprotective effects of GLP-1RAs, commonly through inhibition of the NF-κB pathway.
- Evidence from randomized controlled trials suggests that OA-related knee pain and function improve with semaglutide but not with liraglutide treatment, and observational studies suggest that GLP-1RA use reduces the risk of surgery for knee OA.
- More data are needed to clarify the effects of GLP-1RAs on the incidence of OA, RA, PsA and axSpA, as well as on disease activity and progression in these conditions.
- Muscle loss with GLP-1RAs is probably proportional to the extent of weight loss, and resistance exercise with adequate protein intake is recommended to preserve muscle mass and function.

Introduction

Globally, nearly one in six adults lives with obesity, a state of excess adiposity commonly defined as BMI ≥30 kg/m^2 (ref. 1). Excess adipose tissue is pro-inflammatory and relevant across common arthritides[2] (Table 1). In rheumatoid arthritis (RA) and psoriatic arthritis (PsA), for example, systematic reviews have shown that obesity is associated with increased disease activity[3] as well as poorer response to biologic DMARDs, particularly TNF inhibitors[4]. Among people with RA or PsA, the odds of achieving remission or minimal disease activity are ~40–50% lower for those with obesity[5–7]. Moreover, excess body weight can cause biomechanical stress, entheseal microtrauma and deep koebnerization at weight-bearing sites, provoking local inflammation in PsA[8]. In axial spondyloarthritis (axSpA), systematic reviews have revealed that higher weight is associated with both higher disease activity and radiographic progression[3,9]. Persistent pain and functional impairments are probably major reasons why people with obesity and RA, PsA or axSpA experience more difficult-to-manage disease[3,5–7,10].

People with osteoarthritis (OA) and obesity also experience higher levels of pain than those without obesity[3]. Excess and dysfunctional adipose tissue amplifies OA-related pain through various mechanisms that extend beyond increased mechanical loading (for example, increased production of adipokines and/or pro-inflammatory cytokines leading to enhanced nociceptive pain and peripheral and central sensitization)[11]. Furthermore, Mendelian randomization studies have shown causal relationships between elevated BMI and the development of OA[12,13] and gout[13,14], the two most common forms of arthritis worldwide[15,16]. A rise in BMI by one standard deviation leads to 1.5-fold and 1.7-fold increases in the incidence of OA and gout, respectively[13], and it has been estimated that nearly one-third of incident gout cases among American men could be prevented if none was overweight (that is, had a BMI of <25 kg/m^2)[17].

Additionally, excess adiposity significantly increases cardiometabolic risk[18]. Every five-unit increase in BMI above 25 kg/m^2 is associated with a 40% increase in cardiovascular mortality in the general population[19], and cardiovascular disease (CVD) is the leading cause of death for people with OA, gout, RA, PsA and axSpA[20–22]. The greater burden of CVD in people with arthritis is attributable, in part, to inflammation from arthritis accelerating atherogenesis, to the use of medications (such as glucocorticoids and NSAIDs) that can increase cardiovascular risk, and to the increased prevalence of cardiometabolic conditions[23]. Across common arthritides, reducing cardiovascular risk through the management of cardiometabolic conditions such as obesity is therefore a priority for care providers[24–27]. In this regard, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), which have weight loss, antidiabetic, and cardioprotective and nephroprotective properties, have emerged as promising therapeutic drugs.

In this Review, we summarize the physiology of GLP-1 and the multisystem effects of activating the GLP-1 receptor, discuss the established pleiotropic benefits of this increasingly popular drug class, and appraise the data on GLP-1RAs in OA, gout, RA, PsA and axSpA (rheumatic diseases for which the influences of excess adiposity are best studied). We conclude with a discussion of practical points clinicians should consider when prescribing a GLP-1RA to a patient with arthritis. In this Review, we include tirzepatide (a glucose-dependent insulinotropic polypeptide (GIP)–GLP-1 receptor co-agonist) when referring to GLP-1RAs.

The GLP-1 pathway and its activation

GLP-1 is produced by L cells (enteroendocrine cells predominantly located in the ileum and colon) and secreted at low levels in the fasted state[28]. Following a meal, secretion of GLP-1 and GIP rise, facilitating glucose-dependent insulin secretion by the pancreas, which lowers blood sugar levels. Interestingly, the GLP-1 response following a glucose load is reduced in individuals with obesity[29]. Activation of GLP-1 receptors in the gut, brain, kidney and cardiovascular and immune systems by native GLP-1 or GLP-1RAs leads to various extrapancreatic effects, as discussed below[28].

The evolving landscape of GLP-1RAs

Since 2005, when the first GLP-1RA (twice-daily subcutaneous exenatide) was approved for use in type 2 diabetes mellitus (T2DM), advances have led to the development of daily GLP-1RAs (for example, liraglutide and lixisenatide) and then weekly subcutaneous GLP-1RAs (dulaglutide, semaglutide), followed by daily oral GLP-1RAs (semaglutide) and weekly GIP–GLP-1 receptor co-agonists (tirzepatide)[30]. Promising results of phase II trials of novel agents including orforglipron (small-molecule oral GLP-1RA)[31], retatrutide (GIP–glucagon–GLP-1 receptor triple agonist)[32], and combination amylin analogue–GLP-1RA therapy with cagrilintide and semaglutide[33] illustrate the ongoing progress in expanding the drug class.

Cardiometabolic and renal effects of GLP-1 receptor agonism

Although initially a drug class for the treatment of T2DM, the pleiotropic effects of GLP-1RAs have been translated into meaningful clinical benefits in large-scale randomized controlled trials (RCTs)[34–46] (Table 2). Placebo-subtracted weight loss, for example, ranged from

approximately 3% with liraglutide administered at the standard dose for diabetes in people with T2DM[34] to 18% with tirzepatide administered at the (higher) dose for obesity in people with obesity without T2DM[40]. GLP-1RAs facilitate weight loss by increasing satiety and reducing appetite through the stimulation of the anorexigenic POMC–CART pathway, inhibition of the orexigenic NPY–AgRP pathway[47] and slowing of gastric emptying and small-bowel motility[28]. Of note, among people with obesity, those with T2DM experience less weight loss than those without T2DM, even with equivalent GLP-1RA dosing (Table 2).

From a cardiorenal perspective, a 2025 meta-analysis of 11 RCTs involving 85,373 participants showed 16% reduction in risk of renal failure, 14% reduction in risk of major adverse cardiovascular events (MACE), and 13% reduction in risk of all-cause mortality with the use of GLP-1RAs compared with placebo[41]. Pharmacologically activating GLP-1 receptors throughout the cardiovascular system reduces blood pressure (if hypertensive) and cardiac ischaemic injury, possibly decreases vascular inflammation and atherosclerosis (currently being investigated), and increases heart rate[28]. The mechanisms through which GLP-1RAs affect kidney health remain uncertain. Beneficial effects of GLP-1RAs on metabolic dysfunction-associated steatohepatitis have also been observed in phase II trials[48–50]. Because hepatocytes do not express GLP-1 receptors, these benefits might relate to anti-inflammatory mechanisms that are both dependent on and independent of weight loss[51].

Immunomodulatory effects of GLP-1 receptor agonism

Independent of their effect on adiposity, synthetic human GLP-1 and GLP-1RAs have anti-inflammatory effects in humans, suppressing key pro-inflammatory cytokines such as IL-6, TNF and IL-1β[52,53]. Such findings have ignited interest in exploring the effects of GLP-1 receptor agonism in arthritis. In vitro and preclinical in vivo experiments in OA, RA and psoriasis models have consistently demonstrated beneficial immunomodulatory effects of GLP-1RAs[54,55]. Across studies, significant, often dose-dependent, reductions in pro-inflammatory cytokines (TNF, IL-6, IL-1β) and cartilage-degradative enzyme expression and/or activity have been observed[55–62]. Human chondrocytes express the GLP-1 receptor[55]. Activating this receptor has been shown to be chondroprotective in OA. People with OA have lower serum GLP-1 levels[63], and intra-articular liraglutide injection alleviates pain[55] and attenuates cartilage degradation in OA mouse models[63]. GLP-1RAs reduce MMP3-related and MMP13-related degradation of type II collagen and ADAMTS4-related and ADAMTS5-related degradation of aggrecan[56–58,61,62], two fundamental components of articular cartilage. Novel discoveries related to a gut–joint axis explaining the connection between the gut microbiota, GLP-1 and OA progression illustrate a potential disease-modifying role of native GLP-1 and GLP-1RAs in OA[63] (Fig. 1).

Whereas various mechanisms seem to contribute to the observed immunomodulatory properties of GLP-1RAs, inhibition of a common signalling pathway has been reported across OA, RA, and psoriasis models: the NF-κB pathway[57–59,61,62,64–67] (Fig. 2). In OA and RA, GLP-1RAs have been shown to inhibit this pathway by preventing phosphorylation of IκBα[58,65,66], a key inhibitory protein that, in its unphosphorylated form, prevents nuclear translocation of NF-κB transcription factors[68]. GLP-1RAs also inhibit phosphorylation of p38, thus preventing nuclear translocation of RelA[61,65], and reduce TNF production and thereby TNF-induced activation of NF-κB signalling[62] (Fig. 2). In psoriasis, phosphorylation of AMP-activated protein kinase (AMPK) leads to activation of an enzyme (sirtuin 1 deacetylase) that deacetylates RelA, preventing its entry into the nucleus[69]. The net effect of all these mechanisms is reduced downstream production of pro-inflammatory cytokines. The clinical implications of the weight-loss-independent anti-inflammatory effects of GLP-1RAs in arthritis, which can occur alongside weight-loss-dependent anti-inflammatory effects resulting from the reduction of pro-inflammatory adipose tissue, merit further study.

Table 1 | Associations between excess weight and risk, activity and/or severity, and progression of common arthritides

	Incidence (risk)	Disease activity or severity	Radiographic progression	Response to treatment
OA	Increased[12,13]	Increased[3]	Greater radiographic progression seen with high BMI in 12 of 24 and 4 of 11 studies in systematic reviews[3,162]	Probably no clinically meaningful effect of preoperative weight on persistent post-TKA pain[163,164]
Gout	Increased[13,14]	Increased[a] (refs. 3,165–167)	Not studied	Decreased[b] (refs. 168–171)
RA	Increased[13,111]	Increased[3,5]	Lower radiographic progression with high BMI in 6 of 7 studies[3]	Reduced response to TNF inhibitors[4]
PsA	Increased[13,172]	Increased[3]	Not studied	Reduced response to TNF inhibitors[4]
axSpA	Increased[13]	Increased[3]	Increased[9]	Reduced response to TNF inhibitors[4]

The table is based on systematic reviews, meta-analyses and Mendelian randomization studies, unless otherwise specified. axSpA, axial spondyloarthritis; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TKA, total knee arthroplasty. [a]Based on three large observational studies, two showing increased risk of recurrent gout flares in patients with obesity[166,167] and one showing that weight gain increases the risk of recurrent gout attacks while weight loss decreases the risk (suggesting a dose–response relationship)[165]. [b]Based on one cross-sectional study[171], one prospective cohort[168], pooled data from one observational cohort plus two randomized controlled trials[170], and a post hoc analysis of one randomized controlled trial[169].

Effects of GLP-1RAs in common forms of arthritis

Considering the prevalence and effects of obesity across common forms of arthritis, questions around whether GLP-1RAs can improve arthritis symptoms, protect against adverse cardiovascular events in high-risk patients, or prevent arthritis onset altogether are being actively explored.

Osteoarthritis

Association with disease incidence. Data related to the risk of OA following exposure to GLP-1RAs are emerging, although the relationship remains unclear. Since 2024, four retrospective cohort studies have been performed by two research groups, and conflicting results have been reported[70–73].

In two US studies using Medicare data from a closed claims database, individuals with obesity, without prior OA, prescribed GLP-1RAs were compared with randomly selected individuals with obesity without anti-obesity medication use within 1 to 2 years[70,71]. Both groups were followed for 6 to 24 months for OA incidence. Cox proportional

Table 2 | Multi-system effects of GLP-1RAs based on RCT data

Outcome	Magnitude of effect (compared with placebo)	Refs.
Glycaemic control	1–2% improvement in HbA_{1c}	35,38,39,44,46
Weight loss	T2DM with or without obesity: Liraglutide[a] 3–4% Semaglutide[b] 5–6% Tirzepatide[c] 7–12%	34,35,37–39,44
	Obesity without T2DM: Liraglutide[a] 5% Semaglutide[b] 12% Tirzepatide[c] 18%	36,40,43,45
Mortality	13% reduction in risk	41
MACE	14% reduction in risk	41,42
Hospitalization for heart failure	11% reduction in risk	42
Renal failure	16% reduction in risk	41

GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, serum haemoglobin A_{1c}; MACE, major adverse cardiovascular events; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus. [a]For T2DM without obesity, 1.8 mg per day (subcutaneous); for obesity with or without T2DM, 3 mg per day. [b]For T2DM without obesity, 1 mg per week (subcutaneous); for obesity with or without T2DM, 2.4 mg per week. [c]For T2DM without obesity, 5 mg per week (subcutaneous); for obesity with or without T2DM, 15 mg per week.

hazards models (with adjustment for age, sex, socioeconomic status and selected comorbidities unbalanced at baseline) revealed a 16% lower risk of incident OA with semaglutide use than without[70], and a 27% lower risk with liraglutide, semaglutide or tirzepatide relative to no anti-obesity medications[71]. However, misclassification was possible as diagnosis was based on a single International Classification of Diseases, Tenth Revision (ICD-10) code for OA, and a 1-year look-back might have been too short to confidently exclude prevalent cases. The 21% incidence of OA after 1 year of follow-up in one of the studies could reflect these issues[70]. Furthermore, in one of two studies, the methods specify that only formulations of liraglutide, semaglutide and tirzepatide FDA-approved for weight loss were considered, suggesting that off-label use of formulations approved for T2DM were not captured[71].

By contrast, GLP-1RA exposure was associated with an increased risk of OA in two US studies that used data from TriNetX, a global network of electronic health records (EHR) data[72,73]. Individuals with obesity, without prior OA, prescribed GLP-1RAs were compared with propensity score-matched individuals without a GLP-1RA prescription. Propensity scores were calculated using age, sex, race, BMI, T2DM and, in those with T2DM, serum haemoglobin A_{1c} (HbA_{1c}) level. OA incidence, defined as one ICD-10 code for knee or hip OA, was determined using follow-up periods of 1 year[73] or ≥5 years[72]. Both studies found an increased incidence of hip and knee OA in the groups with a GLP-1RA prescription, with the risk being ~30–40% higher after 1 year and ~50–60% higher after 5 years. Baseline BMI after propensity score matching was not balanced between the groups exposed and unexposed to GLP-1RAs. Residual confounding by indication (that is, participants with high BMI being more likely to receive GLP-1RAs and to develop OA) might have remained. The groups might also have differed with respect to other unmeasured characteristics that influence the likelihood of OA diagnosis, such as access to clinical care or frequency of visits, causing ascertainment bias. Contamination (that is, prescription of a GLP-1RA to initially unexposed patients) during the follow-up period and low adherence were also concerns. At 2 years, only 38–62% of those initially prescribed a GLP-1RA were still being prescribed a GLP-1RA, and weight loss and improvements in HbA_{1c} levels were practically identical in all groups. Thus, the study had limited ability to capture true treatment effects.

All four studies acknowledged the limitations of using data from insurance claims and/or EHRs to evaluate the association between GLP-1RAs and OA incidence, including missing data on potential confounders, information on prescription dispensed rather than used, and the uncertainty of OA diagnosis based on ICD codes. Moreover, studies using EHR data from sources such as TriNetX could be limited in their ability to perform on-treatment or per-protocol analyses if the data are analysed within the platform (rather than being downloaded) and therefore treatment duration cannot be determined. As such, estimates of therapeutic effectiveness from analyses emulating an intention-to-treat approach could be clouded by contamination and early discontinuation. Nonetheless, studies to date have laid the foundation for future research. Moving forward, studies investigating the association between GLP-1RA use and OA incidence would benefit from extended look-back periods (to exclude prevalent cases of OA), several-year follow-up periods (given the slow development and progression of OA)[74], validated algorithms for diagnosing OA (to minimize misclassification)[75,76], analyses estimating on-treatment effects, and statistical methods to reduce risk of confounding.

Effect on OA disease outcomes. Excitement around GLP-1RAs as a therapeutic option for people with OA and excess adiposity has grown given the well-recognized benefits of weight loss in this population[77] as well as results from the STEP 9 trial[78]. This multicentre, international, double-blind RCT in 407 adults with obesity, moderate clinical and radiographic knee OA and no diabetes evaluated the effectiveness of semaglutide versus placebo as an adjunct to regular physical activity and dietary counselling over 68 weeks (Table 3).

Study participants who received semaglutide with lifestyle counselling lost 13.7% of their body weight, whereas those who received placebo with counselling lost 3.2% of their body weight, yielding a 10.5% absolute difference in weight reduction. Also, in the semaglutide group, 70% and 87% of people achieved ≥5 and ≥10% weight loss, respectively, a range in which several obesity-related complications improve[79]. Normalized Western Ontario and McMaster Universities OA index (WOMAC) pain score improved from baseline to week 68 by 42 points with semaglutide compared with 28 points with placebo. The 14-point greater improvement with semaglutide exceeds previously described minimal clinically important differences of ~10 points for knee OA interventions[80,81]. Similarly, significantly greater improvements in physical function, measured on WOMAC and SF-36 subscales, were observed with semaglutide relative to placebo. Rates of serious adverse events were similar between the groups and were consistent with the findings in prior trials of semaglutide[36,37,82]. Of the 87% of people who completed the treatment period with semaglutide, 90% were taking the full (2.4 mg) dose at the end, indicating good adherence and tolerance.

Although the generalizability of this trial's results to individuals with milder OA and/or less excess weight can be questioned, it demonstrated significantly greater, and clinically relevant, improvements in weight, pain and function with semaglutide compared with placebo, alongside lifestyle counselling.

Prior to the STEP 9 trial, one trial had evaluated the effects of GLP-1RAs on OA-related outcomes[83] (Table 3). This 52-week investigator-initiated single-centre triple-blind RCT was performed in 156 adults with mild-to-moderate symptomatic knee OA and elevated

BMI (≥27 kg/m^2). No difference in pain was observed with liraglutide relative to placebo[83]. However, prior to randomization, all participants underwent an 8-week diet intervention and only those achieving >5% weight loss (156 of 168) entered the trial and were randomly allocated to liraglutide treatment or placebo. The effects of this pre-randomization intervention were large: participants lost an average of 12.5 kg and pain decreased by 12 points on the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale, both clinically meaningful changes[79,84]. In contrast to the STEP 9 trial, participants had lower mean BMI (32 kg/m^2) and milder OA at baseline. Although changes in weight at 1 year were significantly different between groups (2.8 kg loss with liraglutide versus 1.2 kg gain with placebo), no differences in pain, function or quality of life were observed. The lack of improvement with liraglutide might have been partially attributable to a ceiling effect from the benefit of the pre-randomization intervention. After the initial improvement, mean KOOS pain score (0–100, with 100 representing no pain) at randomization was 78, leaving limited room for further improvement. Furthermore, liraglutide induces less weight loss than newer-generation GLP-1RAs (Table 2), and more weight loss (>7%) might be necessary to improve OA-related symptoms[77].

Observational studies have also provided important evidence highlighting that improvements in OA outcomes can be seen with varying degrees of excess weight and with different GLP-1RAs[73,85,86]. In the Shanghai Osteoarthritis Cohort, for example, the risk of undergoing knee surgery for OA was significantly lower with GLP-1RA exposure than without (1.7% versus 5.9%) after adjustment for age, sex, BMI, OA severity (Kellgren–Lawrence grade) and WOMAC total score[85] (Table 3). Furthermore, 32% of this effect was mediated through weight loss. The cohort comprised adults with specialist-diagnosed OA, T2DM, and ≥5 years of follow-up data, 233 of whom had ≥2 years of GLP-1RA exposure and 1,574 had no GLP-1RA exposure. Mean BMI at baseline (~25 kg/m^2) was lower than in the RCTs by Bliddal et al.[78] (STEP 9) and Gudbergsen et al.[83], and people receiving GLP-1RAs lost 4.6 kg over the follow-up period whereas unexposed people gained 2.7 kg (ref. 85). In the group receiving GLP-1RAs, WOMAC pain score improved by 3.4 more points, the number of intra-articular injections per year was ~0.1 lower, and there was 0.02 mm less cartilage loss per year. However, although statistically significant, these differences probably fall below thresholds for clinical relevance[80,81]. That said, pain at baseline was mild (~18/100 on the normalized WOMAC pain subscale, with 0 representing no pain), limiting room for improvement. Furthermore, significantly more people achieved a minimal clinically important change in pain score of 9 points with GLP-1RAs (35%) than without (28%). Certain potentially confounding factors were not accounted for (for example, socioeconomic status or comorbidities such as CVD that might increase GLP-1RA prescription and decrease the probability of undergoing surgery due to perioperative risk), and excluding those with <2 years of exposure to GLP-1RAs (17 people) could have introduced selection bias. Nonetheless, the results were consistent with those of three subsequently published observational studies[63,73,86] (Table 3).

Appraising experimental and observational evidence to date, GLP-1RAs are a promising therapy for the management of OA in people with excess adiposity. Ongoing trials evaluating retatrutide (NCT05931367) and tirzepatide (NCT06191848) in knee OA are estimated to conclude as early as December 2025 and May 2027, respectively (Supplementary Table 1).

Management of comorbidities. People with OA are at increased risk of various cardiometabolic and renal comorbidities and complications relative to those without OA[87–89], and GLP-1RAs have established

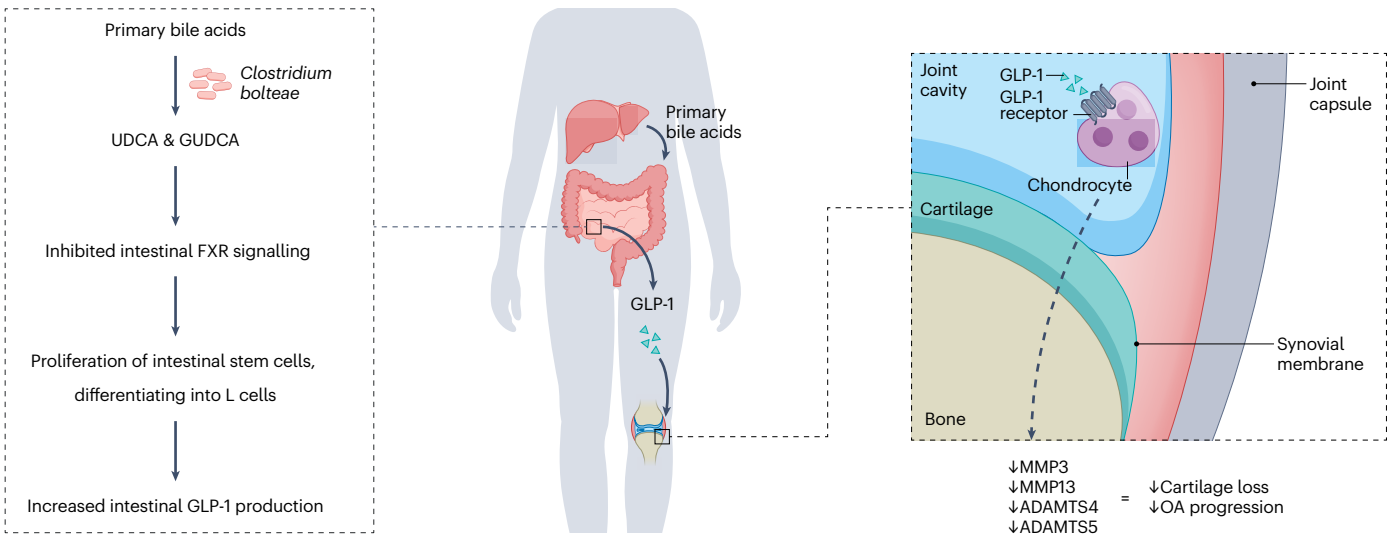

Fig. 1 | The GLP-1-mediated gut–joint axis in osteoarthritis. Evidence demonstrates a pathway linking the gut microbiota, glucagon-like peptide-1 (GLP-1) and joint health[63]. The gut microorganism *Clostridium bolteae* facilitates the conversion of primary bile acids, which are synthesized in the liver, to ursodeoxycholic acid (UDCA). UDCA is a precursor of glycoursodeoxycholic acid (GUDCA), a secondary bile acid that inhibits intestinal farnesoid X receptor (FXR) signalling. Both *C. bolteae* and GUDCA are less abundant in people with osteoarthritis (OA) than in those without OA, resulting in upregulated intestinal FXR signalling (which is pathogenic in OA)[63]. When FXR is inhibited by GUDCA, there is increased proliferation of intestinal stem cells that differentiate into L cells, the cell type responsible for producing GLP-1. Intestinal GLP-1 then travels to joints, where it binds to GLP-1 receptors on chondrocytes. Here, activation of GLP-1 receptors results in reduced expression of key catabolic enzymes including MMP3, MMP13, ADAMTS4 and ADAMTS5 (refs. 56–58,61,62), attenuating cartilage breakdown and OA progression[63]. This gut–joint axis could explain why serum levels of GLP-1 are decreased in people with OA and illustrates the disease-modifying potential of targeting GLP-1 receptors expressed in synovial joints[63].

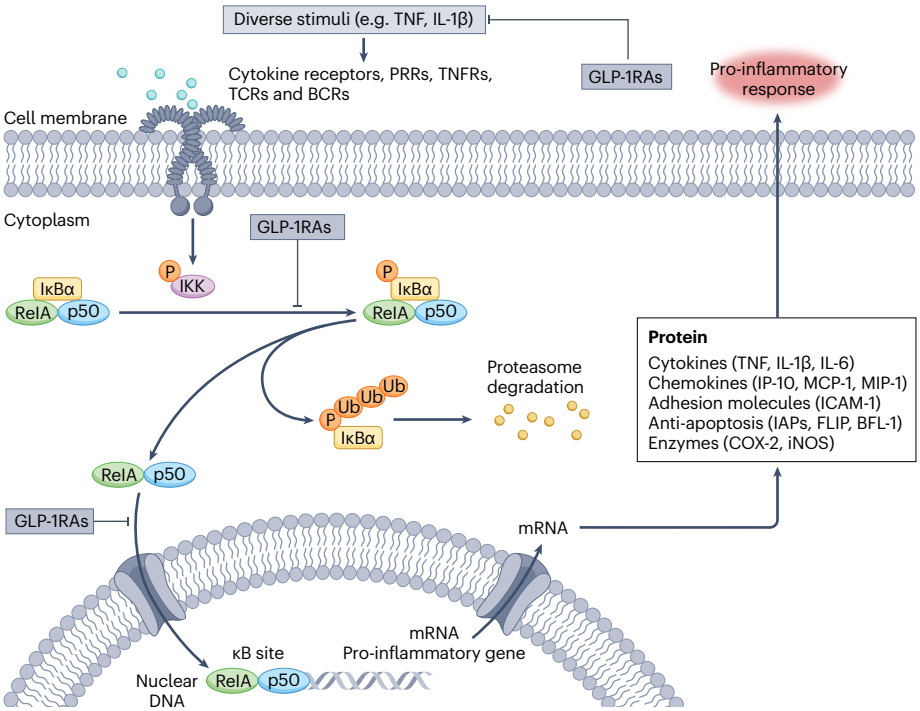

Fig. 2 | Inhibition of the NF-κB pathway through GLP-1 receptor agonists. The NF-κB pathway consists of a group of inducible transcription factors which, when activated, leads to the expression of various genes that encode important pro-inflammatory cytokines and chemokines. These transcription factors are normally sequestered in the cytoplasm by inhibitory proteins, the most important being IκBα. The NF-κB pathway is activated when IκBα is phosphorylated. Phosphorylation of IκBα (via the IKK complex) is normally triggered by stimuli such as cytokines (for example, TNF and IL-1β), growth factors, mitogens, microbial components or stress agents, and leads to degradation of IκBα. Phosphorylation of IκBα enables nuclear translocation of NF-κB transcription factors and subsequent expression of pro-inflammatory genes that encode cytokines (IL-1, IL-6, IL-12, IL-23, TNF) pertinent in osteoarthritis, rheumatoid arthritis and/or psoriatic disease. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) reduce levels of cytokines that activate the NF-κB pathway. GLP-1RAs also preventing phosphorylation of IκBα and nuclear translocation of RelA (one of five NF-κB family members). Through these effects, GLP-1RAs reduce downstream pro-inflammatory cytokine and chemokine production and resultant inflammation. BCR, B cell receptor; PRR, pattern recognition receptor; TCR, T cell receptor; TNFR, TNF receptor. Adapted from ref. 68, Springer Nature.

benefit in preventing or treating these conditions[34–46] (Table 2). Of note, walking difficulty and/or disability is a major driver of the elevated cardiovascular risk observed in people with OA[90,91], and exercise, even just once weekly, might attenuate the excess risk of cardiovascular events in people with knee OA[87]. In the STEP 9 trial, along with improvements in patient-reported physical function, 6-min walk distance improved by 43 m more with semaglutide than with placebo[78]. Hence, for people with OA and excess adiposity, GLP-1RAs might improve cardiometabolic health directly, through cardioprotective class effects, and indirectly, by increasing capacity for physical activity.

Gout

Effects on disease risk. Several studies, including a network meta-analysis of RCTs, have shown that GLP-1RA use is not associated with a decreased incidence of gout[92–94]. GLP-1RAs have also been frequently compared with sodium–glucose cotransporter 2 (SGLT2) inhibitors in observational cohort studies using large datasets to estimate the risk of developing gout[93,95–97]. SGLT2 inhibitors (for example, canagliflozin, empagliflozin and dapagliflozin) are another second-line T2DM drug class with cardioprotective and nephroprotective effects[98]. They too induce weight loss (~1.5–2 kg more than placebo), albeit to a lesser degree than GLP-1RAs[99]. Consistently, the risk of gout has been reported to be ~20–40% lower with SGLT2 inhibitor exposure than with GLP-1RA exposure. Considering all available evidence, SGLT2 inhibitors probably reduce the risk of developing gout when compared with GLP-1RAs, and GLP-1RAs probably do not reduce this risk relative to placebo. Mechanistically, SGLT2 inhibitors directly reduce serum urate concentrations in a clinically meaningful way[100], whereas GLP-1RAs do not[101,102]. Post-hoc analyses of four controlled clinical trials found no clinically relevant changes in serum urate concentrations following GLP-1RA exposure, neither immediately nor after several weeks of therapy[101]. Of note, only exenatide, lixisenatide and liraglutide were assessed, weight loss relative to placebo was only 1.4–1.9 kg after 8–12 weeks, and only 17–22% of participants across the four trials were hyperuricaemic at baseline (median serum urate concentration 321–377 μmol/l). A 2022 meta-analysis also found no significant urate-lowering effects of GLP-1RAs compared with placebo, but semaglutide was used in only one study[102]. Because GLP-1RAs have no direct uricosuric effect, any potential benefit in lowering serum urate levels would probably need to be mediated through weight loss (that is, indirectly)[103]. Since newer-generation GLP-1RAs such as semaglutide and tirzepatide facilitate greater weight loss than older GLP-1RAs, opportunities exist to explore whether these newer agents could indirectly lower serum urate concentrations long-term.

Effects on disease outcomes. GLP-1RAs have been studied as active comparators in two population-based studies evaluating SGLT2 inhibitors in people with pre-existing gout[104,105]. In both studies, the risk of recurrent flares (calculated after applying propensity score-based methods to account for baseline differences between groups) was approximately 30% lower with SGLT2 inhibitors than with GLP-1RAs.

Management of comorbidities. National estimates of comorbidity burden show that Americans with gout have 21% higher prevalence of obesity (53.3% versus 32.8%, adjusted OR 2.4), 18% higher prevalence of T2DM (25.7% versus 7.8%, adjusted OR 2.4), and 12% higher prevalence of myocardial infarction (14.4% versus 2.9%, adjusted OR 2.4) compared with people without gout[106]. Although available evidence does not suggest a role for GLP-1RAs in the primary or secondary prevention of gout flares, they do have a role in managing these cardiometabolic conditions[41,98,107].

Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis

Effects on disease risk. Our literature review revealed no full-length articles on the risk of PsA or axSpA following GLP-1RA exposure. Data on the association between GLP-1RAs and the development of RA

Table 3 | Studies evaluating effects of GLP-1RAs on disease outcomes in OA

Study (year)	Design	Sample and baseline characteristics	Main results	Ref.
STEP 9 trial (2024)	68-week multicentre international double-blind RCT evaluating effectiveness and safety of semaglutide (up-titrated to 2.4 mg SC weekly) versus placebo, along with lifestyle counselling every 4–8 weeks, for weight loss, pain, and function in knee OA plus obesity	407 adults (mean age 56 years, 82% women, 61% white) with obesity (mean BMI 40 kg/m^2), moderate clinical and radiographic knee OA (mean normalized WOMAC pain 70.9/100; KL grade 2 or 3), and no diabetes[a]	10.5% absolute difference in weight loss with semaglutide compared with placebo (−13.7% versus −3.2%; $P<0.001$) 14.1-point greater improvement in WOMAC pain with semaglutide (−41.7 versus −27.5; $P<0.001$) 14.9-point greater improvement in WOMAC physical function with semaglutide (−41.5 versus 26.7; $P<0.001$) Similar incidence of serious AEs (10% versus 8.1%), but more permanent discontinuations with semaglutide (6.7% versus 3%)	78
Gudbergsen et al. (2021)	52-week investigator-initiated single-centre triple-blind RCT evaluating effectiveness and safety of liraglutide (up-titrated to 3 mg SC daily) versus placebo on weight loss, pain and function in OA plus high BMI; randomization was preceded by an 8-week diet intervention	156 adults (mean age 59 years, 65% female) with BMI ≥27 kg/m^2 (mean BMI 32 kg/m^2), mild-to-moderate knee OA (mean KOOS pain score 77.8/100; KL grade 1–3), and no diabetes[b]	3.9 kg absolute difference in weight loss with liraglutide compared with placebo (−2.8 kg versus +1.2 kg; $P=0.008$) No difference in KOOS pain score, function or serious AEs	83
Shanghai OA Cohort (2023)	Multicentre prospective cohort study assessing associations between GLP-1RA exposure (≥2 years versus none) and incidence of surgery for knee OA[c], use of pain medications and intra-articular injections, as well as changes in WOMAC scores and medial knee cartilage thickness	1,807 adults >45 years old (mean age 61 years; 73% female; mean BMI 25 kg/m^2) with specialist-diagnosed OA (mean WOMAC pain score 17.5) and T2DM who received ($n=233$) or did not receive ($n=1,574$) GLP-1RAs	Mean treatment duration 5 years Significantly lower incidence of knee surgery with ≥2 years of GLP-1RA use versus no use (1.7% versus 5.9%; $P=0.014$)[d], 32% mediated by weight loss −7.3 kg mean difference in weight change (4.6 kg loss with GLP-1RAs versus 2.7 kg gain without; $P<0.001$)[d]	85
Yang et al. (2025)	Retrospective cohort study in adults with diabetes mellitus and knee OA that used IMRD EHR data to assess risk of knee replacement in GLP-1RA new users versus non-users matched for age, sex, BMI and calendar year	3,816 adults with diabetes mellitus and knee OA (mean age 64 years; 58% women; mean BMI 37 km/m^2), including 915 GLP-1RA new users and 2,901 matched individuals	Lower risk of knee replacement with GLP-1RA use over a 4-year mean follow-up (RD −5.4 (95% CI −10.0 to −0.8) per 1,000 person-years; adjusted HR 0.73 (95% CI 0.54–0.99)[e])	63
Porto et al. (2025)	Retrospective cohort study using TriNetX EHR data to assess rates of THA, TKA and major joint injections within 1 year for patients with OA plus obesity prescribed GLP-1RAs versus PS-matched individuals without GLP-1RA prescriptions[f]	45,676 participants total; 22,838 people with obesity and knee or hip OA prescribed GLP-1RAs PS-matched in a 1:1 ratio to individuals without GLP-1RA prescriptions (mean BMI 37 kg/m^2, mean age 63–64 years)	Lower incidence of THA (1.1% versus 2.2%; HR 0.6 (0.45–0.79)) and TKA (1.4% versus 2.1%; HR 0.75 (0.63–0.89)) within 1 year of GLP-1RA prescription, but no difference in weight loss or major joint injections	73
Samajdar et al. (2024)	Uncontrolled retrospective cohort study describing changes in outcomes 6 months after starting dulaglutide for the treatment of T2DM in older adults with OA	98 patients ≥60 years old (mean age 67 years; 59% male; mean BMI 31 kg/m^2) with T2DM and bilateral knee OA (mean VAS pain 6.9/10)	10.2% weight loss plus 3.8-unit improvement in mean VAS pain 6 months after starting treatment with dulaglutide (unadjusted $P<0.001$ for both)	86

AE, adverse event; EHR, electronic health record; GLP-1RA, glucagon-like peptide-1 receptor agonist; IMRD, IQVIA Medical Research Database; KL, Kellgren–Lawrence; KOOS, knee injury and osteoarthritis outcome score; OA, osteoarthritis; PS, propensity score; RCT, randomized controlled trial; RD, rate difference; SC, subcutaneous; T2DM, type 2 diabetes mellitus; THA, total hip arthroplasty; TKA, total knee arthroplasty; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index. [a]Other relevant exclusions beyond relative and absolute contraindications to GLP-1RAs included joint replacement or other joint pathology in the target knee, symptomatic hip OA, chronic widespread pain, and history of major depressive disorder within 2 years of screening, severe psychiatric disorder, or prior suicide attempt. [b]Only participants achieving >5% weight loss with the pre-randomization diet intervention underwent randomization (156 of 168), and this intervention led to clinically meaningful weight loss (−12.5 kg) and reduction in pain (−11.1 points). [c]Total knee arthroplasty, unicompartmental knee arthroplasty, arthroscopic procedures and high tibial osteotomy. [d]Adjusted for age, sex, BMI, KL grade and WOMAC total score. [e]Adjusted for BMI, socioeconomic deprivation index, haemoglobin A_{1c}, T2DM and OA duration, smoking and alcohol use, comorbidities, medications and hospital utilization. [f]Study also separately assessed risk of developing knee or hip OA with versus without GLP-1RA exposure in patients without existing OA (described in the text but not in the relevant table).

(or an RA-like syndrome) are limited to two case reports and one large retrospective cohort study[108–110]. In both case reports, patients' arthritis symptoms improved after stopping treatment with GLP-1RAs. In one report in which arthritis developed 3 months after dulaglutide initiation, the patient was found to be dual seropositive for RA and began improving with DMARD therapy before dulaglutide was stopped[108]. Hence, the patient's arthritis might have been independent of dulaglutide exposure. The other report described a 42-year-old man who developed seronegative polyarthritis (resistant to treatment with glucocorticoids and NSAIDs) 6 months after starting liraglutide[109]. The arthritis fully resolved 1 week after stopping liraglutide.

The association between GLP-1RA exposure and risk of RA was further explored in a retrospective cohort study using EHR data from TriNetX[110]. Cohorts of adults with either T2DM (n = 854,197) or obesity (n = 230,782), treated with GLP-1RAs, were propensity score-matched 1:1 to individuals without GLP-1RA treatment. After 5 years of follow-up, a lower risk of incident RA was observed with GLP-1RA exposure in individuals with obesity without T2DM. Four excess cases of RA per 1,000 patients followed over 5 years were identified in the unexposed compared with the exposed cohort (19.5 versus 15.5 cases per 1,000 patients). No difference was observed in the groups with T2DM. The findings should, however, be interpreted with caution. Although propensity score matching was applied to balance baseline covariates, only age, sex and ethnicity were mentioned as being included in the propensity score. Analyses did not account for other potential confounders such as comorbidities or factors influencing access to care that could have created ascertainment bias. Furthermore, the duration of GLP-1RA exposure and the competing risk of death were not considered. Although obesity is a risk factor for developing RA[13,111], the observed incidence rates for RA (19–24 new cases per 1,000 individuals followed for 5 years) were roughly six to eight times higher than reported estimates for American and Northern European populations of similar ages[112,113]. The high incidence rates might have been attributable to the RA definition used, which required only a single ICD-10 code billing. Also, the look-back period to exclude prevalent cases was not specified. Nonetheless, this study provides preliminary evidence of a potential protective effect of GLP-1RAs on RA incidence in individuals with obesity. Further studies are needed to clarify the effect of GLP-1RAs on the risk of autoimmune inflammatory arthritides.

Effects on disease activity. Published data on the effects of GLP-1RAs on disease activity in RA and PsA are sparse, and, to our knowledge, absent in axSpA. Several basic science experiments using models of RA or psoriasis have demonstrated anti-inflammatory properties (for example, significant reductions in TNF, IL-6, IL-17 and IL-23 expression) with GLP-1RA treatment, but the clinical implications of these effects have yet to be fully elucidated[54]. A scoping review that we performed in 2022 (ref. 54) identified two conference abstracts: one case report of a patient with RA treated with liraglutide for T2DM, and one uncontrolled prospective cohort study in 15 patients with T2DM and a concomitant diagnosis of either RA (n = 11) or PsA (n = 4) treated with liraglutide for 24 weeks[114,115]. In the case report, the patient's 28-joint Disease Activity Score (DAS28) improved from 5.5 to 3 with 12 weeks of liraglutide treatment. In the cohort study, 9 of 15 patients were deemed DAS28 responders, with significant reductions in DAS28 (from 4.2 to 2.7) and swollen joint count (from 3 to 1) with liraglutide treatment. Mean weight loss and HbA_{1c} improvement in these nine patients were 3.4 kg and 1.4%, respectively. The other six patients did not experience improvements in DAS28, swollen joint count, weight or HbA_{1c} level despite having comparable baseline characteristics. We did not find reports of any additional studies investigating the effects of GLP-1RAs on RA disease activity but identified one case series of ten patients with PsA (mean disease duration 10 years) and obesity (mean BMI 40 mg/m^2) treated with liraglutide 3 mg daily[116]. At baseline, one patient had minimal disease activity; after 3 months of liraglutide treatment, eight of the ten patients achieved minimal disease activity. Mean scores on Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI) improved by 54% and 62%, respectively[116].

More data have been published on the effects of GLP-1RAs in people with psoriasis and T2DM and/or elevated BMI, including three small RCTs, but either people with PsA were excluded[117] or articular outcomes were not reported[118,119]. Nonetheless, two of the three RCTs identified significant improvements in PASI and DLQI with GLP-1RA treatment[118,119]. Limitations of these trials, however, included small sample sizes (20–31 participants each), predominantly male populations, lack of blinding or an injected control (in two of three trials), and short durations (8–12 weeks). Furthermore, in one of the trials[119], randomization was mentioned in the title and abstract but not in the methods, the control group was assigned to receive no therapy (as opposed to placebo or an active comparator), and between-group differences in PASI or DLQI at the end of the trial were not formally tested for significance.

Overall, although promising, the paucity of data in RA, PsA and axSpA highlights that more research is required to determine whether GLP-1RAs can improve disease activity. Findings from phase III RCTs, TOGETHER-PsO (NCT06588283) and TOGETHER-PsA (NCT06588296), will shed light on the potential disease-modifying effects of adjunctive tirzepatide in active psoriatic disease (Supplementary Table 1).

Management of comorbidities. Immunocompromised individuals were either not described in or excluded from RCTs demonstrating the effectiveness of GLP-1RAs for reducing risk of MACE and all-cause mortality in adults with T2DM or obesity[107,120–122]. To determine whether people with immune-mediated inflammatory diseases (IMIDs) would derive similar benefits from GLP-1RAs as these broader populations, we conducted a population-based cohort study using administrative health data from a Canadian province[121]. We identified nearly 11,000 adults with T2DM and IMIDs, including RA, psoriatic disease (encompassing both psoriasis and PsA), axSpA, inflammatory bowel disease and systemic autoimmune rheumatic diseases (systemic lupus erythematosus, systemic sclerosis, Sjögren disease, idiopathic inflammatory myopathies and systematic vasculitides), who were incident users of GLP-1RAs or dipeptidyl peptidase-4 (DPP4) inhibitors. Like GLP-1RAs, DPP4 inhibitors (for example, linagliptin, sitagliptin and saxagliptin) are second-line T2DM agents that increase GLP-1 receptor signalling[98,123]. They do so more modestly than GLP-1RAs by preventing breakdown of native GLP-1 rather than by directly stimulating the GLP-1 receptor, and, unlike GLP-1RAs, DPP4 inhibitors are weight-neutral and cardioneutral[98,120]. Propensity score overlap weighting was applied to achieve balance in baseline covariates (including sociodemographic variables, comorbidities, T2DM duration and complications, IMID duration, use of other relevant medications and health-care utilization) and Cox proportional hazards models were used to estimate the risks of all-cause mortality and MACE. Risks of all-cause mortality and MACE were 52% and 34% lower with GLP-1RA than with DPP4 inhibitor exposure, yielding numbers-needed-to-treat of 107 and 96 for preventing one death or one MACE, respectively. Analyses were repeated in age-matched and sex-matched adults with T2DM without

IMIDs to assess whether people with IMIDs derived greater benefit from GLP-1RAs given their higher baseline cardiovascular risk. This was not the case, as a similar reduction in risk was found in people with and without IMIDs. Observed reductions in relative risk were larger than findings from RCTs, potentially because of differences in sample selection and unmeasured confounding. Our population-based sample included individuals who might not have participated in RCTs, such as those with very high cardiovascular and mortality risk.

Practical considerations when prescribing GLP-1RAs

Weighing risks versus benefits is essential when prescribing GLP-1RAs. Contraindications include personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (ref. 124). These contraindications are based on data from studies in rodents showing that GLP-1RAs act directly on thyroid C cells to cause C cell hyperplasia and tumours in a dose-dependent and duration-dependent manner[125]. The relevance of these findings to humans remains unknown. Clinicians should also review contraception in women of childbearing age. Weight loss can improve fertility, and it is currently recommended that women generally avoid GLP-1RAs during pregnancy owing to limited data and the potential for harm[126]. The most commonly reported adverse effects of GLP-1RAs are gastrointestinal (nausea, vomiting, diarrhoea and constipation), the majority of which are mild to moderate, occur with drug initiation and dose escalation, and improve over weeks[30,36,40]. Agents should be started at low doses and up-titrated slowly (for example, every 4 weeks for semaglutide and tirzepatide). If adverse effects lead to reduced oral intake, patients are at risk of acute kidney injury[127]. Gallbladder-related diseases have also been observed with greater frequency in patients treated with GLP-1RAs than in groups unexposed to these agents, attributable to direct effects (that is, acutely attenuated gallbladder emptying) and potentially indirect effects mediated by rapid weight loss[30,128]. Because of delayed gastric emptying, concerns regarding aspiration of residual gastric contents despite preoperative fasting have been raised; however, existing data do not support the view that increased residual gastric content from GLP-1RA use increases aspiration rates or aspiration-related complications[30,129].

Although findings from some cohort and pharmacovigilance studies have raised concerns related to GLP-1RA use and self-harm and/or suicidality[130–133], most studies have not identified elevated risk of self-harm, suicidal ideation or behaviours, or death from suicide among people using GLP-1RAs[134–139]. The FDA has stated that available data do not suggest a causal link between GLP-1RAs and suicidality[140]. Nevertheless, clinicians should be aware of these reports and patients should be informed of mental health supports as appropriate.

Another key consideration for people with arthritis taking GLP-1RAs is musculoskeletal health. Sarcopenia is prevalent in RA, PsA and axSpA[141,142]. Whereas weight loss interventions are intended to reduce adipose tissue, loss of lean mass (including muscle) is common[30], as are increased bone turnover and decreased bone mineral density (BMD). Observational and RCT data, however, suggest that GLP-1RA therapy does not increase the risk of fragility fractures[30,143] and might in fact decrease fracture risk in people with T2DM[144]. RCTs in adults without T2DM reveal reductions in BMD with GLP-1RAs, probably from weight loss lessening mechanical load[145,146]. In one study, regular exercise alongside liraglutide treatment permitted significant weight loss with preserved BMD[146]. Additional studies on bone health with long-term follow-up in adults with obesity and other high-risk features (including inflammatory arthritis) are warranted.

Box 1 | Do GLP-1RAs cause disproportionate loss of muscle tissue?

In the STEP 1 trial, a subgroup analysis of 95 participants who underwent dual energy X-ray absorptiometry (DEXA) scanning to assess changes in body composition following treatment with the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide or placebo revealed that loss of fat-free (lean) mass accounted for 39% of total weight loss in the group receiving semaglutide[36]. Of nearly 14 kg total weight loss, 5.3 kg was from losses in lean mass. This fraction was higher than that commonly estimated with diet alone (~25–30%)[147,148], raising concerns. Three factors, however, argue against disproportionate loss of muscle tissue with GLP-1RAs. First, the percentage of lean mass loss in the placebo arm of the STEP 1 trial was 57% (1.8 kg lean mass loss out of 3.2 kg total weight loss). Second, in the 255 participants in the SURMOUNT-1 trial who underwent DEXA scanning before and after treatment with tirzepatide or placebo, the ratio of fat loss to lean mass loss was similar in both groups (~3.1% fat loss per 1% lean mass loss)[40]. Third, muscle tissue is not synonymous with lean (that is, fat-free) mass and adipose tissue is not synonymous with fat mass[150]. Body composition assessments with DEXA measure lean and fat mass, not skeletal muscle tissue and adipose tissue[173]. Beyond skeletal muscle protein, lean mass includes water, other sources of protein (including the lean component of adipose tissue), glycogen stored within organs and muscle, non-fat lipids and minerals in soft tissues[173–175]. Interestingly, ~15% of adipose tissue (the greater part of its 'lean' component) is water[175,176], meaning that when a person loses 6 kg of adipose tissue, DEXA will record ~1 kg of lean mass loss. Furthermore, because ~73% of lean mass is water[174], only a minor part of lean-mass losses measured by DEXA represent true loss of skeletal muscle protein. More data are needed to understand the effect of GLP-1RAs on muscle mass and function[177].

Concerns about disproportionate muscle mass loss with GLP-1RAs were raised when a subgroup analysis of 95 participants from the STEP 1 trial revealed that fat-free (lean) mass loss, measured by dual energy X-ray absorptiometry, accounted for 39% of total weight loss in the group that received semaglutide[36]. This percentage was higher than that typically found with diet alone (that is, ~25–30%)[147,148]. However, a closer look at these findings along with results from the SURMOUNT-1 trial (in which a similar ratio of fat loss to lean mass loss was observed with tirzepatide and placebo)[40] cast doubt on whether muscle loss with GLP-1RAs is truly disproportionate (Box 1). Nonetheless, efforts to minimize muscle mass loss and preserve (or improve) function are critical for people with arthritis beginning any mode of weight-loss therapy. Two suggested strategies are resistance training (at least twice per week)[149,150] and prioritizing protein intake (1.2–1.6 g/kg daily)[150,151]. We recommend engaging allied health professionals where possible, such as kinesiologists and physiotherapists to recommend exercises tailored to a patient's functional capacity, and dietitians to facilitate implementation of sustainable healthy eating patterns. Another promising option is bimagrumab, a monoclonal antibody that blocks activin receptor II to preferentially reduce adipose tissue while sparing muscle[30]. Phase II trials assessing bimagrumab versus placebo in either individuals with T2DM and elevated BMI or in older adults with sarcopenia have shown significant fat loss and concurrent lean mass

Box 2 | Outstanding research questions

- How do glucagon-like peptide-1 receptor agonists (GLP-1RAs) affect the risk of developing osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic disease or axial spondyloarthritis (axSpA)?
- By inducing greater weight loss, can newer-generation GLP-1RAs (such as semaglutide and tirzepatide) indirectly lower serum urate concentrations by a meaningful extent?
- Do GLP-1RAs, through anti-inflammatory mechanisms that are dependent on or independent of weight loss, improve disease activity in RA, PsA or axSpA?
- What are the effects of GLP-1RAs on musculoskeletal health, and what are the implications of these effects for patients with arthritis?
- Does the presence of diabetes modify potential weight-loss-independent benefits of GLP-1RAs in arthritis?
- Does bimagrumab, with or without GLP-1RAs, effectively reduce adiposity while preserving muscle mass in individuals with arthritis?

gain with bimagrumab[152,153]. Final results of phase II trials assessing this agent alone or in combination with semaglutide (NCT05616013) or tirzepatide (NCT06643728 and NCT06901349) in people with excess adiposity, with or without T2DM, are awaited (Supplementary Table 1). Whether bimagrumab can mitigate GLP-1RA-related lean mass loss in individuals with arthritis is one of several remaining questions (Box 2).

Clinicians should also consider the cost and risk of weight regain following discontinuation of GLP-1RAs. The STEP 4 and SURMOUNT-4 trials provide insights into expected weight regain after stopping GLP-1RAs[154,155]. Following a 20-week or 36-week open-label run-in, adults were randomized to continue semaglutide (STEP 4) or tirzepatide (SURMOUNT-4) or switch to placebo in a blinded manner. After 1 year, participants switching off GLP-1RAs regained roughly half to two-thirds of the weight they initially lost. Because participants in these trials were followed closely and continued to receive lifestyle counselling, weight regain might be greater in real-world settings. If full-dose GLP-1RA therapy is not feasible in the long term, strategies to minimize weight regain with GLP-1RA deprescribing need to be considered, although evidence supporting each approach is currently limited[156]. Options include tapering to a lower dose or less-frequent administration schedule[157], switching to less costly generic medications with weight-loss properties (for example, metformin, topiramate or bupropion)[158], or prescribing regular moderate-to-vigorous (supervised) exercise[159].

Lastly, the use of GLP-1RAs is lower in low-income and marginalized groups, independent of cardiovascular risk[160,161]. Barriers such as cost could widen existing health inequities, and advocacy efforts are needed to support patients in accessing a class of medications that has been shown to prolong survival, reduce leading causes of morbidity, and, in people with OA, improve pain and function.

Rheumatologists often establish longitudinal relationships with their patients and are therefore well-positioned to identify cardiometabolic comorbidities that could be treatable with GLP-1RAs. Because scope of practice is setting-dependent, we recommend that GLP-1RAs be prescribed and managed by providers who have comfort and experience with these agents. These providers could include family physicians, internists, endocrinologists, cardiologists, nephrologists or rheumatologists.

Conclusions

Exploring the effects of GLP-1RAs in arthritis presents an exciting and timely opportunity. At present, it is clear that this drug class is an effective option for managing T2DM and obesity, as well as for reducing the risk of mortality and major adverse cardiovascular and renal outcomes. Emerging data suggest they can help improve pain and function in OA, mediated only partly through weight loss. In vitro and in vivo evidence of immunomodulatory, chondroprotective and anti-inflammatory effects of GLP-1RAs in arthritis illustrate a potential weight-loss-independent disease-modifying effect worthy of further clinical research. As the use of GLP-1RAs increases, experience accumulates, and the class expands to include additional co-agonists, triple agonists and oral small molecules, many knowledge gaps can be filled. Much is left to learn, but the potential benefits of this medication class for rheumatological diseases are highly encouraging.

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Perspective

Check for updates

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.

Sections

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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.

International guidelines provide recommendations to navigate the available treatments for knee OA[11–13] and advocate for a multimodal 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.

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.

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 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.

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.

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

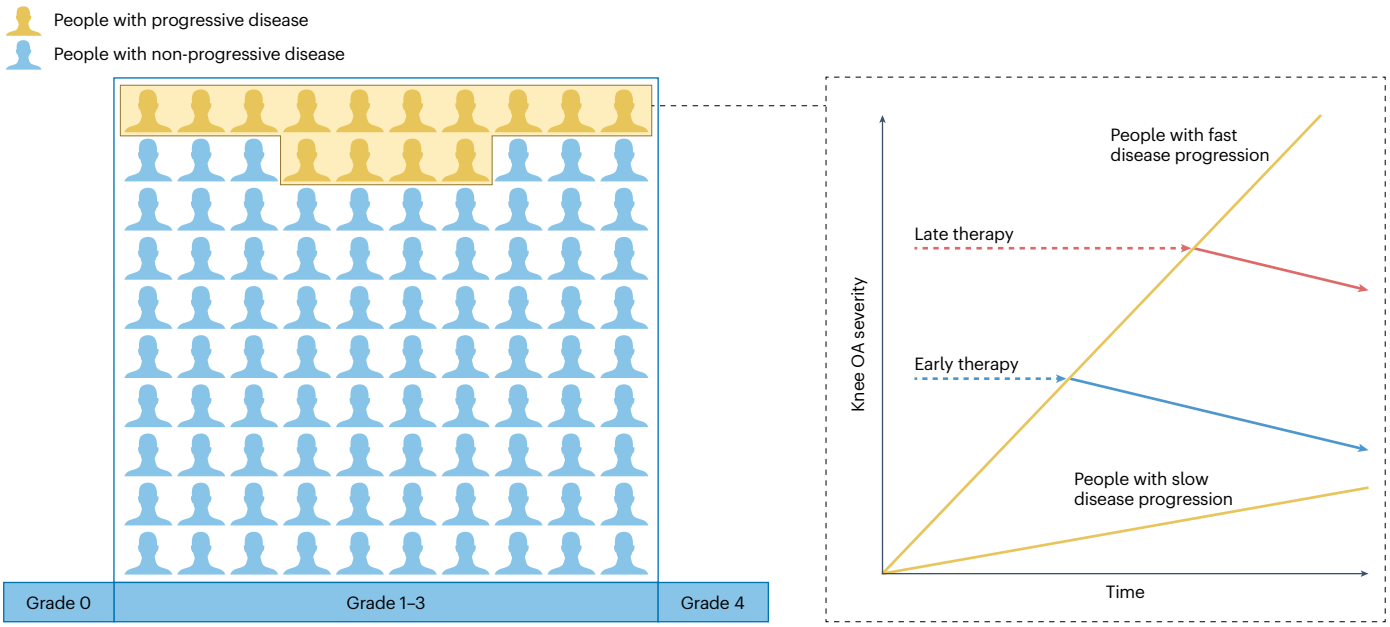

Fig. 1 | Progression and trajectory of knee osteoarthritis. Of patients with knee osteoarthritis (OA) who have a Kellgren–Lawrence grade between 1 and 3, 14% will probably have progressive disease (over 8 years)[49]. The trajectories of fast and slow disease progression differ, and early diagnosis and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

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.

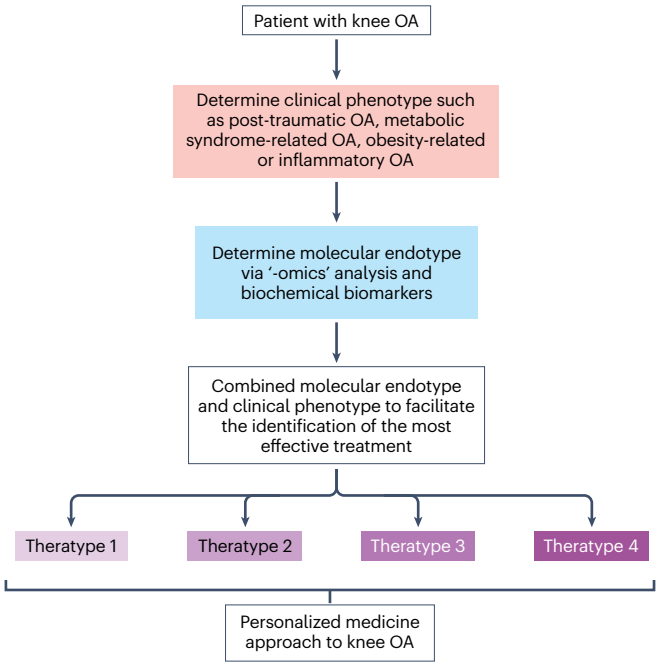

Fig. 2 | A personalized medicine approach to knee osteoarthritis. A patient with knee osteoarthritis (OA) presents and is assessed for clinical phenotype (including post-traumatic, metabolic syndrome-related, obesity-related, inflammatory), endotyped (via '-omics' analysis and biochemical biomarkers) 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.

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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Author contributions

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Competing interests

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