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INVITED REVIEW

Beyond the horizon: Innovations and future directions in axial-spondyloarthritis

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ABSTRACT

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease of the spine and sacroiliac joints. This review discusses recent advances across multiple scientific fields that promise to transform axSpA management. Traditionally, axSpA was considered an immune-mediated disease driven by human leukocyte antigen B27 (HLA-B27), interleukin (IL)-23/IL-17 signaling, biomechanics, and dysbiosis. Diagnosis relies on clinical features, laboratory tests, and imaging, particularly magnetic resonance imaging (MRI) nowadays. Management includes exercise, lifestyle changes, non-steroidal anti-inflammatory drugs and if this is not sufficient to achieve disease control also biological and targeted-synthetic disease modifying anti-rheumatic drugs. Beyond long-recognized genetic risks like HLA-B27, high-throughput sequencing has revealed intricate gene-environment interactions influencing dysbiosis, immune dysfunction, and aberrant bone remodeling. Elucidating these mechanisms promises screening approaches to enable early intervention. Advanced imaging is revolutionizing the assessment of axSpA's hallmark: sacroiliac bone-marrow edema indicating inflammation. Novel magnetic resonance imaging (MRI) techniques sensitively quantify disease activity, while machine learning automates complex analysis to improve diagnostic accuracy and monitoring. Hybrid imaging like synthetic MRI/computed tomography (CT) visualizes structural damage with new clarity. Meanwhile, microbiome analysis has uncovered gut ecosystem alterations that may initiate joint inflammation through HLA-B27 misfolding or immune subversion. Correcting dysbiosis represents an enticing treatment target. Moving forward, emerging techniques must augment patient care. Incorporating patient perspectives will be key to ensure innovations like genetics, microbiome, and imaging biomarkers translate into improved mobility, reduced pain, and increased quality of life. By integrating cutting-edge, multidisciplinary science with patients' lived experience, researchers can unlock the full potential of new technologies to deliver transformative outcomes. The future is bright for precision diagnosis, tightly controlled treatment, and even prevention of axSpA.

Keywords: Artificial intelligence, axial spondyloarthritis, future directions, imaging, innate immunity.

Spondyloarthritis refers to a group of chronic inflammatory diseases that share common clinical features including inflammatory back pain, peripheral arthritis, enthesitis, uveitis, psoriasis, and inflammatory bowel disease (IBD). This disease concept encompasses several interrelated but distinct disorders: axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), reactive arthritis (ReA), IBD-associated arthritis, and undifferentiated spondyloarthritis (Figure 1).[1] They each possess distinct clinical phenotypes and patterns of joint involvement. AxSpA primarily affects the spine and sacroiliac joints (SIJ); PsA manifests mainly as peripheral-often asymmetric-oligoarthritis, axial disease, enthesitis, and dactylitis; ReA classically follows certain infections and presents with lower extremity arthritis and enthesitis; IBD-associated spondyloarthritis occurs in patients with IBDs like Crohn disease and ulcerative colitis.[1]

Specifically, axSpA refers to a group of chronic inflammatory diseases primarily affecting the SIJ and spine.[2] AxSpA commonly includes two clinical pictures: non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA), historically termed ankylosing spondylitis (AS), depending on whether the axial disease has caused visible radiographical lesions on X-ray (fulfilling the modified New York Criteria (NYc) or not).[3] On the contrary, the

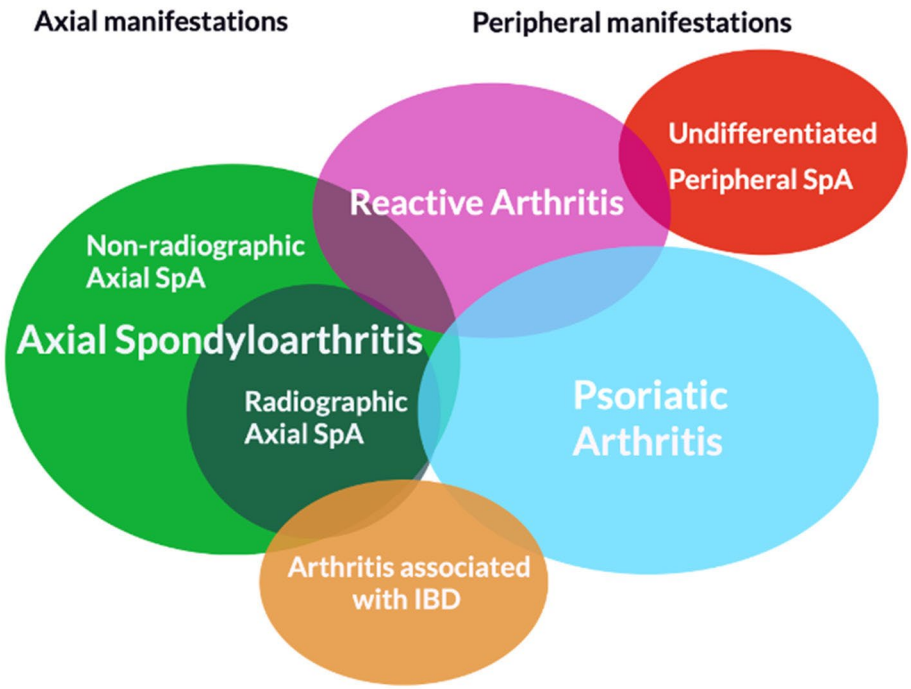

Figure 1. Spondyloarthritis spectrum from axial to peripheral involvement.

SpA: Spondyloarthritis; IBD: Inflammatory bowel disease.

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notion of nr-axSpA frames the early phases of the disease, in which the axial involvement is marked by the presence of bone-marrow edema (BME) in the SIJ visible on magnetic resonance imaging (MRI). Therefore, these two entities essentially represent a continuum between an early and a more advanced stage of the same disease.[4]

The global prevalence of axSpA is estimated between 0.1-1.4%, with considerable geographic variation mainly attributed to differences in human leukocyte antigen B27 (HLA-B27) prevalence. HLA-B27, present in 8-10% of the general population, is positive in up to 90% of axSpA patients and is a major genetic risk factor. Prevalence is highest in Arctic and Northern European regions where HLA-B27 rates approach 50%, such as among the Haida native peoples of Western Canada with axSpA prevalence from 6-10%. In contrast, prevalence is markedly lower in Japan and Arab populations where HLA-B27 rates are only 1-3%[5-7]. On the population level, prevalence estimates range from 0.24% in Greece to 1.8% in Northern Norway.[8,9] A systematic review reported mean axSpA prevalence in Europe of 24 per 10,000 people. In Asia the estimate was 17 per 10,000, while North America ranged from 13 to 32 per 10,000.[10] Although less studied than prevalence, incidence rates ranged from 5 to 15 per 100,000 person-years across studied populations.[11]

The onset of axSpA symptoms usually begins in early adulthood, resulting in a substantial lifetime burden. Patients suffer from chronic back pain typically with inflammatory characteristics, spinal stiffness, and reduced mobility.[12] Therefore, the disease is also associated with major economic implications stemming from direct medical costs and indirect costs due to lost work productivity. Furthermore, structural damage is irreversible and leads to increasing disability, loss of quality of life, and need for surgical interventions over time.[13-15]

Despite the availability of effective treatments, an unsolved problem remains the average delay from symptom onset to diagnosis, which remains around 5-10 years globally.[16,17] This diagnostic

delay has motivated intensive research to better understand the pathophysiology and natural history of axSpA, and to optimize strategies for early identification and treatment.[18] The emergence of MRI has been revolutionary, allowing direct visualization of SIJ inflammation years before radiographic changes appear and with this giving the opportunity for early and intensified treatments by suppressing the inflammatory activity enabling to even preventing the development of such structural changes. Therefore, incorporation of MRI findings into classification criteria has enabled earlier diagnosis and treatment.[19]

The discovery of tumor-necrosis factor-alpha (TNF-α) and interleukin (IL)-17 as major inflammatory cytokines in axSpA led to the rise of biologic drugs targeting these mediators. Biologics have drastically advanced management of axSpA, though significant unmet needs remain.[20] Treatment responses vary widely and many questions persist surrounding their long-term impacts on controlling symptoms, preserve function, prevent the development of structural damage, and extra-articular manifestations. There is a need for prognostic biomarkers to predict disease course and response to therapies.

While advances in MRI imaging and biologic therapies have transformed treatment for many patients with axSpA critical gaps remain in reducing the years-long diagnostic delays that many patients face. To address this, optimizing screening and referral strategies in primary care is crucial, particularly for at-risk individuals with chronic back pain. Incorporating clinical, laboratory, genetic, and imaging biomarkers into predictive models is a promising approach to quantify axSpA risk earlier and enable prompt diagnosis and treatment, with the goal of improving long-term outcomes. Looking ahead, further research on disease mechanisms and new collaborations across disciplines will be key to advancing the field of axSpA and reducing the associated burden of the disease. Emerging fields include genetics to identify new risk factors, immunology to elucidate pathogenic pathways, microbiome studies to understand links with gut dysbiosis, advanced imaging techniques to improve diagnosis and monitoring, and digital tools for automated analysis and personalized medicine.

In summary, leveraging new technologies in genetics, immunology, microbiome research, imaging, and artificial intelligence (AI) holds tremendous potential to uncover axSpA disease insights, enable precision diagnosis and treatment, and ultimately improve the lives of patients struggling with this challenging disease. By pursuing a multidisciplinary approach across these exciting fields, researchers can pave the way for the next generation of innovations in axSpA care.[21]

TRADITIONAL UNDERSTANDINGS

Pathophysiology

Axial spondyloarthritis results from multiple interacting factors including genetic risks, immune dysregulation, biomechanics, and environmental triggers.[22] While PsA is traditionally considered an enthesitis-driven disease,[23] in axSpA several evidence indicates bone marrow inflammation is a central early event.[24,25] Thus, MRI reveals that BME and osteitis frequently precede clinical and radiological enthesitis.[24] Hence, the bone marrow provides an immunologically rich milieu where stromal and immune cells propagate inflammation and aberrant bone remodelling.[26] Then, communication likely occurs between affected marrow and entheses via cytokines, immune cell trafficking, and anatomical links.[26]

Genetically, HLA-B27 is the major risk allele, present in up to 80-90% of AS patients,[2] but the exact pathogenic mechanisms remain unclear. Many other genes related to cytokine signaling, antigen processing, and innate immunity also contribute.[27]

In terms of immune dysregulation, both arms of the immune system contribute to axSpA pathogenesis. A key pathway implicated is the IL-23/IL-17 axis.[28] IL-23 produced by antigen-presenting cells can activate innate lymphoid cells such as type 3 innate lymphoid cells (ILC3s), as well as innate-like T cells including MAIT and γδ T cells, stimulating them to produce IL-17, IL-22, and other inflammatory mediators. Expanding populations of IL-17-secreting cells drive tissue inflammation and damage.[29-32] Although adaptive $CD4^+$ T_H17 cells also expand in axSpA patients, the relative contribution of innate versus adaptive

sources of IL-17 remains unclear. An imbalance exists between pro-inflammatory T_H17 cells and regulatory T cells that normally maintain self-tolerance. Other relevant cytokines driving inflammation include TNF-α, IL-1, and IL-22. The role of B cells and autoantibodies is still emerging.[33,34]

Biomechanics contribute through microtrauma and stresses at entheses that could initiate inflammation in susceptible individuals.[35] Mechanical instability helps propagate and localize inflammation. Hence, facet joints, SIJ, and spinal entheses endure considerable stresses and are early sites of inflammation.[36,37]

Environmental triggers like dysbiosis, leaky gut, and infections provide further stimulation. The linkage between gut and joint inflammation supports the gastrointestinal immune environment's contribution.[38]

In summary our understanding of axSpA pathophysiology has progressed substantially in recent years. The foundation of such evolving perspective is the recognition of the multilayered, intricate interactions underlying disease pathophysiology. Genetic risks, immune dysregulation, biomechanical factors, and environmental triggers collectively propagate aberrant inflammation and tissue damage. Communication likely occurs between affected sites via cytokines, trafficking immune cells, and anatomical connections. Of particular significance is the bone marrow inflammation nowadays considered as an early central event, often preceding clinical signs. MRI bone marrow findings frequently emerge first, providing an immunologically rich nexus where inflammation originates.[26]

Diagnosis

The diagnosis of axSpA can be challenging due to the lack of a single confirmatory test. AxSpA should be suspected in patients with chronic back pain starting before the age 45 along with signs and symptoms suggestive of SpA. The typical features of inflammatory back pain include insidious onset, improvement with exercise but not rest, pain at night, and morning stiffness lasting over 30 minutes. Other indications for axSpA include presence of HLA-B27, a family history of SpA, elevated C-reactive protein (CRP) levels, extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease), peripheral arthritis, enthesitis, and good response to non-steroidal anti-inflammatory drugs (NSAIDs).[39]

Imaging plays a fundamental role in the diagnostics process, with conventional radiography of the SIJ being the recommended first imaging modality in suspected axSpA.[40] Radiographic sacroiliitis (erosions, sclerosis, joint space widening, ankylosis) confirms a diagnosis, but has low sensitivity in early disease.[41] If radiographs are negative or equivocal, MRI of the SIJ should be performed. MRI can detect BME and osteitis indicating active inflammation. Various structural lesions may also be seen including erosions, sclerosis, fat lesions, and ankylosis. However, there are some limitations with MRI. Bone marrow edema is not entirely specific for axSpA, as it can occur to some degree with mechanical back pain, postpartum, heavy exercise, and even in healthy individuals.[42,43] Location, extent, and combination with structural lesions may increase specificity. Therefore, MRI interpretation requires experienced readers.[21,44,45] MRI of the spine has minimal incremental value for diagnosing axSpA when MRI of the SIJ is already performed. However, in patients where SIJ MRI is equivocal or normal, additional spine MRI may increase diagnostic sensitivity by 15-20%.[44] On the other hand, it should be taken into account that vertebral corner BME and fat metaplasia also occur in healthy individuals and those with non-specific back pain.[46] Hence, MRI of both the spine and SIJ is not universally recommended,[47] although spine MRI can be considered in certain circumstances such as high clinical suspicion despite normal SIJ MRI.[44] Moreover, spine MRI may predict disease progression since inflammation or fat metaplasia has been traditionally considered to be associated with new syndesmophytes formation,[48,49] even if new evidence found that vertebral corner inflammation may actually lead to new bone formation, but only in a minority of cases via visible fat deposition.[50]

No serologic markers are confirmatory for axSpA. HLA-B27 positivity has about 90% specificity, but sensitivity around 50%.[51] Elevated CRP supports inflammation but is normal in a relevant proportion of axSpA patients[52] and can also be seen in other inflammatory circumstances.

Various classification criteria for axSpA have been developed to standardize enrolment in clinical trials and research. However, no universal diagnostic criteria exist. The Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria allow MRI evidence of sacroiliitis to substitute for radiographic damage.[19] It is of great importance to underline that classification criteria might be used and are intended only to recruit a homogeneous group of patients into clinical trials and not to establish a clinical diagnosis. While intended for classification, the ASAS criteria are often used misused clinically, which may lead to some over-diagnosis.[53]

The diagnosis of axSpA comes from a thorough and multifactorial assessment of the patients which is the combination of clinical, laboratory, genetical and imaging evaluation. There should be a high index of suspicion in the appropriate demographic with suggestive symptoms and signs. Diagnostic evaluation incorporates patient history, physical exam, laboratory tests, and imaging to support the diagnosis, rule out mimics, and assess for poor prognostic factors that may guide therapy.[54]

Treatment

The 2022 ASAS-European Alliance of Associations for Rheumatology (EULAR) recommendations update emphasize a personalized approach to managing axSpA, with treatment tailored to the individual patient. A combination of non-pharmacological and pharmacological treatments is recommended.[55]

For non-pharmacological management, all patients should receive education about axSpA and be encouraged to exercise regularly and stop smoking. Physiotherapy and supervised exercise programs should be considered, particularly for patients who do not exercise independently, as they have proven benefits.[55]

For pharmacological treatment, NSAIDs are recommended as first-line drugs to control pain and stiffness. Continuous NSAID use is preferred if needed to control symptoms, but intermittent 'on-demand' use can be considered if continuous treatment is not required. If NSAID treatment fails, is contraindicated, or poorly tolerated, biological (b) or targeted synthetic (ts) DMARDs should be considered for patients with high disease activity despite conventional treatments. Eligibility criteria include confirmed diagnosis of axSpA: for r-axSpA high disease activity (Ankylosing Spondylitis Disease Activity Score [ASDAS] ≥2.1 or Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4) and failure/contraindications for NSAIDs, while in nr-axSpA in addition to high disease activity and failure/contraindications for NSAIDs evidence of objective signs of inflammation (elevated CRP and/or positive MRI of the SIJ)[55] are needed.

According to the international treatment recommendations, it is current practice to start with TNF inhibitors (TNFi) or IL-17 inhibitors due to greater clinical experience and longer safety data. Janus kinase inhibitors (JAKi), like tofacitinib and upadacitinib are newer small molecule tsDMARDs that inhibit intracellular JAK-Signal Transducer and Activator of Transcription (STAT) signaling pathways and have demonstrated efficacy for active axSpA in clinical trials. However, long-term safety data for JAKi in axSpA patients is still limited compared to TNFi and IL-17i. Caution is advised when using JAKi in older patients and those with cardiovascular risk factors, until more safety evidence accumulates. Choice of b/tsDMARD may also be guided by extra-articular manifestations. Anti-TNF monoclonal antibodies are preferred for patients with recurrent uveitis or active IBD, while IL-17i may be preferred for patients with significant skin psoriasis (PsO). If the initial b/tsDMARD fails, switching to another b/tsDMARD should be considered after re-evaluating the diagnosis and comorbidities. On the contrary, if a patient is in sustained remission, tapering of a bDMARD can be considered. At this regard, an increasing number of evidence shows that abruptly withdrawing bDMARDs may lead to a high proportion of flares. On the contrary, tapering was shown to be successful in maintaining treatment response efficiently in a relevant number of patients.[55]

Radiographic damage and loss of function may require surgical interventions like total hip arthroplasty or spinal osteotomy, even if fortunately, this is not frequently needed anymore. Moreover, potential fractures should be evaluated in patients with sudden worsening symptoms.[55]

In summary, the 2022 ASAS-EULAR recommendations provide an up-to-date, evidence-based guide for optimal management of axSpA, with a focus on individualized treatment approaches.

INNOVATIONS IN THE FIELD OF AXSPA

a. Genetics

Axial spondyloarthritis has a strong genetic component, with heritability over 90%. The major genetic association is with HLA-B27, which accounts for approximately 20-30% of overall disease risk. However, HLA-B27 alone is not sufficient to cause axSpA. In addition to HLA-B27, over 100 non-MHC susceptibility loci have now been identified through genome-wide association studies (GWAS).[56] Each not-HLA variant confers only modest individual risk, reflecting the highly polygenic nature of axSpA. The majority of implicated genes are involved in antigen presentation (ERAP1/2), cytokine signaling (IL23R, IL12B, TYK2), T-cell differentiation (RUNX3, IL7R), and innate immunity (CARD9, TNFRSF1A). These genetic findings implicate altered adaptive and innate immune responses in axSpA pathogenesis.[27,56,57]

While HLA-B27 is unequivocally the major axSpA genetic factor, its precise molecular role has remained elusive despite extensive research. Proposed mechanisms include altered peptide binding and presentation, induction of endoplasmic reticulum (ER) stress and unfolded protein response, and homodimer formation. Recent T cell repertoire studies have provided some support for the long-debated arthritogenic peptide model.[58-62] These have identified expanded clonotypes of $CD8^+$ T cells in AS patients that recognize specific HLA-B27-bound self-peptides, suggesting HLA-B27 may aberrantly present certain joint-derived autoantigens to autoreactive T cells. More functional genomics work is still needed to clarify the mechanisms behind most genetic findings in axSpA, including HLA-B27. Resolving these knowledge gaps remains an area of active investigation and is critical to understand axSpA pathogenesis at the molecular level.

Recent genetic studies have revealed intriguing differences between male and female axSpA patients. The association of HLA-B27 appears stronger in men, and certain non-MHC variants like progressive ankylosis protein homolog (ANKH) are associated with r-axSpA specifically in males.[63,64] Females likely require a higher cumulative genetic burden to develop axSpA, possibly due to X-chromosome effects and protective mechanisms like estrogen. One important observation is that in MRI studies, HLA-B27 associates with more sacroiliac inflammation in axSpA males but not females. In females, factors like obesity and pregnancy history are more relevant to MRI sacroiliitis findings.[65] This indicates HLA-B27 positivity should be interpreted differently in women with chronic back pain versus men. These sex differences have led to proposals that rather than a classical susceptibility allele, HLA-B27 may act as a modifier influencing disease severity and progression in those who develop axSpA. In this model, HLA-B27 promotes more severe axial inflammation and radiographic changes in males once disease is triggered. In females, axSpA is less HLA-B27 dependent and possibly involves more complex gene-hormone-environment interactions.

The genetic discoveries in axSpA are beginning to enable personalized medicine approaches, although clinical translation remains limited. Polygenic risk scores (PRS) combining hundreds of risk alleles could effectively stratify individuals by genetic disease risk to guide prevention and early intervention.[66] A polygenic risk score incorporating HLA-B27 and other genetic loci shows excellent predictive power for diagnosing axSpA in European cohorts with a receiver operating curve (ROC) analysis that showed an area under the curve (AUC) of 0.924 (95% CI: 0.920-0.928), superior to HLA-B27 testing alone, the latter with an AUC of 0.869 (95% CI: 0.865-0.874).[67] Pharmacogenomics may eventually allow genetics-tailored treatments, as response to TNFi associates with certain HLA and cytokine genotype variants. However, substantial validation is still required before genetics-based management can be widely implemented. The predictive utility of PRS for prognosis or treatment response is still

uncertain. PRS have poor predictive value for general population screening. In addition, most findings derive from populations of European descent, indicating PRS may need customization for diverse ethnic groups.[67]

In summary, ongoing genomic research and translation of genetic findings into clinically applicable tools is critical to achieve the promise of personalized axSpA prevention, diagnosis, prognosis, and treatment based on an individual's genetic makeup.

b. Immunology and serum biomarkers

Innate immune responses likely play the central role initiating inflammation in axSpA. Cells of the innate and innate-like immune systems exhibit functional alterations and accumulate at target tissue sites. Monocytes/macrophages, mast cells, and innate lymphoid cells (ILCs) produce inflammatory cytokines including IL-23, IL-17, TNF-α, and are expanded systemically and locally in axSpA patients.[31,68,69] Furthermore, neutrophils demonstrate enhanced NETosis.[70,71] γδ T cells and mucosal-associated invariant T (MAIT) cells, though technically T cells, exhibit innate-like behaviors and are also implicated as sources of IL-17.[29,30,72,73]

The contributions of adaptive immunity in disease onset are less defined but likely important in propagating chronic inflammation. Autoreactive TH1 and T_H17 cell populations recognizing joint-derived antigens accumulate in target tissues, which may be driven by molecular mimicry between microbial and self-antigens.[58,59,74] Though B cells and ectopic lymphoid neogenesis can be detected in tissue lesions, the functional relevance of autoantibodies like anti-CD74 remains uncertain.[75]

The IL-23/IL-17 axis is consistently implicated in early and established axSpA. IL-23 appears important in initial inflammation but becomes less critical once IL-17-secreting innate populations are expanded, which may explain the failure of IL-23 inhibition in treating active axSpA. Thus, ongoing innate production of IL-17 independent of IL-23 stimulation likely sustains chronic inflammation.[76]

Immune function could be influenced and stimulated by several stimuli, each of them known as an etiological factor in axSpA. Therefore, dysbiosis enables translocation of microbial ligands that can trigger innate immune activation both locally and systemically.[38] The unfolded protein response and ER stress induced by HLA-B27 misfolding may further stimulate cytokine production in antigen presenting cells.[60] Finally, biomechanical factors also influence disease initiation and progression, potentially through microdamage sensed by resident innate immune cells.[36] In summary, both arms of the immune system make important contributions to axSpA pathogenesis. However, dysregulated innate immunity may play the dominant role in initiating and perpetuating disease; moreover, recent works indicated an involvement of the complement system as well, a cornerstone of the innate immune system.[77]

The identification of serum biomarkers that improve upon current tools for diagnosing and managing axSpA remains an active area of investigation. Most efforts have focused on analytes reflecting activation of the innate immune pathways implicated in disease. Acute phase reactants like CRP and erythrocyte sedimentation rate (ESR) lack sensitivity and specificity for axSpA. Similarly, cytokines like IL-17, IL-23, TNF-α, and matrix metalloproteinases (MMPs) demonstrate intermittent elevation in patient subgroups but perform inconsistently in diagnosis and monitoring. Calprotectin levels correlate with MRI inflammation in some studies but do not outperform clinical criteria.[78]

Anti-CD74 antibodies exhibit diagnostic potential given their high specificity, but failed validation in certain cohorts. Additional autoantibodies like anti-sclerostin and anti-noggin may have utility in patient subgroups but require larger scale confirmation. Bone turnover markers like sclerostin showed to be reduced in axSpA compared to healthy controls but this is not a specific finding. Circulating collagen fragments, cartilage oligomeric matrix protein (COMP), aggrecan, and other tissue breakdown products appear elevated in-patient serum. Combinations of these biomarkers of cartilage/matrix destruction show promise in predicting MRI and radiographic defined inflammation and damage in preliminary studies. However, they require validation in larger patient cohorts.[78]

Transcriptomic profiling has identified miRNA signatures that can differentiate axSpA from

chronic back pain. miR-29 is among the most reproducibly dysregulated across studies and influences pathways of relevance to axSpA pathogenesis, although larger studies are needed to validate the clinical utility of miRNA profiles.[78,79] In summary, currently described serum biomarkers have generally failed to outperform CRP for diagnosing and monitoring axSpA in the clinic. Combinations of tissue breakdown products, autoantibody profiles, microRNAs, and gene scores may eventually provide superior biomarkers to guide management, though extensive further validation is still required.

c. Microbiome

The gut microbiome refers to the vast community of microorganisms inhabiting the gastrointestinal tract. This includes bacteria, viruses, fungi and other microbes living in a complex, interdependent ecosystem. In this regard, dysbiosis refers to an imbalance or alteration of this microbial ecosystem. It is associated with several autoimmune, inflammatory, and metabolic diseases.[80] In axSpA, particularly, dysbiosis may contribute to disease through various mechanisms:

a) Interaction with HLA-B27

Animal studies of HLA-B27 transgenic rats indicate gut microbes may initiate HLA-B27 misfolding and improper immune reactions that ultimately drive inflammatory responses against joints and spine.[81,82] For example, germ-free HLA-B27 rats do not develop SpA symptoms, while conventional rats with normal gut microbiota do.[83] Specific bacteria like *Klebsiella pneumoniae* showing molecular mimicry to HLA-B27 could be triggering factors.[84]

b) Increased intestinal permeability

In axSpA patients, even without clinically apparent bowel inflammation, microbial imbalance and inflammatory cytokines may impair intestinal barrier integrity. This "leaky gut" enables translocation of bacteria and their products across the intestinal wall, activating immune cells and promoting systemic inflammation. Hence, studies show reduced expression of tight junction proteins and increased intestinal permeability in axSpA patients compared to healthy controls; perhaps, targeting increased gut permeability could be a potential disease modifying strategy.[84,85]

c) Immune system dysregulation

The gut microbiota interacts extensively with intestinal immune cells, regulating processes like immunoglobuline (Ig)A production, epithelial barrier function, and T-cell differentiation through pattern recognition receptors (PRRs) like toll-like receptors. Dysbiosis in axSpA patients may alter these communications and dysregulate intestinal and systemic immunity. For instance, altered microbiota composition may disrupt the T_H17/Treg balance, driving pro-inflammatory T_H17 responses.[86] Segmented filamentous bacteria are potent inducers of T_H17 cells while specific Clostridia strains promote Treg differentiation.[87,88] Correcting such immune deviations could help restore homeostatic equilibrium.

d) Metabolite changes

The microbiome produces many bioactive metabolites through its metabolic activities. For example, bacterial fermentation of dietary fibers yields short-chain fatty acids (SCFAs) like butyrate which have anti-inflammatory properties.[89] In axSpA, reduced abundances of SCFA-producing symbionts like *Faecalibacterium prausnitzii* could decrease levels of beneficial metabolites.[90] Additionally, increased pathobionts or altered microbial gene expression may favor production of detrimental mediators like lipopolysaccharides (LPS), contributing to immune activation. Metabolomic analyses can identify microbiome-derived metabolites that drive or suppress inflammation.[84]

Therefore, researchers have made great strides in characterizing the involvement of the gut microbiome in axSpA using advanced genetic sequencing techniques. 16S rRNA gene sequencing of stool samples has revealed altered bacterial diversity and species richness in axSpA patients compared to healthy individuals. This altered diversity indicates an unstable gut ecosystem prone to dysbiosis that lacks resilience against inflammatory triggers.[91] Specific bacterial taxa linked to inflammatory processes appear increased in abundance in the microbiome profiles of axSpA patients. For example, *Klebsiella pneumoniae* and *Proteobacteria*, which can trigger HLA-B27 reactions, are often elevated.[91] In contrast, potentially anti-inflammatory bacteria like *Faecalibacterium prausnitzii*, a major butyrate producer, consistently decline in axSpA

patients.[89] Reduced levels of beneficial microbes linked to enhanced mucosal barrier function are also commonly observed. The lower amounts of these symbiotic microbes may perpetuate inflammation.[91,92]

Metagenomic shotgun sequencing provides insights into microbiome functionality by profiling microbial genes and metabolic pathways. In axSpA patients, alterations are seen in genes involved in vitamin biosynthesis, LPS production, and tryptophan metabolism. Of note, tryptophan can be converted to several molecules which are able to shape the function of the immune system and the inflammatory functions, like kynurenines or anti-inflammatory indole derivatives based on the microbial profile.[93-95] Importantly, many of these microbiota changes correlate with clinical and inflammatory markers of axSpA. For instance, bacterial dysbiosis associates with levels of CRP, calprotectin, and IL-17. Mucosal inflammation and intestinal lesions are more severe in patients with higher dysbiosis levels. Microbiome parameters also correlate with ASDAS score indicating microbial alterations may reflect axSpA disease activity and pathogenic processes.[96,97]

In summary, the gut microbiota is complexly involved in axSpA pathogenesis. Ongoing research is unravelling unique microbial signatures in patients and identifying new therapeutic opportunities based on restoring gut homeostasis.

d. Imaging

Imaging plays a critical role in the diagnosis and management of axSpA. Recent technological advances along with standardized image acquisition protocols and validated definitions for positive imaging findings have led to dramatic improvements in axSpA imaging and enhanced diagnostic confidence.

Conventional radiography has been the traditional first-line imaging modality when axSpA is suspected clinically.[40] However, growing evidence indicates important limitations of radiography in detecting early inflammatory lesions or structural damage compared to advanced cross-sectional imaging now available.[98,99] Pelvic radiography is widely accessible but imparts radiation exposure. In contrast, multiple studies have demonstrated poor reliability and high interobserver variation in interpreting SIJ radiographs, even among experienced readers.[100] Compared to MRI or CT, radiography has inferior sensitivity for visualizing the entire spectrum of inflammatory and structural lesions that may develop in the SIJ and spine throughout the disease course of axSpA. Given the clear limitations of radiography and the presence of state-of-the-art alternatives providing unmatched visualization of early axSpA lesions, it may be time to re-assess the role of pelvic radiography as a first-line imaging modality when axSpA is suspected in routine clinical practice.[101,102]

Magnetic resonance imaging has become an imaging cornerstone of axSpA, offering unparalleled detection of early inflammatory and structural lesions. Recent advances in 3T MRI technology further optimize axSpA evaluation with substantially higher signal-to-noise ratio, improved spatial resolution, and accelerated parallel imaging capabilities compared to conventional 1.5T MRI systems.[103-105] Consensus definitions for positive MRI findings in axSpA have been proposed through international collaborations like the ASAS MRI group.[106] Recently, this group reported data-driven cut-offs for MRI lesions considered highly suggestive of axSpA after two large-scale reading exercises.[106] Importantly, these cut-offs incorporate both active and structural lesion types. For active lesions, the presence of BME in at least four quadrants of the SIJ or in three consecutive MRI slices demonstrated high specificity for axSpA. The positive predictive value of BME is further increased when erosion or other structural lesions are also visible. Meanwhile, structural lesions including erosions affecting at least three SIJ quadrants or fat metaplasia lesions in five or more quadrants were found to be highly specific for axSpA. Having erosion visible on at least two consecutive MRI slices or fat lesions on at least three consecutive MRI slices was also deemed highly suggestive of axSpA. Fat lesions with a depth over 1 cm were also proposed as a cut-off. These cut-offs reinforce interpreting SIJ MRI based on the collective impact of concomitant inflammatory and structural lesions rather than potentially non-specific findings in isolation. This contextual approach to image assessment enhances diagnostic confidence compared to outdated qualitative paradigms focused predominantly on BME.[106]

Beyond conventional MRI, quantitative MRI techniques enable objective, sensitive quantification of inflammation.[107-109] However, substantial work remains to standardize protocols, demonstrate multicenter reproducibility, and validate clinical utility before quantitative MRI is ready for clinical adoption.

Some candidate quantitative MRI methods include T2 mapping, diffusion weighted imaging, and dynamic contrast enhanced MRI. Each of these techniques provides quantitative biomarkers reflecting pathophysiological processes like edema, cellularity, and perfusion. In the future, quantitative MRI has enormous potential to enable sensitive disease monitoring to guide personalized treatment decisions. It could also improve sensitivity for detecting change in clinical trials or observational studies. However, large multicenter trials will be instrumental to validate these techniques across diverse MRI platforms before quantitative MRI can reach its full potential.[110,111]

While MRI excels at assessing inflammatory lesions, CT remains unsurpassed for visualizing structural bone damage, especially subtle cortical breaks.[112,113] However, standard CT protocols result in high cumulative radiation exposure, precluding routine use for lifelong monitoring in axSpA patients. Low-dose CT protocols provide an elegant solution through modulating tube current and voltage to substantially reduce radiation dose while maintaining sufficient image quality to assess structural lesions. Noise is controlled through iterative reconstruction algorithms.[114,115] Early research consistently demonstrates the superiority of low-dose CT protocols compared to radiography for detecting erosions, sclerosis, and syndesmophytes while delivering a similar radiation exposure. Low-dose CT provides an alternate means to evaluate structural damage in cases where MRI is indeterminate or contraindicated.[116] However, MRI remains necessary to visualize active inflammation. The precise clinical role for low-dose CT as a supplement to or replacement for MRI or radiography continues to be defined through ongoing studies.

Finally, beyond the traditional visual and qualitative elaboration of imaging data, radiomics involves the high-throughput extraction of quantitative imaging features that can capture tissue heterogeneity and microarchitecture that is not discernible through visual assessment.[117-119] Radiomics is an emerging technique that may have utility for improving evaluation of axSpA. In radiomics, a large number of quantitative imaging features are extracted from medical images through automated algorithms. Studies have investigated using radiomic analysis of MRI images of the SIJ to identify imaging biomarkers associated with sacroiliitis, SpA diagnosis, and subclassification into axial *vs.* peripheral subtypes.[120-123] For example, one study extracted over 1,200 texture features from manually segmented SIJ MRI images and identified features that showed significant differences between positive and negative sacroiliitis cases.[122] A radiomics signature combining multiple features demonstrated good discrimination for diagnosing sacroiliitis with an AUC of 0.82.[121] Another study found certain features differed between axial and peripheral SpA and could distinguish subtypes with excellent accurac.[120]

These preliminary results suggest radiomics can potentially identify imaging biomarkers linked to disease characteristics, activity, and outcomes. This could enable more objective, quantitative evaluation of important MRI features like BME that currently rely on subjective visual assessment. However, there are several limitations. Small sample sizes, lack of independent validation cohorts, and variability in methods across studies make findings exploratory.

There is a need for larger, multicenter studies to validate the reproducibility and added value of radiomic techniques compared to current imaging methods. Extraction of radiomic data requires segmentation of target regions, which can be time-consuming and limit adoption. Automated segmentation methods optimized for SIJ are needed. The complex, multivariate nature of radiomics data also requires specialized biostatistical and machine learning expertise. Despite promising preliminary results, it remains to be determined whether radiomics provides sufficient added diagnostic, prognostic, or monitoring value above current MRI techniques in axial SpA. As methods mature, radiomics may become a useful imaging biomarker for precision medicine approaches, but significant research is still needed to demonstrate clinical utility in SpA.

Table 1. Imaging in axSpA

Imaging modality	Role in axial SpA diagnosis and management	Advantages	Limitations	Potential future developments	References
Conventional radiography	Traditional first-line imaging when axSpA is suspected clinically.	Widely accessible	Radiation exposure, limited sensitivity for early inflammatory and structural lesions. High interobserver variation.	Reassess role in routine clinical practice.	40,101
MRI	One-stop shop for detecting early inflammatory and structural lesions.	High sensitivity for both inflammation and structural damage. Ongoing technological advancements (3T MRI).	Requires specialized equipment, expert readers, higher cost compared to radiography.	Quantitative MRI techniques for sensitive inflammation quantification.	103-106
CT	Unsurpassed for visualizing structural bone damage, including subtle cortical breaks.	Low-dose CT protocols reduce radiation exposure while maintaining image quality.	Radiation exposure, limited for assessing inflammation.	Defining clinical role as a supplement or replacement for MRI or radiography.	112-116
Quantitative MRI	Potential for sensitive quantification of inflammation.	Provides quantitative biomarkers reflecting edema, cellularity, and perfusion.	Standardization, multicenter reproducibility, and clinical validation required.	Enabling personalized treatment and improving sensitivity in clinical trials.	107-111
Radiomics	Emerging technique for improved evaluation.	High-throughput extraction of quantitative imaging features capturing tissue heterogeneity.	Limited by small sample sizes, lack of independent validation, and variability in methods.	Validation in larger multicenter studies, development of automated segmentation methods.	117-121

axSpA: Axial spondyloarthritis; SpA: Spondyloarthritis; MRI: Magnetic resonance imaging; CT: Computed tomography.

In summary, advanced imaging technologies now provide diverse options beyond conventional radiography to assess the myriad lesions occurring in the axial skeleton throughout the course of axSpA. Dedicated SIJ MRI offers unparalleled visualization of early inflammatory and structural damage while low-dose CT provides exquisite detail of cortical breaks. Quantitative MRI shows enormous promise for enabling sensitive quantification of inflammation to guide personalized medicine approaches. Further research and multidisciplinary collaboration will be key to validate these technologies and fully translate their potential to improve patient care into clinical practice (Table 1).

e. Artificial intelligence

Interpretation of axSpA imaging can be challenging due to complex anatomy, variable disease manifestations, and overlap with degenerative changes. There has been increasing interest in using AI and machine learning to improve and automate axSpA imaging analysis.

For conventional radiography, most research has focused on using convolutional neural networks (CNNs) to classify sacroiliitis severity based on the modified New York criteria. Multiple studies have shown CNNs can differentiate normal from definite sacroiliitis (Grade ≥2 bilaterally or ≥3 unilaterally) with accuracy of 89-97%, sensitivity of 79-91%, and specificity of 79-96%, comparable to rheumatologists. CNNs have also been applied to directly localize SIJ erosions, sclerosis, and ankylosis.[124]

In MRI of the SIJ, common machine learning applications include detecting BME, a hallmark of inflammation.[125-128] Various supervised and deep learning approaches have been explored, including thresholding, classical machine learning with hand-crafted features, and CNNs. Reported diagnostic accuracy has been variable, likely

related to differences in MRI protocols, gold standards, and class balance across single-center studies. However, several CNNs have achieved sensitivity and specificity comparable to experts, with a retrospective multicenter study showing a deep neural network outperforming non-musculoskeletal expert radiologists.[128] Spatial attention mechanisms, multi-sequence analysis, and clinical data integration have improved model performance. Recent studies show feasibility of automating full SpondyloArthritis Research Consortium of Canada (SPARCC) scoring with CNNs, although reliability in this case remains inferior to human experts.[129] For spinal MRI, limited research has applied CNNs to detect vertebral corner inflammatory lesions or total inflammatory lesions, but substantial challenges exist in automating full spine analysis given the large search space and lack of robust gold standards.[130]

Alternative AI applications in axSpA imaging include predicting radiographic progression with CNNs,[131] response to bDMARDs treatments[132,133] and generating synthetic MRI/CT images. Synthetic CT generated from MRI has recently emerged as a promising technique to improve assessment of structural lesions in axSpA. Deep learning-based algorithms allow reconstruction of CT-like images from specific MRI sequences. Several studies have demonstrated that synthetic CT can visualize SIJ erosions, sclerosis, and ankylosis with greater sensitivity and specificity compared to standard MRI sequences. The improved cortical bone delineation enables more reliable detection of subtle structural lesions that may be overlooked on routine MRI. Enhanced diagnostic performance was confirmed using conventional CT as the reference standard. Synthetic CT imaging may thus expand the utility of MRI for evaluating early structural damage in axSpA, without requiring additional CT radiation exposure.

While AI techniques are being applied to improve imaging-based assessments in axSpA, large language models like GPT-4, LLaMA, Bard or Claude have the potential to act as surrogate patient reported outcome measures (PROs) by generating text summarizing patient symptoms and experience.[134,135] By analyzing the text from language models, quantitative measures of symptoms could be extracted to track outcomes over time. Potential benefits of using language models as surrogate PROs include reducing patient burden, enabling more frequent tracking of outcomes, and capturing richer qualitative information on patient experience. Challenges include ensuring the language model text accurately reflects patient symptoms, mapping text to quantitative outcomes, and validating performance against traditional PROs.[134,135]

Despite promising results, adoption of AI techniques remains limited in clinical practice. Key challenges include model generalization across scanners and populations, insufficient training data, variable evaluation frameworks, and lack of clinician trust. Most importantly, large multi-center studies are needed to determine if AI tools improve diagnostic accuracy, enhance workflow efficiency, and benefit patient outcomes compared to standard imaging interpretation. But if AI performance and reliability reaches expert-level, these technologies could expand access to consistent quantitative imaging analysis and objective disease monitoring in axSpA.

CLINICAL IMPLICATIONS

The emerging scientific fields will profoundly transform management of axSpA through enhanced prognostication, quantification, and treatment customization (Figure 2). Genomic medicine has reached an inflection point where polygenic risk scores could soon stratify individuals by genetic disease risk to enable targeted strategies. Advanced imaging modalities now allow direct visualization and sensitive quantification of inflammation in axial joints, paving the way for tightly controlled treat-to-target approaches seeking to achieve remission or low disease activity. The gut microbiome decisive role in shaping immune function suggests future therapies may deliver disease modification by correcting underlying dysbiosis. Together, these advances promise a shift from reactive to predictive, personalized medicine.

Despite remarkable progress, substantial unmet needs persist given the incomplete efficacy and side effects of current biologics; therefore, new therapeutic targets are required and are being investigated nowadays. In this regard, the

pleiotropic cytokine granulocyte macrophage-colony stimulating factor (GM-CSF) promotes multiple inflammatory and osteoproliferative processes in axSpA pathogenesis, hence it has been considered a possible therapeutic target.[22] However, phase II results for the GM-CSF inhibitor namilumab were disappointing (NCT03622658). This highlights the ongoing challenge of effectively targeting a single cytokine in a multifactorial disease. In contrast, the dual IL-17A/F inhibitor bimekizumab has now definitively demonstrated efficacy in phase 3 trials for active axSpA,[136] and therefore added to the therapeutic armamentarium. Looking ahead, the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway represents an appealing target given its dual role regulating aberrant IL-17 responses and pathologic new bone formation.[137,138] Preclinical studies indicate PI3Kδ and mTOR inhibition can potentially control both inflammation and osteoproliferation.[139,140] Such multifaceted strategies may be essential for enhanced treatment responses.

The potential impact of translating scientific advances into patient benefit remains immense yet unfulfilled. Incorporating polygenic risk scores into predictive algorithms could redefine screening approaches to enable unprecedented early detection in at-risk groups, thereby preventing accumulated damage. MRI inflammation quantification may allow treat-to-target strategies aimed at disease remission or low disease activity, an approach which preliminary evidence suggests correlates with better long-term outcomes. Applying machine learning to standardized imaging data could expand access to quantitative monitoring. However, rigorous comparative effectiveness studies are imperative to validate if emerging tools add value over current standards of care in improving patient-centered outcomes.

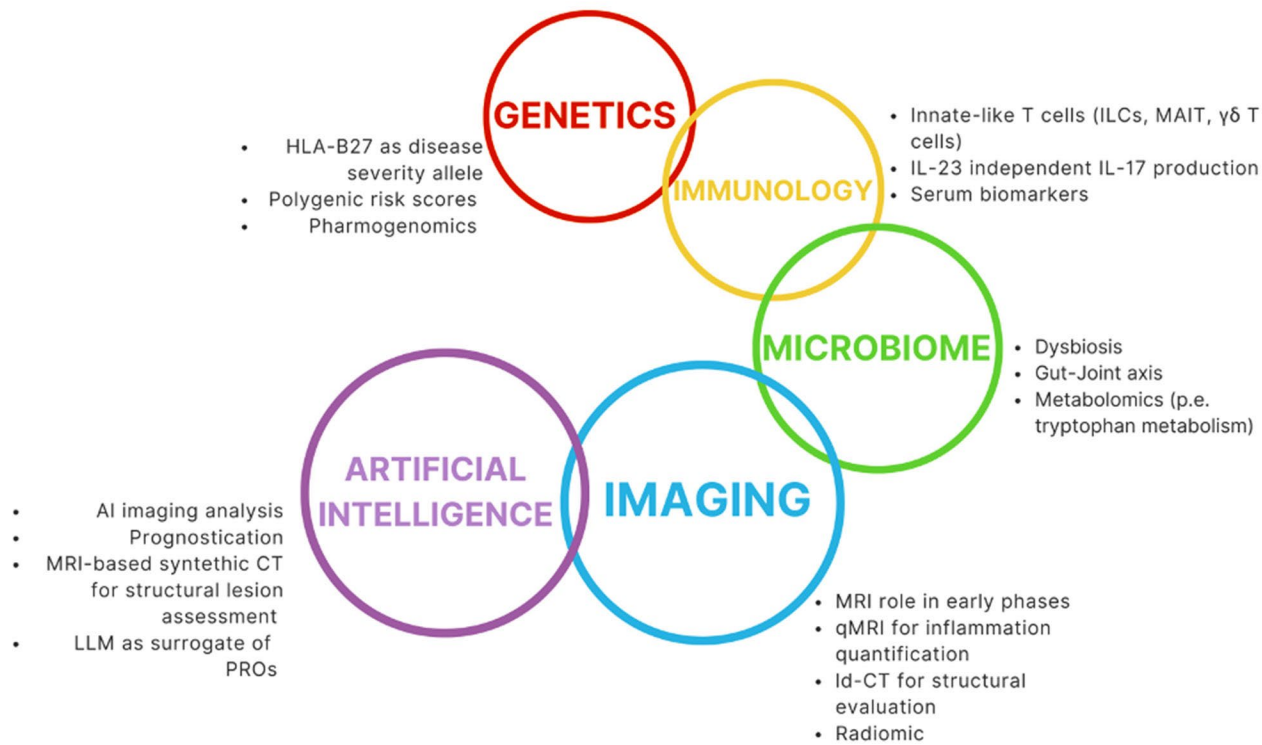

Figure 2. New frontiers in axSpA. An overview of emerging areas of research. Key areas highlighted include immunology, genetics, microbiome studies, imaging techniques, and artificial intelligence. Specific examples in each domain are listed. This illustrates the range of innovative techniques being applied to gain new insights into axSpA.

HLA-B27: Human leukocyte antigen B27; ILCs: Innate lymphoid cells; MAIT: Mucosal-associated invariant T; CT: Computed tomography; MRI: Magnetic resonance imaging; LLM: Large language model; axSpA: Axial spondyloarthritis.

INNOVATIONS AND FUTURE DIRECTIONS

Ongoing advances in high-throughput sequencing continue to unravel the intricate gene-environment interactions underlying pathogenesis, powered by integrative multi-omics approaches defining mechanisms linking the microbiome and immune system. Concurrently, quantitative MRI techniques progress toward clinical adoption for responsive disease monitoring, soon to be augmented by multimodal machine learning tools like hybrid synthetic MRI/CT imaging. Thus, emerging areas will synergize to provide a multidimensional understanding of disease processes from molecular profiling to advanced imaging.

Multiple research gaps remain. Detailed immunophenotyping by single cell sequencing is needed to discern heterogeneity and predict treatment response. The optimal application of microbiome assessment and therapeutics remains uncertain. And crucially, robust validation in large multicenter studies is critical before these tools can be incorporated into updated management guidelines.

Finally, the perspective of patients must remain central in determining unmet needs and developing new technologies. Solving the right problems through co-creation with patients will ensure emerging innovations bring added value to improve outcomes and quality of life. In terms of treatments, new modes of action as well as combination therapies leveraging existing mechanisms are actively being explored to provide more comprehensive disease control. Multitarget approaches may overcome limitations of current monotherapies and lead to superior clinical efficacy. However, careful assessment of safety and real-world effectiveness will be needed as these novel agents and combinations advance through clinical trials.

In conclusion, scientific progress in understanding axSpA pathogenesis has been remarkable, powered by breakthroughs in sequencing, multi-omics profiling, advanced imaging, and machine learning. Collectively, these innovations promise to enable more accurate diagnosis, tightly controlled treatment, and substantially improved patient outcomes. Cross-disciplinary efforts anchored on solving patient needs through co-creation will ultimately determine success in unleashing the benefits of the new fields to reduce the burden of this disease. As we embark on a future illuminated by cutting-edge sequencing, advanced imaging and machine learning, the synergy of these innovations promises a new era in precision medicine, with patient-centric solutions driving transformative outcomes in axSpA.

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