Editorial introduction

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editor for this issue.

EDITOR

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Dr Polly Ferguson received her BS and MD from the University of Iowa. She completed her Pediatric Residency and Pediatric Rheumatology & Immunology Fellowship and Post-Doctoral Research Fellowship at the University of Virginia. She is currently the Marjorie K. Lamb Professor of Pediatrics and Director of Pediatric Rheumatology at the University of Iowa Carver College of Medicine. She is an NIH funded investigator and her research program is focused on the etiology of autoinflammatory disorders including chronic recurrent multifocal osteomyelitis (CRMO) and neuroinflammation. She is an author on more than 100 peer reviewed publications, book chapters and reviews. Her work has been cited more than 5000 times.

Update on streptococcal-associated rheumatic disease

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Purpose of review
This review provides a comprehensive perspective on poststreptococcal rheumatic manifestations in pediatric patients by integrating recent updates and a literature review, with particular focus on poststreptococcal reactive arthritis and acute rheumatic fever.

Recent findings
Poststreptococcal reactive arthritis presents with a unique clinical profile, distinguishing it from other poststreptococcal conditions in pediatric patients, especially acute rheumatic fever. Recent updates underscore the importance of diligent monitoring and management to mitigate potential cardiac complications, despite the relatively low incidence of carditis following poststreptococcal reactive arthritis.

Summary
The diagnosis of poststreptococcal reactive arthritis is often challenging due to significant overlap with other poststreptococcal syndromes, particularly acute rheumatic fever. Given the potential for cardiac complications in acute rheumatic fever, accurate differentiation between the two conditions is imperative. Ongoing research continues to refine diagnostic criteria and treatment approaches, emphasizing the need for clinicians to remain vigilant in recognizing and differentiating between the two syndromes.

Keywords
acute rheumatic fever, group B streptococcus, post streptococcal, postinfectious arthritis, poststreptococcal reactive arthritis

INTRODUCTION

Group A Streptococcus (GAS) manifestations arise due to direct bacterial invasion, immune-mediated responses, and toxin production [1]. Clinical manifestations can be classified as: 1. Direct infection, for example, pharyngitis and invasive infections (e.g. necrotizing fasciitis, septic arthritis, etc.) [1]. 2. Immune-mediated sequelae, for example, acute rheumatic fever (ARF), poststreptococcal reactive arthritis (PSRA), acute poststreptococcal glomerulonephritis, etc. 3. Toxin-mediated effects, for example, streptococcal toxic shock syndrome. These emphasize the diverse clinical spectrum of GAS infection.

Global rates of invasive GAS were rising before the COVID-19 pandemic and have surged since 2022 [2]. A hospital-based survey [3] indicates a significant rise in severe pediatric invasive GAS cases since early 2022, including some fatalities. Thus, clinicians should be alert to unusual presentations. While GAS remains universally susceptible to penicillin, increasing macrolide and lincosamide resistance is being reported.

Despite intensive control efforts, sustainable reduction in the burden of GAS remains challenging, with vaccine development offering the most promising long-term solution [4]. Recent advances regarding vaccine development have shown that M protein-based vaccines have greater promise than do non-M protein-based options [5]. Peptide-based subunit vaccines induce long-term immunity and reduce autoimmune responses and inflammation. Comprehensive understanding of the intricate mechanisms underlying infection-associated inflammation could facilitate development of therapeutic strategies for preventing immune-mediated complications [6].

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KEY POINTS

- Poststreptococcal reactive arthritis is a separate entity from acute rheumatic fever (ARF), with low incidence of cardiac involvement.
- The diagnosis and approach to ARF differ according to the incidence in the specific country
- Consider antibiotic prophylaxis when connections to CPAN, psoriasis, HSP, etc. are suspected
- Consider the diagnosis of PANDAS in a child with suspected symptoms.

TYPES OF ARTHRITIS

Postinfectious arthritis

This type of arthritis develops during or soon after an infection elsewhere in the body, and the microorganisms cannot usually be recovered from the joint [7▪].

The prevalence of postinfectious reactive arthritis is 30–40/100 000, while the classic pathogens associated with pediatric postinfectious arthritis are enteric (e.g., salmonella, campylobacter) or genital (e.g., chlamydia trachomatis). Involvement of these pathogens in the context of arthritis is termed "reactive arthritis." Patients usually have a genetic predisposition (e.g., HLA-B27 positive) [7▪]. Other postinfectious etiologies may include additional bacteria (e.g., mycoplasma, *Neisseria gonorrhea*) or viral agents. The main topic of this article is postinfectious arthritis due to GAS, including acute rheumatic fever (ARF) and PSRA. The key differences between classic reactive arthritis and PSRA in pediatric patients are the type of infection, pattern of joint involvement, response to nonsteroidal anti-inflammatory drugs (NSAIDs), genetic association, and the potential for cardiac complications.

Acute rheumatic fever

The revised Jones criteria for the diagnosis of ARF, as updated by the American Heart Association (AHA) in 2015 [8▪▪], are essential for differentiating ARF from PSRA in pediatric patients. Since carditis is the most common and the most serious clinical manifestation of ARF, the new classification criteria have defined echo Doppler findings for diagnosing clinical or subclinical carditis when ARF is a differential diagnosis. The modified Jones criteria consider the complexity of diagnosing ARF in high versus low incidence areas (Table 1), in comparison to the previous criteria, which lacked sensitivity in regions where rheumatic heart disease (RHD) is endemic. Furthermore, they include the major criteria (carditis, arthritis, chorea, erythema marginatum and subcutaneous nodules) and minor criteria (arthralgia, fever, elevated acute phase reactants and prolonged PR interval) (Table 2).

A recent prospective study [9▪] assessed the risk of developing RHD among children who presented with symptoms suggestive of ARF but did not meet the specific criteria for it under the Modified Jones Criteria, in an attempt to evaluate their specificity [8▪▪,9▪] The study evaluated 410 children for ARF and found that RHD was rare (1.5%) and mild among children who initially presented with suspected ARF, but did not meet the revised Jones criteria [9▪]. No cases of moderate or severe RHD, cardiac-related hospitalizations or deaths were observed, supporting the specificity of the modified Jones criteria's. A 2024 study [10] highlighted the revised Jones criteria, which have improved sensitivity and specificity for diagnosing ARF in high-risk populations. Management remains symptom-based, with no treatment proven to alter the disease course or prevent chronic RHD. The updated World Heart Federation guidelines for the echocardiographic diagnosis of RHD advocate for expanded screening efforts to enhance detection in endemic areas.

Dougherty *et al.* [11] discuss challenges and progress in the epidemiology, diagnosis and management of ARF and RHD. They emphasize the persistent burden of the disease in impoverished regions and the need for pragmatic policy solutions to translate current knowledge into meaningful action. Egoroff *et al.* [12] describe a public health

Table 1. Distinguishing high- versus low-risk settings for diagnosing acute rheumatic fever (ARF) according to the 2015 American Heart Association revision [8▪▪]

	Low-risk populations*	Moderate-to-high-risk populations
Definition	The incidence of ARF in school age children is ≤2 : 100 000. All-age rheumatic heart disease prevalence is ≤ 1 : 1000 population per year.	The incidence of ARF in school age children is >2/100 000 per year.

* Populations refer to an area or an ethnic group.
* Nonoriginal. The data regarding the incidence is based on the Modified Jones criteria, as published by the American Heart Association in 2015 [8▪▪].

Table 2. The revised Jones criteria for diagnosing acute rheumatic fever (ARF), including separate criteria according to its incidence in a population

Major criteria	Minor criteria
1. Carditis (clinical/subclinical) 2. Arthritis Low-risk populations: polyarthritis Moderate-to-high-risk populations: monoarthritis, polyarthritis and/or polyarthralgia 3. Chorea 4. Erythema marginatum 5. Subcutaneous nodules	1. Arthralgia *Low-risk populations*: polyarthralgia *Moderate-to-high-risk populations*: monoarthralgia 2. Fever -Low-risk populations: $\geq$ 38.5°C -Moderate-to-high-risk populations: $\geq$ 38°C 3. Elevated acute phase reactants -Low-risk populations: ESR $\geq$60 mm/h and/or CRP $\geq$3.0 mg/dL -Moderate-to-high-risk populations: ESR $\geq$30 mm/h and/or CRP $\geq$3.0 mg/dL 4. Prolonged PR interval: according to age (if carditis is not a major criterion).
Diagnosis of the initial ARF episode	Requires: -2 major criteria -One major criterion + 2 minor criteria + evidence of previous GAS infection
Diagnosis of recurrent ARF	Requires: -2 major criteria -One major plus two minor criteria or -3 minor criteria + evidence of preceding GAS infection

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Nonoriginal. The data is based on the Modified Jones criteria, as published by the American Heart Association in 2015 [8▪▪].

response to an outbreak of ARF in a remote Aboriginal community. The study emphasizes the critical need for strengthened delivery of secondary prophylaxis and improvements in the social determinants of health to prevent such outbreaks.

Poststreptococcal reactive arthritis

Poststreptococcal reactive arthritis (PSRA) is defined as arthritis of one or more joints, associated with a recent GAS infection in a patient who does not fulfil the Jones criteria for the diagnosis of ARF. Although GAS is the major pathogen known to cause PSRA, other nongroup A streptococci, including groups C and G streptococci have also been associated with this syndrome [4]. PSRA is an immune-mediated condition, possibly involving molecular mimicry that sensitizes the immune system towards synovial peptides in genetically predisposed individuals [13▪]. In this process, the immune system becomes sensitized to streptococcal antigens that share structural similarities with synovial peptides such as keratin, vimentin and laminin. This cross-reactivity leads to an autoimmune attack on the synovial tissues, resulting in arthritis in genetically predisposed individuals [13▪,14▪,15]. Certain studies have suggested a link between PSRA and HLA-DRB1∗01 with increased frequency of HLA-DRB1∗01 in PSRA patients compared with ARF patients and healthy individuals [16]. Unlike PSRA, ARF is associated with HLA-DRB1∗16. This genetic difference further supports the assumption that PSRA is a distinct clinical entity [15].

The symptoms of PSRA usually appear within 10 days following GAS infection, with the total duration of arthritis ranging from 1 week to 8 months (it tends to persist longer in adults) [13▪].

PSRA manifests as acute arthritis that is characterized by being less migratory compared to ARF (Table 3). It is often cumulative and persistent but does not lead to deformities and can affect any joint, including the axial skeleton. It does not respond readily to NSAIDs, which is a distinguishing feature from ARF [13▪].

Carditis

Carditis is a common manifestation in ARF, occurring in 50–70% of initial episodes (often presenting as pancarditis, with valvulitis a consistent feature) [17,18▪].

In contrast, the incidence of carditis in PSRA is very low [18▪,19▪]. Additionally, the onset of carditis related to PSRA has been reported to occur 1–18 months after the manifestation of arthritis, while ARF carditis usually manifests no longer than 1 week after arthritis onset [17].

Monitoring for carditis

The risk of cardiac involvement in PSRA remains a point of debate. Some studies suggest that a small

Table 3. Differentiating poststreptococcal reactive arthritis (PSRA) from acute rheumatic fever (ARF)

Variable	ARF	PSRA
Age	5–15 years (peak incidence around 12 y)	Bimodal: 8–14 y, 21–37 y
Latent period between GAS pharyngitis and arthritis	14–21 days	<10 days
Temperature >38°C (100.4°F)	In most patients	Uncommon
Joints involved	Primarily large joints	Large joints, small peripheral joints, axial skeleton
Arthritis	Migratory, transient	Nonmigratory, nonerosive, additive, persistent
Acute phase reactants	Markedly elevated	Moderately elevated
Genetic markers	Increased frequency of the HLA-DRB1∗16 allele	Increased frequency of HLA-DRB1∗01
Response to treatment with NSAIDs	Rapid	Does not respond dramatically
Carditis	Common (50–70%), often severe (a major diagnostic criterion)	Uncommon
Antibiotic prophylaxis	Long-term secondary antibiotic prophylaxis	Antibiotic prophylaxis for 1 year if the initial echocardiogram is normal

* Nonoriginal. The differences between PSRA and ARF are based on a 2021 article (poststreptococcal reactive arthritis in children: a distinct entity from acute rheumatic fever) [7▪].

proportion of patients with PSRA may develop valvular heart disease. Even though its effectiveness is not well established, secondary antistreptococcal prophylaxis for up to 1 year is recommended, with discontinuation if cardiac involvement is not observed [14▪,19▪]. Given the lower incidence of carditis, the AHA recommends that patients with PSRA receive follow-up echocardiography for several months to investigate clinical evidence of carditis [14▪,19▪].

Diagnosing poststreptococcal rheumatic syndromes

A recent GAS infection may be confirmed by microbiology or by serologic testing. Laboratory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate are usually moderately elevated (75%) in PSRA patients (as opposed to ARF) [20▪], while leukocyte count is usually normal in PSRA. Microbiological confirmation including rapid antigen detection test (RADT) and throat culture. RADT provides a quick, point-of-care result with ≥95% specificity but lower sensitivity (70–90%). Thus, a negative RADT result should not be considered definitive in excluding the diagnosis. Serologic confirmation is based on antistreptolysin O (ASLO) and antideoxyribonuclease B titers. Two serum samples should be obtained 2–4 weeks apart. ASLO titers rise one week postinfection, peaking at 3–6 weeks. A twofold increase in the second ASLO sample has been suggested to confirm a recent infection [7▪,21]. Clinicians may encounter various challenges when attempting to confirm an antecedent streptococcal infection, including pharyngeal carrier state [7▪], laboratory and age-dependent antibody cutoff values, prolonged antibody persistence, etc.

Other poststrep rheumatic conditions

Strep and axial spondyloarthropathy (SpA). A 2019 review described 3 HLA-B27-negative patients who developed psoriatic SpA approximately 8 days after confirmed GAS tonsillopharyngitis. It was characterized clinically by back pain and supported by MRI findings of inflammatory spinal lesions and acute bilateral sacroiliitis [22]. However, comprehensive data on the association between psoriatic arthritis and axial SpA remain limited. Tenosynovitis and dactylitis have also been reported [22].

Guttate psoriasis is a rare form of psoriasis that typically develops 2–3 weeks following a GAS infection that is characterized by the sudden onset of red and scaling papules on the skin. Studies have shown that streptococcal infections can induce a TH17-dominant immune response, which is implicated in the pathogenesis of guttate psoriasis [23].

Erythema nodosum is a form of panniculitis presenting as tender, erythematous nodules, usually on the anterior shins. It can be triggered by various infections, including GAS, and is associated with immune complex depositions in the subcutaneous fat. Studies have reported erythema nodosum co-occurring in patients with PSRA, suggesting a shared immunological response to the streptococcal antigens [24,25].

Uveitis associated with poststreptococcal syndrome can present with a range of ocular manifestations

including anterior uveitis, vitritis, and panuveitis, with a significant proportion of cases expressed as bilateral disease. Furthermore, there is a noted seasonal preponderance, with most cases presenting in winter and spring, which may be related to the higher incidence of streptococcal infections during these periods [26,27,28].

Poststreptococcal myalgia and myositis occurs about 2 weeks after a GAS infection and mainly affects the limbs. Diagnosis involves medical history, physical examination and detecting elevated CRP and ASLO antibodies. MRI serves as the gold standard for identifying inflammatory changes, while ultrasound provides a promising adjunct for monitoring the disease [29].

IgA vasculitis. Henoch-Schönlein purpura (HSP) is a systemic small-vessel IgA vasculitis characterized by palpable purpura, arthralgias or arthritis, abdominal pain and renal involvement. Pathogenesis involves immune complex deposition of primary IgA in small vessels, leading to inflammation and characteristic clinical features [30]. GAS is the most identified pathogen in the pathogenesis of IgAV [31]. A 2024 study analyzed the incidence of HSP in 9790 children and its association with common seasonal pathogens. Around 60% of HSP cases were linked to GAS and pneumococci [30].

Polyarthritis nodosa (PAN), a systemic or cutaneous (CPAN) necrotizing vasculitis affecting medium-size arteries, can be triggered by infections, mainly streptococcal. It involves a broad range of systemic symptoms, including renal, gastrointestinal and neurological manifestations [32,33].

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

A recent American Academy of Pediatrics clinical report defined pediatric autoimmune neuropsychiatric disorders associated with streptococcal (PANDAS) as part of the pediatric acute onset neuropsychiatric syndrome (PANS) [34▪]. Although PANDAS encompass few criteria, the most important is the unusual, very acute onset of obsessive compulsive behaviors and tics, which quickly increase in severity, together with some or all the following: emotional lability, irritability, anxiety, developmental regression and deterioration in school performance. A 1998 report attributed the symptoms to GAS [35▪]. The American Academy of Pediatrics suggests that when there is evidence of current strep-related pharyngitis, it is usually recommended to give a 10 day course of antibiotics. Other therapies such as a prolonged course of azithromycin/amoxicillin, NSAIDs, steroids, IVIG, plasma exchange, and tonsillectomy are used, but with low level of evidence, to date [36,37]. A retrospective cohort study [38] analyzed 345 children with PANDAS (most with positive antistreptococcal antibodies) who received an initial course of amoxicillin/clavulanic acid followed by long-term prophylaxis with benzathine benzylpenicillin. The treatment led to significant improvement in 75% within 3–5 months; relapses occurred in 45%. However, evidence regarding the effectiveness of antibiotic prophylaxis is limited, and concerns about antibiotic resistance persist [39].

Treating post streptococcal rheumatic conditions

ARF. The current treatment strategies for ARF are based on guidelines from the AHA and the American College of Cardiology [40▪]. They involve several key components: antibiotic therapy to eradicate GAS from the pharynx using intramuscular benzathine penicillin G as first-line treatment [41]; anti-inflammatory treatment. Acetylsalicylic acid has been traditionally used but other NSAIDs were found to be as effective, with fewer side-effects [42,43]; corticosteroids for severe carditis. Prednisone may reduce inflammation and prevent further cardiac damage. The management of heart failure, if present, primarily includes diuretics; secondary prophylaxis. Long-term prophylaxis with intramuscular benzathine penicillin G every 4 weeks, is essential to prevent recurrence. The duration of prophylaxis depends on the presence and severity of carditis, ranging from 5 years to lifelong in high-risk patients.

PSRA. The treatment of PSRA in pediatric patients includes NSAIDs for symptom management, antibiotic prophylaxis for up to one year to prevent carditis, and careful monitoring for cardiac involvement. NSAIDs are typically the first-line treatment for managing the arthritis associated with PSRA. Treatment cessation is considered when arthritis resolves and acute-phase reactants normalize [17]. However, it is important to note that PSRA does not always respond well to NSAIDs, especially in comparison to ARF. In these cases, corticosteroids are recommended [44]. The AHA recommends antibiotic prophylaxis for up to one year after the onset of symptoms for patients with PSRA and normal initial echocardiography, due to the possibility of delayed onset carditis [17]. If there is no clinical evidence of carditis after one year, prophylaxis can be discontinued [14▪,17] but this issue is controversial. If valvular involvement is evident, antibiotic treatment should be continued.

When there is evidence of recent strep infection, antibiotic prophylaxis should be considered for other conditions that might be related to strep, mainly recurrent HSP, CPAN, or PANDAS.

CONCLUSION

PSRA remains a distinct clinical entity; however, its diagnosis can be challenging due to significant overlap with other poststreptococcal syndromes, particularly ARF. It is critically important to differentiate PSRA from ARF given the potential for cardiac sequelae associated with ARF. The updated Jones criteria emphasize the role of both clinical and subclinical carditis, the specific pattern of arthritis, and the therapeutic response to distinguish ARF from PSRA. Notably, carditis is more prevalent in ARF and necessitates more intensive monitoring, whereas its incidence in PSRA is much lower, and the need for long-term prophylaxis remains a point of debate. NSAIDs are the first-line therapy for PSRA, although some patients need corticosteroids as a secondary therapeutic option. Antibiotic prophylaxis for up to one year is recommended, with careful surveillance for cardiac involvement. While there have been no major breakthroughs in the management of PSRA in recent years, ongoing research continues to explore its pathogenesis, optimal diagnostic criteria, and treatment strategies. Clinicians should remain vigilant in recognizing PSRA and in differentiating it from other poststreptococcal syndromes to ensure appropriate management and follow-up.

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Conflicts of interest

The authors declare that they have no competing interests

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AI am the future: artificial intelligence in pediatric rheumatology

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Purpose of review
There is a growing interest in the applications of artificial intelligence in pediatric rheumatology. Although concerns with training datasets, ethical considerations, and the need for a major utilization of explainable artificial intelligence are still ongoing challenges, significant advancements have been made in recent years. In this review, we explore the most recent applications of artificial intelligence in pediatric rheumatology, with a special focus on machine learning models and their outcomes.

Recent findings
Supervised and unsupervised machine learning models have been largely employed to identify key biomarkers, predict treatment responses, and stratify patients based on disease presentation and progression. In addition, innovative artificial intelligence driven imaging tools and noninvasive diagnostic methods have improved diagnostic accuracy and emerged as encouraging solutions for identifying inflammation and disease activity. Large language models have been utilized for patient-based questions with promising results. Nevertheless, critical examination and human oversight are still crucial in interpreting artificial intelligence's outputs.

Summary
Artificial intelligence is revolutionizing pediatric rheumatology by improving diagnosis and disease classification, patient stratification and personalized treatment. However, we are only at the beginning, and the adventure has just begun.

Keywords
artificial intelligence, large language models, machine learning, pediatric rheumatology

INTRODUCTION

Artificial intelligence is an emerging field of computer science that is able to provide systems performing activities that usually require human intelligence. Typical tasks include understanding language, making decisions, evaluating images, and solving complex problems [1]. "AI" is an umbrella term that refers to several informatic techniques, usually classified in two main groups. The first one is that of logic systems based on predefined instructions. The second group is composed of machine learning algorithms that utilize sophisticated technologies to learn from existing data and evolve without needing detailed instructions for each task.

The rarity and complexity of pediatric rheumatology diseases represent notable challenges. These conditions often present with nonspecific symptoms, making early diagnosis difficult. The ability of machine learning techniques to learn from existing data opens a revolutionary scenario for their applications in this field [2]. Indeed, machine learning models can be useful for diagnostic support, identifying subgroups of patients, analyzing radiological and clinical images, predicting disease progression, and optimizing treatment plans based on patients' characteristics [3–8]. However, there are some challenges limiting the application of machine learning models in clinical practice. First, they require appropriate training, and development is often challenging due to limited access to

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KEY POINTS

- The applications of artificial intelligence are reshaping several aspects of pediatric rheumatology, providing diagnostic models, identifying key biomarkers, and stratifying patients based on labeled and unlabeled characteristics.
- Concerns are still present in the use of artificial intelligence in medical settings, primarily due to limitations with the machine learning training processes, ethical considerations, and a wider need for explainable artificial intelligence.
- The next years will be characterized by a growing utilization of artificial intelligence tools in pediatric rheumatology. Therefore, understanding their limitations and possibilities is crucial for their proper utilization.

adequate training datasets (ideally larger and more diverse). Another point that should always be considered in the use of machine learning models for health-related purposes is the explainability of the model, a concept known as explainable artificial intelligence (XAI) [9,10]. In fact, what is crucial is not only having accurate predictions but also understanding how the model arrives at its decision, for ethical and scientific reasons [10]. XAI techniques make the machine learning model's decision-making process more transparent, showing what variables – such as specific laboratory results or symptoms – are most influential in the prediction, or highlighting areas of an image that are most relevant to the output, allowing the user to verify that the model is focusing on the correct regions [11]. In this review, with these critical aspects in mind, we explore the main applications of artificial intelligence in pediatric rheumatology.

SUPERVISED MACHINE LEARNING MODELS

Supervised machine learning uses labeled datasets (containing already classified data such as diagnostic images, blood exams, clinical characteristics) to train algorithms, typically for diagnostic implications, disease classification and treatment response prediction. In these algorithms, the desired outcome or target variable is clearly defined. In this regard, the word "supervised" stands as the training involves a dataset where the correct answers are provided. Such models continuously learn the relationships between the features to provide detailed outcomes.

New potential genetic biomarkers for juvenile systemic lupus erythematosus (jSLE) were identified through supervised machine learning models by analyzing differentially expressed genes (DEGs) from the GEO database (Table 1) [12]. The hub genes *CCR1* and *SAMD9L* were identified by using feature selection methods such as the Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression, which decreased data dimensionality, and the Support Vector Machine (SVM)-Recursive Feature Elimination (SVM-RFE), which eliminated less important features. These two genes are primarily involved in cellular response to chemokines, interferon-gamma, and neutrophil migration, highlighting their potential diagnostic value as biomarkers for jSLE [12]. Then, CIBERSORT, a deconvolution algorithm that quantifies the sensitivity and specificity distinctions and abundance of 22 human immune cell phenotypes using gene expression data, identified significant differences in immune cell composition between affected patients and healthy controls. The algorithm documented a higher proportion of neutrophils and a lower abundance of $CD8^+$ T cells and resting $CD4^+$ memory T cells in jSLE patients than controls [12]. A similar methodology with LASSO, random forest, and RF-RFE was used to identify the key genes *ALDH1A1, CEACAM1, YBX3*, and *SLC6A8* as DEGs in patients with systemic juvenile idiopathic arthritis (JIA) [13]. The CIBERSORT algorithm was employed to assess immune differences between affected patients and healthy controls. A random forest based diagnostic model was built using the identified key genes, providing interesting insights of systemic JIA pathogenesis like the possible role of immune pathways and cell death processes like mitophagy and ferroptosis [13]. A different study group developed the machine learning derived diagnostic model "Th2/Th17 classifier" for systemic JIA detection, based on Mendelian randomization and transcriptome examination through 111 different machine learning algorithm combinations. Extreme Gradient Boosting (XGBoost) and the XAI technique "SHapley Additive exPlanations" (SHAP) highlighted the role of *HRH2* as a key genetic marker and a potential therapeutic target [14]. By using both supervised and unsupervised machine learning algorithms, other studies identified key genes potentially involved in immune response associated with JIA [15,16]. Specifically, the genes *SOCS3, JUN, CLEC4C*, and *NFKBIA*, mainly involved in pathways related to tumor necrosis factor signaling, were detected through weighted gene co-expression network analysis (WGCNA) and a protein-protein interaction network by analyzing transcriptome and single-cell RNA sequencing datasets. The selection of DEGs was refined by using three supervised machine learning algorithms (LASSO, random forest, and RFE), while CIBERSORT was used to evaluate the proportion of

Table 1. The most relevant recent applications of artificial intelligence tools in pediatric rheumatology

Reference	Research outcomes	ML technique	Dataset	Performance metrics	Clinical validation	Limitations	Future Perspectives
Supervised machine learning approach							
Deng *et al.*, [12]	Identified the genetic biomarkers *CCR1* and *SAMD9L* in jSLE and immune cell infiltration analysis	Supervised: LASSO regression, SVM-RFE, CIBERSORT	GEO datasets: GSE148810, GSE27427, GSE65391(overall, 949 jSLE and 91 healthy controls)	AUC (for the three datasets): *CCR1* (0.98, 0.92, 0.84), *SAMD9L* (1, 0.95, 0.89)	Yes, validated in multiple independent datasets	Limited sample size for some datasets	Development a diagnostic test based on these DEGs genes and modulation of immune infiltration
Ding *et al.*, [13]	Developed a genetic-based diagnostic model for sJIA using 4 key genes (*ALDH1A1*, *CEACAM1*, *YBX3*, *SLC6A8*)	Supervised: LASSO regression, RF-RFE, RF classifier, CIBERSORT	GEO datasets: GSE11907, GSE8650-GPL96, GSE13501 (overall 125 sJIA and 92 heathy controls)	AUC > 0.95 (5-fold cross-validation), AUC = 0.99 (validation)	Yes, validated on independent dataset GSE7753	Limited dataset size, possible overfitting	Expand the model validation with larger datasets and real-world applications
Zhang *et al.*, [15]	Identified four key genes in JIA (*SOCS3*, *JUN*, *CLEC4C*, *NFKBIA*) involved in immune cell heterogeneity	Supervised: LASSO regression, RF, RFE, CIBERSORT Unsupervised: WGCNA, PCA	GEO datasets: GSE13501, GSE112057, GSE205095 (overall, 344 JIA, 61 healthy controls)	AUC (ROC for key genes) > 0.5, C-index = 0.86 (nomogram)	Yes, RT-qPCR validation	Limited validation sample, potential bias in dataset sources	Expand clinical validation and explore therapeutic targeting of identified pathways and drugs
Tu *et al.*, [17]	Developed a diagnostic model for JIA based on gut microbiota	Supervised: LASSO regression, XGBoost (XAI: SHAP, Permutation Importance Analysis)	Metagenomic data from the NCBI project PRJNA379123 (203 JIA and 28 healthy controls).	XGBoost: AUC: 0.98, accuracy: 0.91, F1 Score: 0.95	Yes, internal validation	Dataset from a single center, lack of species-level data	Multicenter studies including diverse ethnic groups to enhance generalizability
Habgood-Coote *et al.*, [19]	Developed a 161-transcript panel capable of classifying febrile illnesses in 18 infectious and inflammatory diseases	Supervised: LASSO, Ridge regression	12 publicly available gene expression microarray datasets (1212 patients)	AUC: variable by disease, specificity/sensitivity > 0.9 for most classes	Yes, validated with RNA-seq dataset	Limited dataset availability, underrepresentation of some diseases	Develop a cost-effective diagnostic test using the transcript panel for clinical use
Hu *et al.*, [20]	Developed the "ESIM" model for risk prediction of JDM-ILD, aiding early diagnosis and prognosis	Supervised: Logistic regression, Nomogram	93 children with JDM (discovery cohort, n = 58; validation cohort, n = 35)	AUC: 0.736 (discovery), 0.79 (validation)	Yes, internal validation	Single-center cohort, limited generalizability	Expand validation to multicenter cohorts and refine individualized treatment strategies
Nie *et al.*, [21]	Developed an AI-based model to differentiate abdominal HSP from acute appendicitis, identified key indicators	Supervised: XGBoost, AdaBoost, GNB, MLP, SVM (XAI: SHAP)	6965 children (2201 with abdominal HSP, 4764 acute appendicitis)	XGBoost: AUC > 0.95 (after optimization), Accuracy: 0.82, Kappa value: 0.62	Yes, internal validation	Limited applicability to other gastrointestinal diseases, no imaging data included	Expand model to include imaging data and validate with diverse gastrointestinal conditions
Unsupervised machine learning approach							
Shoop-Worrall *et al.*, [22▪]	Identified distinct response subtypes to methotrexate in JIA, revealing six response clusters	Unsupervised: Group-based trajectory modeling	1898 children and young people across four UK JIA cohorts (two cohorts from the UK JIA Biologics Register, CAPS, CHARMS)	AUC: 0.65–0.71 for predictive models	Yes, models were verified in independent cohorts	Limited frequency of data collection, inability to verify all identified clusters statistically, limited generalizability to other populations	Explore predictors between clusters, include more granular data collection, and validate across diverse populations

Table 1 (*Continued*)

Reference	Research outcomes	ML technique	Dataset	Performance metrics	Clinical validation	Limitations	Future Perspectives
Hounkpe *et al.*, [23]	Identified transcriptomic signatures of classical monocytes in polyarticular juvenile idiopathic arthritis, revealing heterogeneity with two patient clusters exhibiting varying levels of inflammation.	Unsupervised: k-means clustering Supervised: RFE using SVM	17 healthy subjects and 18 premenopausal women with pJIA	Not specified	Not specified	Small sample size, low disease activity in participants	Further validation in larger cohorts, potential for gene classifiers to predict immunopathology categories
Rypdal *et al.*, [24▪▪]	Identified four disease activity trajectories in JIA using longitudinal clustering. The PaGA was the most important driver of disease activity into adulthood assessed by cJADAS10	Unsupervised: Longitudinal clustering algorithm based on a discrete mixture model	427 JIA patients from the population-based Nordic JIA cohort with an 18-year follow-up period	Not specified	Not specified	Missing data for some variables, no regular visits between 8-year and 18-year follow-up, first study visit occurred after treatment may have been initiated	Develop guidelines for homogeneous scoring of the patient's and physician's global assessments, explore early targeted interventions to improve long-term outcomes
Zeng *et al.*, [25▪▪]	Identified three distinct subgroups within children suspected of having Sjögren disease	Unsupervised: LCA, k-means clustering, Supervised: RF, LASSO regression, PLS-DA, Gradient Boosted Decision Tree, ANN, Super Learner	Clinical and laboratory data from 217 symptomatic pediatric patients suspected of Sjögren disease	AUROC (best model): Class I = 1, Class II = 0.95, Class III = 0.97, Kappa value (3-class LCA model) = 0.85	Yes, internal validation	Single-center cohort, retrospective study, limited external validation, pediatric-specific diagnostic challenges	Validate in larger cohorts, develop pediatric-specific diagnostic criteria, explore longitudinal patient trajectories
Baxter *et al.*, [26]	Identified distinct immune cell signatures in treatment-naïve jSLE patients, identifying an extrafollicular B cell expansion signature associated with lupus nephritis	Unsupervised: hierarchical clustering; Supervised: Neural network-based algorithm (*CellCnn*)	Gene expression data and high-dimensional mass cytometry data from 24 treatment-naïve jSLE patients and age-matched healthy controls	Not explicitly reported	Yes, validated with 5-fold cross-validation and longitudinal follow-up	Small cohort size, limited external validation, lack of formal performance metrics like AUROC	Expand cohort size, validate findings in independent multicenter cohorts, further explore extrafollicular immune signatures and their clinical significance
Peng *et al.*, [27▪▪]	Stratified jSLE patients into distinct baseline CIMT categories and identified metabolomic markers predictive of CIMT progression in the placebo arm	Unsupervised: hierarchical clustering, Supervised: Optimized Sparse Partial Least Squares Discriminant Analysis	151 JSLE patients from the APPLE trial (74 placebo, 77 atorvastatin)	AUC for discriminating high versus low CIMT progression groups (six-metabolite signature combined): 0.81	Yes, but limited to the APPLE cohort	Lack of external validation, potential bias due to a small sample size, and limitations in detecting nonlipid atherosclerosis drivers	External validation in multicenter studies, explore additional nonlipid biomarkers, and develop personalized treatment strategies
Hammam *et al.*, [28]	Identified four distinct clinical phenotypes in jSLE using routine clinical data	Unsupervised: k-means clustering	404 jSLE patients from the clinical database of the Egyptian College of Rheumatology SLE Study Group	Not specified	Not specified	Cross-sectional design, no causal inference, lack of current steroid dose, none of the participants were under biologics	Replication in different populations and exploration of phenotype-based targeted therapies
Computer Vision Applications							
Kian Ara *et al.*, [29]	Diagnosis of active JIA from healthy joints using blood pool images of [99mTc] Tc-MDP scintigraphy	Supervised Self-designed multiinput CNN and three pretrained models (VGG16, ResNet50 and Xception)	1304 blood pool images from 326 children (knee and ankle joints)	AUC: 0.82 (knee), 0.86 (ankle) for self-designed CNN	Yes, internal validation	Small dataset, lack of external validation, variability in image quality	Expand dataset with multicenter studies, include anatomical data, improve positioning and acquisition for more consistent results

Table 1 (*Continued*)

Reference	Research outcomes	ML technique	Dataset	Performance metrics	Clinical validation	Limitations	Future Perspectives
Brown *et al.*, [30▪▪]	Diagnosis of rheumatic heart disease through mitral regurgitation jet analysis in echocardiograms	Supervised 9-feature SVM, 3D-CNN and Multiview Transformer	511 echocardiograms of children (282 with rheumatic heart disease, 229 normal)	SVM: AUC 0.93, Precision 0.83, Recall 0.92, F1 0.87; 3D-CNN & Transformer ensemble: AUC 0.84, Precision 0.78, Recall 0.98, F1 0.87	Yes, internal validation	Limited to Doppler-based MR jet analysis; no spectral Doppler, small dataset for deep learning models	Expand dataset with multicenter studies; integrate additional rheumatic heart disease features (e.g., valve morphology, aortic insufficiency)
Peck *et al.*, [31▪]	Screening for rheumatic heart disease by nonexperts using AI-guided colour Doppler echocardiography	Supervised AI navigational guidance with real-time feedback	462 echocardiograms (362 by novices, 100 by experts) in 50 patients (half rheumatic heart disease, half normal)	Diagnostic images obtained in >90% of studies by novices. Accuracy for rheumatic heart disease presence/absence: 0.89 by novices and 0.86 by experts without AI guidance. Lower scores for apical views and aortic valve assessments.	Yes, internal validation	Short training duration, limited apical view quality, no external validation, no long-term retention assessment	Improve AI guidance for apical views, automate Doppler box positioning, extend training duration, and test scalability in multicenter clinical settings
Kassani *et al.*, [32]	Detection of JDM and prediction of disease activity using nailfold capillaroscopy images	Supervised NFC-Net (CNN)	1120 nailfold capillaroscopy images from 111 JDM patients and 321 images from 31 healthy controls	AUROC: 0.93 (JDM vs. control), 0.76 (total DAS activity); Accuracy: 0.91 (JDM vs. control), 0.74 (DAS activity)	Yes, internal validation	Small dataset, variability in image quality, imbalance in disease activity data (greater accuracy in determining skin than muscle involvement)	Expand dataset with multicenter studies, improve prediction of disease activity, and refine mobile AI tools
Goossens *et al.*, [33]	Automated assessment of JIA using joint acoustic emissions to classify knee joint health and disease activity	Supervised: XGBoost Unsupervised: PCA	273 features extracted from joint acoustic emissions of 116 subjects (86 JIA, 30 healthy controls; 43 active knees)	Accuracy: 0.88 (testing), AUC: 0.81	Yes, internal validation	Subjective labeling of active/inactive knees; no gold standard validation (e.g., MRI or ultrasound)	Expand to multicenter studies, include gold-standard diagnostics, and explore wearable technologies for home monitoring
Goossens *et al.*, [34]	Identification of Achilles tendon inflammation in ErA patients using active vibrational sensing	Supervised: SVM classifier, QDA Unsupervised: PCA	20 JIA patients (6 sxERA, 6 asxERA, 8 asxNERA)	LOSO-CV (feature-based model): Accuracy: 0.86 (sxERA vs. asxNERA), 0.75 (sxERA vs. asxERA); AUC: 0.92 (sxERA vs. asxNERA), 0.75 (sxERA vs. asxERA)	Yes, internal validation	Small dataset; imbalance in age, BMI, and sex; no gold-standard imaging validation	Expand dataset, integrate with imaging-based validation, develop wearable devices for home monitoring
Large language models							
La Bella *et al.*, [38]	Evaluation of GPT-4.0 (Microsoft Copilot) in answering pediatric FMF questions by pediatric rheumatologists	ChatGPT 4.0	15 pediatric FMF questions, repeated three times, evaluated by nine pediatric rheumatologists	Agreement (Krippendorff's alpha): 0.136 (session 1) to 0.089 (session 3); Median scores: 2.00–5.00 to 3.00–4.00	Yes, expert survey	Limited agreement between experts; incomplete or inaccurate AI responses; small expert sample size	Expand to larger, multicenter expert groups; refine AI algorithms; explore hybrid AI-expert workflows for medical applications

Studies were categorized by the primary type of machine learning employed, reflecting the main objective of each study. For studies using multiple approaches, classification was based on the method most central to the research purpose.

ANN, artificial neural network; asxERA, asymptomatic ERA; asxNERA, asymptomatic JIA/non-ERA; AUC, area under the curve; AUROC, area under ROC curve; CIMT, carotid intima-media thickness; cJADAS, clinical Juvenile Arthritis Disease Activity Score; CRP, C-reactive protein; DEGs, differentially expressed genes; EO, eosinophil; ErA, enthesitis-related arthritis; FMF, familial Mediterranean fever; GEO, Gene Expression Omnibus; HSP, Henoch-Schonlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; jSLE, juvenile systemic lupus erythematosus; PaGa, patient's global assessment of well being; pJIA, polyarticular JIA; RF, random forest; RFE, recursive feature elimination; SHAP, SHapley Additive exPlanations; sJIA, systemic JIA; SLE, systemic lupus erythematosus, SVM:, sxErA, symptomatic ErA; Tc-MDP, Technetium 99m-methyl diphosphonate; UK, United Kingdom; XGBoost, eXtreme Gradient Boosting.

immune cells in JIA patients and healthy controls [15]. This research underscores the potential of combining multiomics data with machine learning techniques in order to improve diagnosis and develop tailored treatment plans [15]. With a similar approach, a subsequent study identified *PHLDA1*, *EGR3*, *CXCL2*, and *PF4V1* as DEGs significantly associated with the progression and prognosis of polyarticular JIA [16].

Notably, a predictive diagnostic machine learning model for JIA was developed using fecal microbiota markers [17]. The authors used metagenomic sequencing data and processed fecal samples by using various software tools. Six different machine learning models were built on 10 fecal microbe biomarkers previously identified, with XGBoost demonstrating highly promising [17]. The XAI technique SHAP showed that Proteobacteria and UCG-002 were the most impactful on the predictions [17]. This novel approach to JIA diagnosis emphasizes the role of gut microbiota in JIA pathogenesis and may help in diagnosis alongside traditional clinical and imaging findings. In addition to predictive and diagnostic models, a pilot study was conducted to evaluate the potential link between JIA and an elevated risk of developing breast cancer, with results supporting a common mechanism, especially based on the expression of the *PRRG4* gene [18].

A multiclass supervised machine learning approach was used to accurately classify pediatric febrile illnesses based on RNA expression data [19]. The authors were able to identify 18 distinct disease categories, including rheumatic conditions such as Kawasaki disease (KD), JIA, jSLE, and Henoch-Schönlein purpura (HSP) [19]. This study provided a useful approach to reduce the time needed for diagnosis and improve treatment decisions. In another study, clinical data from patients with juvenile dermatomyositis (JDM) were retrospectively analyzed to identify relevant clinical features associated with JDM-associated lung disease (JDM-ILD) [20]. These included higher levels of interleukin-10 and erythrocyte sedimentation rate, and positivity for MDA-5 antibodies. The nomogram-based predictive model "ESIM" was developed using these three features, representing a useful visual tool for risk assessment [20]. Patients were categorized in low-risk and high-risk groups based on the median nomogram score, and survival analysis confirmed that being in the high-risk group resulted in higher rates of disease progression [20]. The focus of a further study was to employ artificial intelligence to distinguish children with acute appendicitis from those with abdominal HSP [21]. Five supervised machine learning models were trained using a large dataset including patient with both diseases, and 32 discriminative indicators were identified, including C-reactive protein, neutrophil ratio, lymphocyte ratio, and eosinophil count. XGBoost resulted the best machine learning model, and through the XAI technique SHAP, the authors were able to indicate C-reactive protein, albumin, red blood count, and lymphocyte ratio as the most impactful features on the prediction [21].

UNSUPERVISED MACHINE LEARNING MODELS

Unsupervised learning uses unlabeled data to identify underlying associations and patterns such as disease subtypes, patient clustering, and phenotype discovery. Unsupervised techniques are especially advantageous in situations where no predefined outcome or label is available to direct the learning process. These methods facilitate the identification of hidden patterns, the clustering of similar data points, and the exploration of the underlying structure within datasets. The most used clustering algorithms include k-means and hierarchical models.

An unsupervised machine learning approach was recently used to identify distinct JIA subtypes in treatment response to methotrexate (MTX) [22▪]. With the application of group-based trajectory modeling to data from four prospective JIA cohorts, patients were classified in six distinct response patterns to MTX: fast improvers (11%), slow improvers (16%), improve-relapse (7%), persistent disease (44%), persistent physician global assessments (8%), and persistent parental global assessments (13%). The clustering revealed the heterogeneity in therapeutic response over time in the cohorts and the need for more tailored treatment plans [22▪]. Supervised and unsupervised machine learning models were both used to identify comorbidity associations and transcriptomic features related to inflammation in patients with polyarticular JIA (pJIA) [23]. Gene set enrichment analysis identified key DEGs, drivers of hyperinflammation, including *PLAUR*, *IL1B*, *IL6*, *CDKN1A*, *PIM1*, and *ICAM1* [23]. Moreover, k-means clustering identified two pJIA subgroups with diverse levels of inflammation due to differences in the transcriptomic profiles and inflammatory pathways [23]. A longitudinal clustering algorithm based on a discrete mixture model was used to identify disease activity trajectories in 427 patients with JIA over 18 years of follow-up. Patients were grouped using the clinical Juvenile Arthritis Disease Activity Score (cJADAS10), which includes active joint count, physician's global assessment, and patient/parental global assessment (PaGa). Four trajectory groups were defined, representing different levels of disease activity during the time: minimal disease activity to minimal/inactive disease ($n = 168$), that is,

patients with minimal disease activity at baseline throughout the observation period and at the 18-year follow-up; minimal disease activity to moderate disease activity ($n = 104$), that is, minimal disease activity at baseline but increased disease activity towards the 18-year visit; high disease activity to minimal disease activity ($n = 119$), that is, high disease activity at baseline, with decreasing disease activity throughout the observation period; and high disease activity to high disease activity ($n = 36$), that is, high disease activity at baseline and throughout the observation period, with high disease activity at the 18-year follow-up as well [24▪▪]. The authors found that PaGA was often the main driver of increased cJADAS10 scores, even in patients without active joints, highlighting the need for a multidisciplinary treatment approach [24▪▪].

A different approach was used to categorize pediatric patients suspected of having Sjögren disease in distinct subgroups (Table 2) [25▪▪]. The authors applied supervised and unsupervised ML models to build the final "Florida Scoring System" and identified three patient classes, with important implications for clinical management, trial design, and pathobiological research: dryness dominant with positive tests (12.4%), high symptom severity and negative tests (45.2%), and low symptoms with negative tests (42.4%) [25▪▪]. Unsupervised hierarchical clustering was used to distinguish jSLE patients from healthy controls, group them based on gene expression profiles, and analyze their immune cell composition [26]. The authors employed the neural network-based algorithm "CellCnn" to identify specific immune cell populations associated with jSLE and lupus nephritis [26]. Through gene expression data and high dimensional mass cytometry data from 24 treatment-naive patients, the authors identified distinct immune signatures for both jSLE and lupus nephritis. In particular, the machine learning model detected an extrafollicular B cell subset signature associated with lupus nephritis activity and comprising surface marker phenotypes resembling plasmablasts and $CD27^{-}IgD^{-}$ double negative B cells [26].

Unsupervised hierarchical clustering was recently used in the "Atherosclerosis Prevention in Pediatric Lupus Erythematosus" (APPLE) trial, one of the largest randomized controlled trials comparing atorvastatin versus placebo for atherosclerosis progression in jSLE, to stratify patients based on baseline carotid intima-media thickness (CIMT) [27▪▪]. At baseline, 151 jSLE patients were grouped in three classes: high ($n = 44$), intermediate ($n = 64$), and low ($n = 43$) CIMT trajectories. Over 36 months, clustering revealed two distinct CIMT progression patterns in the placebo group, characterized by high ($n = 35$) and low ($n = 25$) progression rates, with higher total and low-density lipoprotein (LDL) cholesterol levels in the high progression group despite being within reference ranges. A metabolomic analysis, mostly composed by lipid metabolites, identified a baseline serum signature predicting high CIMT progression in the placebo arm [27▪▪]. In the atorvastatin group, patients were stratified into three progression groups, and 36% of patients experienced high CIMT progression despite significant reductions in LDL cholesterol, suggesting nonlipid drivers of atherosclerosis in jSLE with possible therapeutic implications [27▪▪].

Demographic, clinical, and laboratory data from 404 jSLE children were used for developing a k-means unsupervised clustering algorithm to categorize jSLE patients in subgroups based on distinct clinical phenotypes [28]. Authors identified four clinical clusters: the first ($n = 103$), characterized mainly by mucocutaneous and neurological manifestations, the second ($n = 101$), characterized by arthritis and pulmonary involvement, the third ($n = 71$), having children with milder manifestations, and the fourth ($n = 129$), characterized by high levels of arthritis, vasculitis, and lupus nephritis. The first and the last one were associated with a higher disease activity index, indicating a more aggressive form of the disease [28]. This stratification may help in better understanding the disease and lead to targeted treatment strategies.

COMPUTER VISION APPLICATIONS

Artificial intelligence based models may increase diagnostic accuracy, especially in the early stages of the disease. An interesting application of machine learning techniques for medical imaging analysis can be found in a study aiming to differentiate healthy children and active JIA patients by using [99mTc] Tc-MDP bone scintigraphy images [29]. Data collection included 1304 blood pool bone scintigraphy images of knees and ankles from 326 individuals. A self-designed multiinput convolutional neural network (CNN) was built, alongside the use of three pretrained models, and applied to the 772 blood pool scintigraphy images of knees and ankles included. The self-designed CNN had the best performance, outperforming the pretrained models [29].

An automated approach for assessing echocardiographic image analysis was developed by using multiple machine learning techniques in two recent studies focusing on patients with rheumatic heart disease (RHD). In the first study, authors used an SVM algorithm to analyze the mitral regurgitation jet, identifying nine key features contributing to RHD diagnosis prediction. Deep learning models were used for more complex analysis, including a

Table 2. Recent applications of artificial intelligence in pediatric rheumatology: purposes and outcomes

Pediatric rheumatology disease	Study proposal	Outcomes	Reference
Enthesitis-related arthritis	Identification of Achilles tendon inflammation using active vibrational sensing	Successful classification of patients with symptomatic ErA, asymptomatic ErA and asymptomatic non-ErA	Goossens *et al.* [34]
Familial Mediterranean fever	Evaluation of LLM's accuracy for questions related to pediatric familial Mediterranean fever	The survey highlighted good accuracy but also misleading responses and threatening "hallucinations" by ChatGPT 4.0	La Bella *et al.* [38]
Febrile illnesses	Development a panel for classifying febrile illnesses	Development of a panel capable of classifying febrile illnesses in 18 infectious and inflammatory diseases	Habgood-Coote *et al.* [19]
Study proposal: development of a panel for classifying febrile illnesses			
Henoch-Schönlein purpura	Development of an AI-based model to differentiate abdominal Henoch-Schönlein purpura from acute appendicitis	Development of a successful predictive model, with C-reactive protein, lymphocyte ratio, eosinophil ratio, eosinophil count, and neutrophil ratio exhibiting strong performance in the differentiation	Nie *et al.* [21]
Juvenile dermatomyositis	Diagnosis and prediction of disease activity using nailfold capillaroscopy images	Nailfold capillaroscopy images were sufficient for detecting often unrecognized disease activity	Kassani *et al.* [32]
	Development of a model for risk prediction of interstitial lung disease	Development of the "ESIM" predictive model based on higher levels of interleukin-10 and erythrocyte sedimentation rate, and positivity for MDA-5 antibodies.	Hu *et al.* [20]
Juvenile idiopathic arthritis	Identification of inflamed joints and healthy joints by using blood pool images of [99mTc] Tc-MDP scintigraphy	Development of a successful deep learning-based classification model	Kian Ara *et al.* [29]
	Implementation of joint acoustic emissions to classify knee joint health and disease activity	Development of machine learning algorithm that successfully classified JIA and healthy knees through joint acoustic emissions, providing a cheap and easy-to-use digital biomarker	Goossens *et al.* [33]
	Identification of disease activity trajectories using longitudinal clustering	Identification of four disease activity trajectories: (i) MiDA-ID ($n=168$), i.e., patients with minimal disease activity at baseline throughout the observation period and at the 18-year follow-up; (ii) MiDA-MDA ($n=104$), i.e., minimal disease activity at baseline but increased disease activity towards the 18-year visit; (iii) HDA-MiDA ($n=119$) i.e. high disease activity at baseline, with decreasing disease activity throughout the observation period; (iv) HDA-HDA ($n=36$), i.e., high disease activity at baseline and throughout the observation period, with high disease activity at the 18-year follow-up as well. The patient or parental global assessment of disease impact on well being resulted the most important driver of disease activity into adulthood assessed by the cJADAS10.	Rypdal *et al.* [24▪▪]
	Identification of distinct response subtypes to methotrexate	Identification of six response clusters: (i) fast improvers (11%), (ii) slow improvers (16%), (iii) improve-relapse (7%), (iv) persistent disease (44%), (v) persistent physician global assessments (8%), and (vi) persistent parental global assessments (13%)	Shoop-Worrall *et al.* [22▪]
	Development of a diagnostic model based on fecal microbiota	Development of a diagnostic model with excellent performance. Proteobacteria and genus UCG-001 provided the most substantial contribution within the top performing models.	Tu *et al.* [17]

Table 2 (*Continued*)

Pediatric rheumatology disease	Study proposal	Outcomes	Reference
	Identification of key genes involved in immune response	Successful identification of the four key genes *SOCS3*, *JUN*, *CLEC4C*, *NFKBIA*	Zhang *et al.* [15]
	Assessment of the mechanism of JIA on cancer risk	Results supported a mechanism between an increased risk of breast cancer and JIA patients, especially based on the expression of the *PRRG4* gene, differently expressed in T cells in JIA and mainly expressed in T cells in breast cancer	Jiang *et al.* [18]
Juvenile idiopathic arthritis – polyarticular course	Identification of key genes in progression and prognosis of the disease	Identification of the key genes *PHLDA1*, *EGR3*, *CXCL2*, and *PF4V1*	Liu *et al.* [16]
	Identification of transcriptomic signatures of classical monocytes	Identification of two subclusters of patients and recognition of the genes *PLAUR*, *IL1B*, IL6, *CDKN1A*, *PIM1*, and *ICAM1* as drivers of chronic hyperinflammation	Hounkpe *et al.* [23]
Juvenile idiopathic arthritis – systemic onset	Development of a diagnostic model	Development of the diagnostic model "Th2/Th17 classifier" based on multiple machine learning approaches. Identification of *HRH2* as a key genetic marker	Wang *et al.* [14]
	Development of a diagnostic model	Development of a successful genetic-based diagnostic model through the key genes *ALDH1A1*, *CEACAM1*, *YBX3* and *SLC6A8*. Identification of the possible role of immune pathways and cell death processes like mitophagy and ferroptosis in the pathogenesis of the disease.	Ding *et al.* [13]
Juvenile systemic lupus erythematosus	Identification of genetic biomarkers with potential diagnostic value and immune cell infiltration analysis	Identification of the genetic biomarkers *CCR1* and *SAMD9L*. Detection of a higher proportion of neutrophils and a lower abundance of $CD8^+$ T cells and resting $CD4^+$ memory T cells in affected patients than controls.	Deng *et al.* [12]
	Identification of distinct clinical phenotypes using routine clinical data	Identification of four distinct clusters of patients: (i) prevalent mucocutaneous and neurologic manifestations ($n=103$), (ii) prevalent articular and pulmonary manifestations ($n=101$), (iii) mild disease intensity ($n=71$), and (iv) highest frequency of arthritis, vasculitis, and nephritis ($n=129$)	Hammam *et al.* [28]
	Patient stratification into distinct baseline CIMT categories and identification of metabolomic markers predictive of CIMT progression	Stratification of patients into three baseline CIMT subgroups: high ($n=44$), intermediate ($n=64$), and low ($n=43$) CIMT trajectories. Identification of two distinct CIMT progression patterns in the placebo group (high progression rate, $n=35$ and low progression rate, $n=25$), with A metabolomic analysis, mostly composed by lipid metabolites, identifying a baseline serum signature predicting high CIMT progression in the placebo arm. In the atorvastatin group, patients were stratified into three progression groups (high progression group, $n=22$, intermediate progression group, $n=24$, and low progression group, $n=25$), with 36% of patients experiencing high CIMT progression despite significant reductions in LDL cholesterol, suggesting nonlipid drivers of atherosclerosis.	Peng *et al.* [27▪▪]

Table 2 (*Continued*)

Pediatric rheumatology disease	Study proposal	Outcomes	Reference
	Identification of distinct immune cell signatures in treatment-naive patients	Identification of extrafollicular B cell expansion signature in affected patients, with increased frequency of CD27-IgD- double negative B cells (DN2), activated anergic autoreactive B cells (Bnd2), plasmablasts, and peripheral T helper cells. The extrafollicular signature correlated with disease activity in lupus nephritis.	Baxter *et al.* [26]
Rheumatic heart disease	Automated diagnosis using echocardiographic images through mitral regurgitation jet analysis	Successful development of a deep-learning-based model with maximum mitral regurgitation jet measurements similar to expert manual measurements	Brown *et al.* [30▪▪]
	Screening by nonexperts using AI-guided color Doppler echocardiography	Artificial intelligence guidance resulted feasible to enable rheumatic heart disease screening by nonexperts, performing better for the mitral than aortic valve	Peck *et al.* [31▪]
Sjögren disease in childhood	Identification of distinct subgroups within children suspected of having Sjögren disease	Identification of three distinct clusters: (i) dryness dominant with positive tests (12.4%), (ii) high symptom severity and negative tests (45.2%), and (iii) low symptoms with negative tests (42.4%)	Zeng *et al.* [25▪▪]

cJADAS10, clinical Juvenile Arthritis Disease Activity Score 10; CIMT, carotid intima-media thickness; ErA, enthesitis-related arthritis; LLM, large language model; HDA-MiDA, high disease activity to minimal disease activity; HDA-HDA, high disease activity to high disease activity; MiDA-ID, minimal disease activity to minimal/inactive disease; MiDA-MDA, minimal disease activity to moderate disease activity; Tc-MDP, Technetium 99m-methyl diphosphonate.

three-dimensional CNN (3D-CNN) and a multiview transformer model, to integrate spatiotemporal information from Doppler images [30▪▪]. This model allowed for a highly accurate diagnosis as an expert manual echocardiogram assessment [30▪▪]. In the second study, a deep learning based artificial intelligence model was integrated into the ultrasound system to provide real-time guidance for novice technicians from a low-resource setting during echocardiographic image acquisition. Novice-acquired images were sufficient for RHD diagnosis in more than 90% of cases, with an accuracy comparable to experts. However, the images were less diagnostic for aortic valve assessment and apical chamber views [31▪].

To assess disease activity and distinguish children with JDM from healthy controls, a deep learning-based approach was utilized for radiological analysis of nailfold capillaroscopy (NFC) [32]. A total of 1120 NFC images from 111 children with JDM and 321 images from 31 healthy controls were analyzed with NFC-Net, a new lightweight convolutional neural network model, revealing strong performance in differentiating JDM patients from healthy controls and moderate performance in predicting disease activity, with better results for skin involvement rather than muscle involvement. These findings suggest that ML models applied to NFC images can be helpful for JDM diagnosis and disease monitoring [32].

Artificial intelligence based models have also been utilized for automated joint assessment in patients with JIA. In a first study, the authors used miniature uniaxial accelerometers to record joint acoustic emissions (JAEs) in order to train an XGBoost model to identify healthy controls and JIA patients [33]. Knees with active inflammation due to JIA were characterized by swelling, tenderness, and limited range of motion. Thus, the XGBoost classifier showed good accuracy in differentiating between different stages of joint involvement [33]. Active vibrational sensing was used to detect inflammation in the Achilles tendon of children with enthesitis-related arthritis (ErA) [34]. Several supervised machine learning algorithms, including SVM and quadratic discriminant analysis, were successfully used to identify symptomatic ErA and distinguish them from asymptomatic non-ErA. However, accuracy was lower in distinguishing symptomatic ErA from asymptomatic ErA [34]. These studies showed how a noninvasive, low-cost diagnostic machine learning based tool can be developed for identifying inflammation in JIA patients.

LARGE LANGUAGE MODELS

Large language models (LLMs) are deep learning models capable of generating human-like content [35,36]. LLMs use advanced natural language processing techniques, and, among them, pretrained

transformers (GPT) are largely used for automating text-based tasks [37]. The reliability of a popular, free LLM (ChatGPT through Microsoft Copilot) in addressing 15 questions repeated thrice about pediatric Familial Mediterranean Fever was evaluated by an expert survey completed by nine pediatric rheumatologists using a Likert-like scale [38]. ChatGPT provided detailed responses but also substantial inaccuracies; moreover, ratings varied among experts, with a decreasing agreement over time. According to the authors, generative artificial intelligence can be useful for answering questions related to pediatric rheumatology, but expert validation and human critical evaluation of the responses remain critical [38].

CONCLUSION

Supervised and unsupervised machine learning approaches have been used to identify key biomarkers, stratify patients based on disease presentation and progression, and predict treatment responses. Artificial intelligence tools have also improved diagnostic accuracy, and several innovative noninvasive methods have been developed for assessing inflammation and disease activity. However, there are still challenges related to training machine learning models and the need for a wider presence of XAI. The history of artificial intelligence in pediatric rheumatology is at the beginning, and the journey has just begun.

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Conflicts of interest

There are no conflicts of interest.

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Biomarkers in juvenile idiopathic arthritis: towards precision diagnosis and personalized therapy?

Luciana Breda, Saverio La Bella and Armando Di Ludovico

Purpose to review
Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, characterized by persistent joint inflammation with heterogeneous clinical subtypes. Early diagnosis and targeted treatment remain critical to improving long-term outcomes. In recent years, research has increasingly focused on the identification and validation of biomarkers to enhance diagnostic precision, predict disease course, and guide therapeutic decisions.

Recent findings
Calprotectin (S100A8/A9) is a pro-inflammatory protein complex released by activated neutrophils and monocytes. In JIA, serum and synovial fluid calprotectin levels correlate with disease activity and may outperform traditional markers like C-reactive protein and erythrocyte sedimentation rate. Evidence suggests that elevated calprotectin levels can predict flares and subclinical inflammation, making it a promising biomarker for monitoring and prognosis in JIA. Novel biomarkers including microRNAs show potential for differentiating disease subtypes and monitoring treatment response. Proteomic and metabolomic profiling are also uncovering candidates that may improve early diagnosis and personalized management.

Summary
Biomarkers have emerged as pivotal tools in the management of JIA, offering significant advantages in both therapeutic decision-making and long-term monitoring. In the future, a robust biomarker framework holds the potential to improve early diagnosis, guide personalized treatment strategies, and enhance outcome prediction—ultimately contributing to more effective and individualized care for patients with JIA.

Keywords
biomarkers, juvenile idiopathic arthritis, predictive tools, serum calprotectin

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood and is characterized by childhood-onset chronic arthritis of unknown cause [1]. The International League of Associations for Rheumatology (ILAR) classification criteria divide JIA into seven categories based mainly on clinical characteristics during the first 6 months from disease onset [2]. These include: systemic arthritis; polyarthritis rheumatoid factor (RF)-positive, polyarthritis rheumatoid factor-negative, oligoarthritis (persistent or extended), enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis [2]. JIA pathophysiology is complex encompassing genetic susceptibility, environmental influences, and dysregulated immune responses that lead to persistent inflammation and tissue damage. A complex network of cytokines and inflammatory cells have shown to play an essential role in the pathogenesis of JIA (Fig. 1).

In the last two decades, thanks to the advances in medical therapy and the recent introduction of biologic drugs, the natural history and prognosis of JIA patients have dramatically improved [1]. Currently, the early use of targeted therapies ensures that up to 80% of JIA patients achieve inactive disease in the first year and about 46–57% of nonsystemic JIA (ns-JIA) patients reach remission within 5 years [3]. However, a high frequency of early flares (50%) after drug discontinuation has been reported in the literature [4,5]. In recent years, significant effort has been dedicated to identifying validated biomarkers that would be able not only to have diagnostic and prognostic values but would also be the guide for a therapeutic targeted approach.

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KEY POINTS

- Serum calprotectin (sCal) is a promising biomarker for assessing subclinical inflammation and predicting relapse in nonsystemic JIA.
- Integration of sCal with musculoskeletal ultrasound enhances precision in defining remission and predicting flares.
- Recent metabolomics studies have identified novel metabolic signatures, such as sphinganine-1-phosphate, with strong diagnostic potential in JIA.
- MicroRNAs and regulatory T cells show emerging value as biomarkers for disease activity, prognosis, and treatment response in JIA.
- Artificial intelligence and multiomics approaches are accelerating biomarker discovery, offering personalized strategies for early diagnosis and management.

Biomarkers are a valid aid in personalized medicine, as they allow to measure and demonstrate disease changes, even subclinical, and to modulate therapy on the basis of these changes [6]. To date, commonly used parameters such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) present some limits because they are markers for systemic inflammation and therefore cannot detect residual inflammation that influences the risk of flares when stopping treatment, neither they can predict the further course of the disease.

Other routinely measured biomarkers in JIA include autoantibody/rheumatoid factor, determining subtypes of polyarticular JIA, and antinuclear antibody (ANA), which associates with increased risk of developing uveitis [7]. However, these markers are utilized for classifying disease subcategory and risks of comorbidities, rather than monitoring disease progression and predicting flares. Serum S100A8/9 and S100A12 are alarmin proteins predominantly released at inflammatory sites by innate immune cells including monocytes, macrophages, and neutrophils; these proteins are considered more specific biomarkers as they reflect local inflammation [8]. Several studies have proposed that serum levels of S100A8/9 correlates with disease activity, might be a predictor of flare, and therapeutic response or disease progression, in JIA [6]. However, the results of investigations about the usefulness and actual clinical applications of serum calprotectin in JIA are, to date, conflicting.

Recent advances in this field have come from genetic studies and proteome analysis [7]. Cellular ratios, gene expression profiling, and proteome analysis of synovial fluid mononuclear cells (SFMCs) have been suggested to identify JIA individuals likely to progress into a more severe category of disease activity to extended oligoarticular JIA [7].

In this review, we will address recent development regarding biomarkers in JIA and will discuss their impact in clinical practice.

SERUM CALPROTECTIN

Serum calprotectin (sCal) is a granulocyte and monocyte complex of calcium-and zinc-binding proteins that belong to the S100 protein family and is released during cell activation and turnover. It is also referred as S100A8/A9, MRP8/MRP14 (myeloid-related protein 8/14), calgranulin A/B, L1 protein, and cystic fibrosis antigen, and is composed by two subunits of 8 and 14 kDa, respectively, of MRP8 and MRP14 [9]. In the inflamed synovium, sCal is released *in situ* by immune-activated cells, thus correlating with local inflammation even when no systemic involvement occurs [9]. SCal quickly passes into the bloodstream and appears to be an excellent potential biomarker of inflammation even subclinical [9]. Indeed, sCal has been identified as an important inflammatory marker in several conditions, including adult rheumatoid arthritis and JIA [10].

It has been shown that sCal helps to assess disease activity, monitor response to treatment, and possibly predicts disease course in JIA. Some studies suggested that sCal is a more specific biomarker of disease activity than either ESR and CRP [11].

SCal appears a promising tool in differentiating systemic-onset JIA (soJIA) from infections, malignancies, and other autoimmune/autoinflammatory diseases, and it may support early diagnosis and timely start of therapy. Phenotypically, soJIA is different from other juvenile arthritis and is characterized by fever, evanescent skin rash, reticuloendothelial involvement, serositis, elevation of inflammatory markers, and joint manifestations. Diagnosis may be challenging, especially at onset when signs and symptoms may be nonspecific. The performance of sCal in differentiating soJIA from other diseases has been recently analyzed in 615 children with fever of unknown origin by Foell and colleagues. They used a sCal Turbo assay on an automated instrument that can provide the results within 1 h. The authors found that sCal could really differentiate sJIA from other diagnoses with significant accuracy [cut-off at 10 500 ng/ml, sensitivity 84%, and specificity 94%, receiver operating characteristic (ROC) area under the curve (AUC) 0.96, $P < 0.001$] [12]. This means that if sCal is higher than 15 000 ng/ml, the diagnosis of soJIA is likely, excluding infections 94% and leukemia 100%; if sCal is higher than 20 000 ng/ml, leukemias and

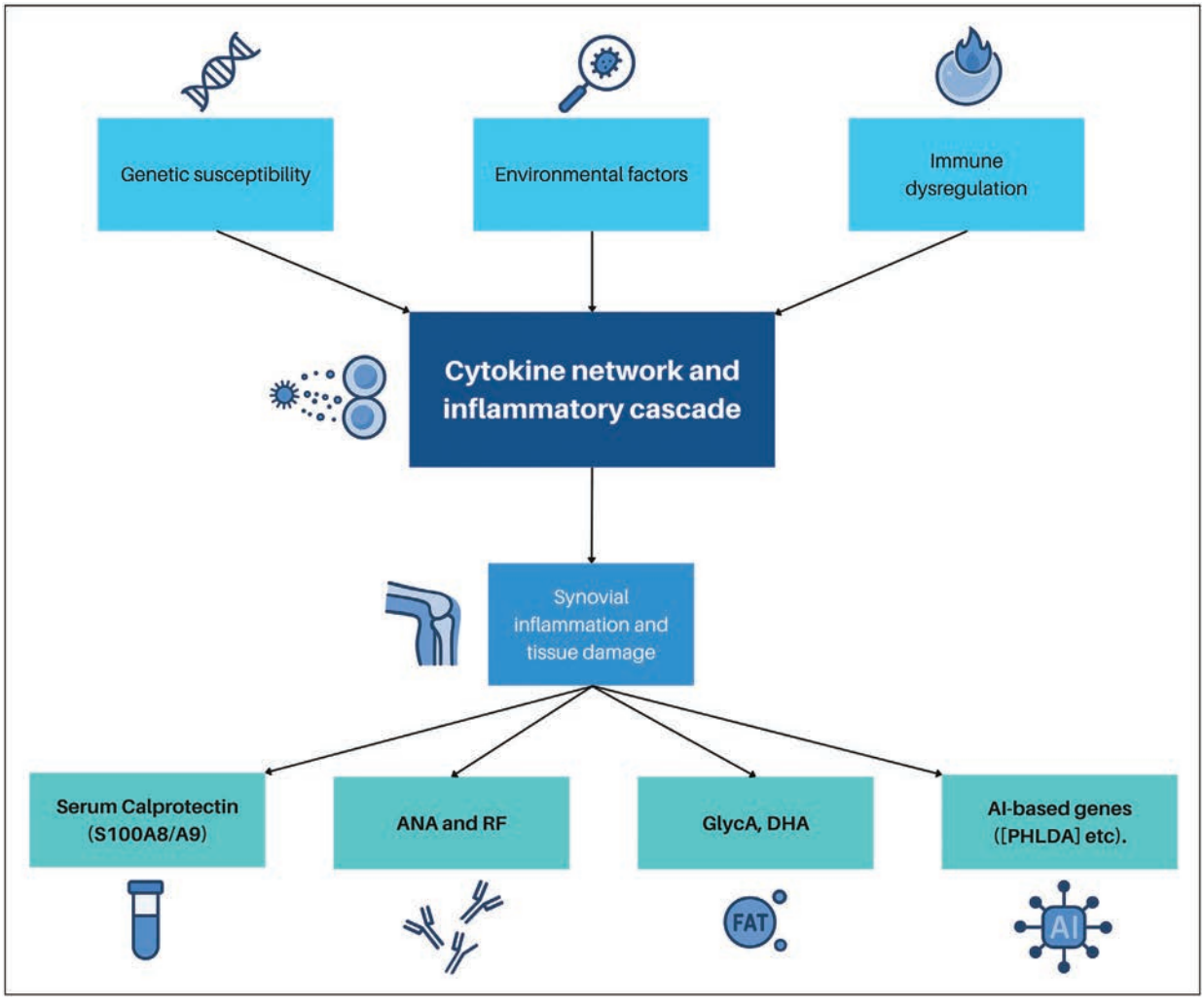

FIGURE 1. Pathogenesis of juvenile idiopathic arthritis and the role of key biomarkers. This diagram summarizes the multifactorial pathogenesis of juvenile idiopathic arthritis (JIA), integrating genetic susceptibility, environmental influences, and immune dysregulation that converge in a pro-inflammatory cytokine network and synovial tissue damage. Key biomarkers are highlighted at the downstream level: serum calprotectin (S100A8/A9) reflects local inflammation and subclinical disease activity; antinuclear antibody (ANA) and rheumatoid factor (RF) support disease classification; metabolomic markers, such as glycoprotein acetyls (GlycA) and docosahexaenoic acid (DHA) reflect systemic inflammation and remission status; artificial intelligence (AI)-discovered genes contribute to stratification and flare prediction. These biomarkers help clinicians personalize management strategies across different disease phases.

infections are highly unlikely [12]. This multicenter study stands out for validating a rapid and highly accurate assay (sCAL Turbo), with immediate translational potential for early and precise diagnosis of sJIA.

In a meta-analysis and systematic review including 10 specific studies, Altobelli *et al*. confirmed that sCal is indisputably higher in active soJIA; these very high concentrations can be found neither in other forms of arthritis nor in other causes of FUO [1]. The second significant result of the meta-analysis was a significant difference between JIA patients with active disease compared to patients with inactive disease and controls. The authors concluded that sCal represents a useful tool in JIA in order to stratify disease activity more accurately and to allow a more tailored drug choice; however, the extreme heterogeneity of the JIA populations studied, especially in terms of treatment, do not allow further conclusive data [13].

The prognostic value of sCal regarding the risk of relapse in patients with JIA has been analyzed in several studies. Currently, thanks to innovative therapies, up to 80% of children with JIA achieve inactive disease in the first year; however, a high frequency of early flares, after drug discontinuation,

occurs [9]. Residual inflammation and subclinical disease cannot be detected by conventional laboratory marker, such as CRP and ESR. Some studies have demonstrated that patients with high sCal levels, at the beginning of methotrexate (MTX) or anti-TNF treatment were more likely to have a better response after 6 or 12 months. In addition, some authors have postulated that increased sCal levels in patients with inactive disease were correlated with subsequent relapse and therefore, this parameter can be considered a sign of subclinical disease and a valid predictive marker of relapse in patients in remission as confirmed by different studies [9].

D'Angelo and colleagues investigated the potential role of sCal in a cohort of 111 nonsystemic JIA children during a follow-up of 18 months. The authors showed that, during follow-up, inactive patients, according to different sCal cut-off levels, presented different outcomes. In addition, patients with sCal values above the cut-off threshold considered, showed a higher risk of disease flare. As a consequence, sCal can be considered a marker of residual disease activity even in the absence of clinical and biological signs of inflammation [9].

Another key point of this study was the confirmation that sCal is a potential marker of good treatment response also shown in other studies. Indeed, calprotectin levels at baseline in patients who went into remission were higher than those who remained active during the follow-up [9].

More recently, the role of sCal and musculoskeletal ultrasound as predictive marker of relapse was investigated in 60 nonsystemic patients with JIA in remission to explore the potential role of SCal and Musculoskeletal ultrasound (MSUS) in predicting disease relapse risk in a group of nonsystemic (ns)-JIA patients in clinical remission [13]. The authors found that in children with JIA in remission at baseline, ultrasound (US) score and US ratio, and not only sCal protein, were associated with an increased overall risk of relapse during 18 months of follow–up [14]. In addition, US score alone was associated with the risk of early relapse at 6 months of follow-up [14]. The authors concluded that sCal, could have a role for the more precise identification of disease state than all other routine laboratory indices and in predicting relapses, but its role in daily clinical practice has yet to be defined. MSUS represents an interesting additional tool to the clinical evaluation, especially in predicting early flare. This prospective study emphasizes the added value of combining sCal with musculoskeletal ultrasound in predicting flares, enhancing precision in remission assessment. The complementary use of both calprotectin and MSUS could improve a precise definition of remission in JIA and offer real support

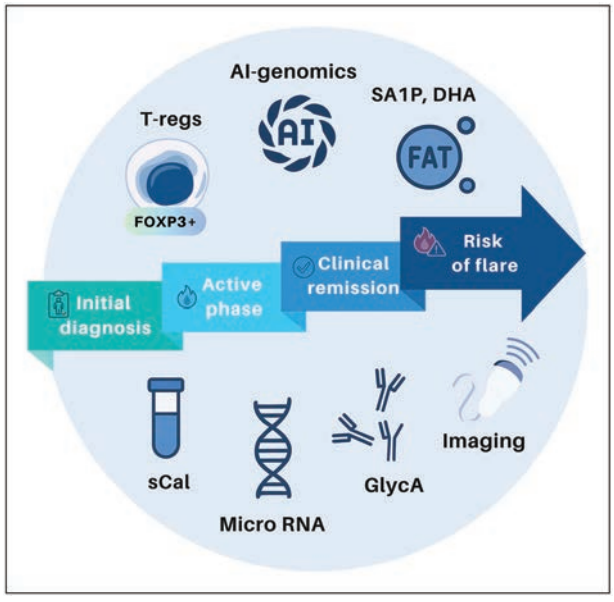

FIGURE 2. Biomarker use across the clinical course of juvenile idiopathic arthritis. This figure outlines the application of biomarkers and diagnostic tools across different disease phases in juvenile idiopathic arthritis (JIA). Serum calprotectin (sCal) supports early diagnosis and monitoring of disease activity. GlycA and metabolomic markers such as sphinganine-1-phosphate (SA1P) and docosahexaenoic acid (DHA) reflect inflammatory status and help stratify remission. Artificial intelligence-driven approaches (AI-genomics) contribute to identifying risk of flare and personalizing treatment. Musculoskeletal ultrasound (MSUS) complements clinical and serological evaluation, particularly in detecting subclinical inflammation and predicting relapse.

to clinicians in guiding therapeutic choices [14] (Fig. 2).

Biomarkers have been investigated as predictors of clinical response to guide selection of appropriate treatment for individual patients with JIA. Several studies have suggested that high levels of sCal are associated with response to both MTX and TNF inhibitors. Data from a phase 3 trial of subcutaneous abatacept in 219 patients with active p-JIA, showed that lower baseline inflammatory levels of S100A8/9, S100A12, and CRP were predictive of better response to abatacept treatment than higher levels. Moreover, decreases in these biomarker levels during the first 4 months of abatacept therapy may also predict longer term response to abatacept in these patients [8]. The authors conclude that levels of S100 proteins may be useful to predict pJIA course in children receiving abatacept therapy [8].

In conclusion, in JIA, sCal helps to assess disease activity, monitor response to treatment, and possibly predict disease course. It does not replace clinical

evaluation but can provide valuable supplemental information in the management of JIA.

Several commercial tests are available to measure sCal, including chemiluminescence immunoassay, enzyme immunoassay, and ELISA, however, the diagnostic accuracy of these tests has not been established [11].

METABOLOMICS

Metabolomics, the comprehensive analysis of metabolites in biological samples, is an emerging field in JIA research, offering insights into disease mechanisms and potential biomarkers for diagnosis and treatment monitoring. Untargeted metabolomics measures a wide spectrum of metabolites in a sample without prior knowledge of their identity, whereas targeted metabolomics focuses on quantifying specific metabolites of interest within a sample defining absolute concentration.

Limited literature exists on the metabolomic profile of plasma samples from JIA patients within the population. Kumar and colleagues recently conducted an untargeted metabolomics analysis on plasma samples from 60 treatment-naive JIA patients compared to 60 non -JIA patients, including children with functional abdominal pain and Crohn's disease [15]. The authors identified five metabolites closely associated with JIA diagnosis including sphinganine-1-phosphate (SA1P), the most distinct biomarker, X-12462 (unknown metabolite), sphingosine-1-phosphate (S1P), palmitoyl-ethanolamide (PEA), and sarcosine. These metabolites hold potential as biomarkers for diagnosing patients with JIA. In particular, SA1P emerged as a top discriminating metabolite with an AUC of 0.98, indicating its potential as a diagnostic biomarker; in addition, its role in lymphocyte trafficking could be a key mechanism contributing to chronic inflammation and disease persistence in JIA [15]. This study represents a breakthrough in JIA biomarker discovery, identifying SA1P as a novel diagnostic metabolite with exceptional diagnostic performance (AUC 0.98).

In another recent study, Known and colleagues evaluated targeted nuclear magnetic resonance metabolomic profiles of plasma in 72 children with JIA compared to 18 controls. Of the 71 metabolic biomarkers investigated, three shows clear differences between patients and controls: glycoprotein acetyls (GlycA), docosahexaenoic acid (DHA), and acetate. GlycA, a marker of cumulative inflammation, was particularly elevated in active disease, while lipid/amino acid were prominent in remission. This metabolomic profile was mostly evident in children with soJIA compared to other subtypes. These findings support GlyA as a novel marker for monitoring disease activity in soJIA [16].

Understanding the causal relationships between metabolites and JIA can provide insights into disease mechanisms. A Mendelian randomization study identified several metabolites with causal associations to JIA, including kynurenine, 3-dehydrocarnitine, cysteine, and pantothenate. These findings suggest that alterations in these metabolic pathways may contribute to the development of JIA [17].

IMPACT OF METHOTREXATE ON METABOLIC PROFILES

MTX is commonly used to treat JIA, but its efficacy varies among patients. Metabolomic analyses have shown that MTX treatment leads to significant metabolic changes. For instance, a study found that MTX was associated with increased levels of free carnitine, suggesting enhanced mitochondrial function. However, in certain JIA subtypes, such as polyarticular and systemic forms, a decrease in acylcarnitines was observed, indicating altered mitochondrial metabolism [18].

Furthermore, specific metabolites have been linked to MTX efficacy. Reductions in metabolites like dehydrocholic acid, biotin, and 4-picoline were associated with a positive clinical response to MTX, highlighting the influence of microbial and exogenous metabolites on treatment outcomes.

In conclusion, metabolomics offers a powerful tool to unravel the complex biochemical alterations associated with JIA. By identifying specific metabolic signatures and understanding their role in disease pathogenesis and treatment response, metabolomics can pave the way for personalized medicine approaches in JIA. However, further research involving larger and more patient cohorts is necessary to validate these findings and translate them into clinical practice.

MICRORNA

MicroRNAs (miRNAs) are small noncoding RNA molecules that posttranscriptionally regulate gene expression. They have been shown to play a critical role in the proliferation, maturation, and differentiation of T and B cells, thus participating in a vast network of regulatory process and immune response. In the last decades, miRNAs have become the focus of intensive investigations ranging from basic biology to clinical applications given their role in modifying gene expression and in the epigenetic regulation of multiple physiologic processes fundamental to human health, including inflammatory responses and immune cell differentiation, maturation, and functions [19]. Accumulating evidence suggests that dysregulation of specific miRNAs not only

contributes to the onset and perpetuation of JIA but also serve as potential biomarkers for disease activity and treatment response.

Several studies have demonstrated that miRNA expression profiles can distinguish JIA patients from healthy controls and, in some cases, differentiate between JIA subtypes [20]. In particular, a small group of differentially expressed miRNAs frequently recurring among the studies can be identified, such as miR-16, miR-125, miR-132, miR-146a, miR-155, and miR-223 refer to, which highlights their potential relevance in JIA, representing a potential biomarker useful for the evaluation of disease activity in JIA [20].

Uveitis occurs in up to 30% of JIA patients and mostly affects girls within the first year after the diagnosis of arthritis [21]. A correlation between miRNA expression and inflammatory process in uveitis has been demonstrated in animal models. To date, very few studies have found an association between high levels of miRNA polymorphisms and uveitis in children. For example, one study identified that the expression of miR-4485-3p was significantly increased in children with uveitis compared to children without ocular involvement.

In conclusion, miRNA represent a promising class of biomarkers in JIA, capable of reflecting disease activity, prognosis, and therapeutic response. However, significant work remains to validate their clinical utility. Emerging technologies, such as single-cell RNA sequencing and machine learning-based classifier models, may further refine miRNA-based diagnostics.

TREGS

Regulatory T cells (Tregs), primarily characterized by the expression of CD4, CD25, CD127, and the transcription factor FOXP3, play a crucial role in maintaining immune tolerance and controlling autoimmune responses [22]. Tregs changes at the site of inflammation in JIA have been well described with enrichment in synovial fluid and large heterogeneity [26]. These findings suggest that Treg dysregulation contributes to disease pathogenesis and may correlate with disease activity, severity, and response to therapy. Consequently, monitoring Treg profiles could aid in patient stratification, prediction of disease flares, and evaluation of therapeutic efficacy in JIA [22].

A preliminary study including 87 participants with all categories of arthritis, found that higher circulating Treg concentration was associated with lower ESR and better quality of life but they were not predictive of inflammatory course during follow-up [22].

A recent study demonstrated altered peripheral blood Treg signatures and subsets as an important factor which could differentiate disease progression versus remission in children with oligoarticular and rheumatoid factor-negative polyarticular JIA. The authors propose that blood Treg fitness measures could serve as a biomarker of disease progression and sustained remission in JIA [22]

EMERGING BIOMARKERS

(1) An exploratory proteomic study identified glial cell line-derived neurotrophic factor (GDNF) as a potential biomarker for pain in JIA. Elevated GDNF levels correlated with pain severity, independent of inflammation markers, suggesting its role in nociceptive pathways and potential as a target for pain management in JIA [10].
(2) Proteomic profiling of extracellular vesicles released in biological fluids has recently emerged as a minimally invasive approach to characterize children with new-onset JIA. The results of preliminary investigations define extracellular vesicle signatures able to discriminate new-onset patients from controls [23]. Moreover, they identify extracellular vesicles clusters that associate with specific clinical features stratifying subgroups of patients with different disease courses [23].
(3) C-reactive protein-to-albumin ratio (CAR) and neutrophil-to-lymphocyte ratio (NLR): in non-systemic JIA, higher CAR, and NLR levels at baseline were predictive of persistent disease activity over an 18-month period. These ratios could serve as accessible, cost-effective tools for monitoring disease progression and anticipating flares [24].

Other biomarker candidate including 14-3-3 Eta protein, selenium metabolism, antiα-1,4-D-polygalacturonic acid (PGA) antibodies, chondroitin/dermatan sulfate, IGF1, IGFBP3, urokinase plasminogen activator receptor, are being studied [25–29].

However, for these new biomarkers, evidence is insufficient to draw any conclusions about their implication in JIA, owing to small sample size and varied results across different studies.

ARTIFICIAL INTELLIGENCE-POWERED JUVENILE IDIOPATHIC ARTHRITIS BIOMARKERS

The growing utilization of artificial intelligence tools is leading to a rapid recognition of JIA biomarkers. The opportunities offered by these fast-developing

technologies consist in identifying hidden patterns, diagnostic tools, feature selections, and immune-related key genes by employing supervised and unsupervised machine learning models. While supervised machine learning algorithms utilize labeled datasets containing already classified data, such as diagnostic images and patient classification to train algorithms, unsupervised machine learning models employ unlabeled data to identify underlying associations and patterns. Both approaches have recently been developed for discovering and identifying key biomarkers in JIA.

As an example, mixed models utilizing supervised and unsupervised approaches in polyarticular JIA identified the genes *PHLDA1, EGR3, CXCL2*, and *PF4V1* as key actors in disease progression and prognosis [30], while transcriptomic signatures of classical monocytes were identified based on the hub genes *PLAUR, IL1B, IL6, CDKN1A, PIM1*, and *ICAM1* as drivers of chronic hyperinflammation, revealing heterogeneity with two patient clusters exhibiting varying levels of inflammation [31]. A similar approach was utilized in identifying the four genes *SOCS3, JUN, CLEC4C*, and *NFKBIA* as drivers of inflammation in JIA patients in a previous study [32▪]. Diagnostic models have also been developed for systemic-onset JIA, such as the 'Th2/Th17 classifier', based on Mendelian randomization and transcriptome examination through multiple machine learning approaches, also highlighting the role of *HRH2* as a disease biomarker [33]. Different authors developed a genetic-based diagnostic model for systemic-onset JIA through the hub genes *ALDH1A1, CEACAM1, YBX3*, and *SLC6A8*, promoting the possible role of ferroptosis and mitophagy in the disease pathogenesis [34]. However, machine learning-based diagnostic models are still subject to concerns regarding the potential bias in training datasets due to small sample size, varying disease activity in patient groups, and often a lack of employment of explainable artificial intelligence (XAI) in the methodology [24]. JIA diagnostic models have also been developed using approaches not based on genetics, such as a recent model based on fecal microbiota, where XAI techniques identified Proteobacteria and genus UCG-001 as the most important contributors [35]. This is one of the first studies to integrate explainable artificial intelligence with microbiota data for non-invasive JIA diagnosis, highlighting novel microbial signatures. A promising deep-learning classification model has also been recently developed based on blood pool images of [99mTc] Tc-MDP scintigraphy, with promising results in identifying inflamed from healthy joints despite a certain variability in image quality and a lack of external validation [36]. Noteworthily, a machine learning algorithm built on joint acoustic emissions successfully classified JIA and healthy knees, resulting in a cheap and easy-to-use automated assessment and underscoring the potential of this novel digital biomarker [37]. The same author group also successfully identified Achilles tendon inflammation in enthesitis-related arthritis by using a mixed supervised and unsupervised machine learning approach by employing active vibrational sensing. Nevertheless, the main limitation of such studies relies on small dataset size and lack of external validation [38].

CONCLUSION

The search for new biomarkers in JIA is rapidly evolving, with promising candidates emerging from molecular, proteomic, and cellular studies. While several markers, such as S100 proteins and miRNAs, are nearing clinical applicability, further research is needed to validate their utility and integrate them into diagnostic and therapeutic algorithms.

Integration of multiomic data (genomics, transcriptomics, proteomics, and metabolomics) using systems biology approaches and machine learning holds great promise for identifying composite biomarker signatures. Such biomarkers could facilitate earlier diagnosis, personalized therapy, and prediction of flares or remission in JIA. Additionally, biobanking and international consortia (e.g. PRINTO and CARRA) are crucial for advancing biomarker discovery and validation.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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OPEN

CURRENT OPINION

Human genetics of Whipple's disease

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Purpose of review
Whipple's disease (WD), triggered by *Tropheryma whipplei* (*T. whipplei*), is a rare, chronic, inflammatory, systemic infectious disease that typically manifests in adults. The most frequent initial manifestations include arthritis, followed by diarrhea, abdominal pain, and weight loss. Half the world's population is exposed to *T. whipplei*, but only one in a million develop WD. This suggests that acquired or inborn errors of immunity (IEI) may underlie WD. Anti-TNF treatment is a well established risk factor for flare-ups of WD.

Recent findings
We have also reported two rare IEI in patients with WD. Six WD patients from two unrelated kindreds were found to have autosomal dominant IRF4 deficiency acting via a mechanism of haploinsufficiency. These patients were otherwise healthy. In addition, a single patient with a history of WD and other infections was found to have autosomal recessive CD4 deficiency.

Summary
Rare IEI can underlie WD. Human genetic studies of patients with WD are warranted for the development of precision medicine for affected kindreds and to improve our understanding of the pathogenesis of this rare infectious disease.

Keywords
CD4 deficiency, genetics, IRF4 deficiency, *Tropheryma whipplei*, Whipple's disease

INTRODUCTION

Whipple's disease (WD) is a rare chronic disease resulting from infection with the intracellular bacterium *Tropheryma whipplei* (*T. whipplei*) [1–3]. Epidemiologically, patients with WD are typically men of European descent, aged between 50 and 60 years [4▪▪]. *T. whipplei* is ubiquitous and transmitted orofecally [4▪▪]. It is estimated that 50% of the general population is exposed to *T. whipplei* during their lifetime, but that only one individual in a million develops WD [4▪▪]. "Classical" WD was originally recognized clinically as associated with systemic and digestive manifestations, with or without localization of the infection in the joints and central nervous system [4▪▪,5,6]. WD has also recently been associated with infections at different sites with no signs of gastrointestinal involvement [4▪▪,5–12]. These chronic localized *T. whipplei* infections may take the form of endocarditis, encephalitis or uveitis [4▪▪,5–13]. However, chronic focal joint infections resulting in intermittent arthritis are the most frequently observed [4▪▪,5,7,8]. Indeed, in more than 80% of cases, intermittent arthritis or arthralgia are the first manifestations, preceding the occurrence of other clinical signs of the disease by several years [4▪▪,5,7,8]. Arthritis can be mono, oligo, or polyarticular and associated with either axial or peripheral involvement [7]. Spondylodiscitis, bursitis, and/or tenosynovitis are seen in some patients, explaining misdiagnosis as rheumatic disorders in some cases [14,15]. Classical WD is diagnosed on the basis of a histological examination, with hematoxylin and eosin (H&E) and periodic-acid-Schiff (PAS) staining of a duodenal biopsy specimen revealing infiltration of the mucosa with foamy macrophages containing *T. whipplei* [4▪▪,16,17,18▪,19]. Isolated WD is diagnosed on the basis of positive

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KEY POINTS

- Whipple's disease is a rare rheumatological and infectious disease.
- Rare inborn errors of immunity can underlie Whipple's disease.
- Human genetic studies should be performed in patients with Whipple's disease, for both medical and scientific reasons.

PCR detection of the bacterium in sterile compartments [4▪▪,20▪]. The disease is marked by a risk of relapse when antibiotics are stopped, and lifelong antibiotic prophylaxis is therefore recommended. The standard treatment is based on lifelong antibiotics [4▪▪], initially associated with hydroxychloroquine during the first year. WD is, thus, a rare adult-onset infectious disease with frequent rheumatological involvement.

THE ENIGMA OF WHIPPLE'S DISEASE PATHOGENESIS

Intriguingly, little is known about the pathogenesis of WD other than the requirement of the *T. whipplei* bacterium *in vivo* and the ability of this bacterium to infect human macrophages *in vitro* [4▪▪,16,17,18▪]. The inoculation of mice with *T. whipplei* results in an acute transient infection that does not mimic WD and is therefore unsuitable for use as a model [21]. One striking finding from epidemiological studies, which have estimated that 50% of the general population is exposed to *T. whipplei* in their lifetime, is that this bacterium replicates asymptomatically in the gut in 2–11% of people, with only about one individual in a million going on to develop WD [4▪▪]. The rarity of WD, despite widespread exposure to *T. whipplei*, suggests that there are host determinants of this disease. What drives the rare cases of WD when so many *T. whipplei*-infected individuals remain asymptomatic? Treatment with various targeted immunotherapies has been shown to modify WD outcome. Adverse effects of interferon (IFN)-α/β on WD have been reported *in vitro* [22]. Conversely, treatment with recombinant IFN-γ, a cytokine also known to be the macrophage activation factor [23], has been reported to be effective *in vivo* in patients with antibiotic-resistant WD [24]. Anti-TNF therapy has been associated with the occurrence of WD flare-ups in several patients, sometimes with life-threatening manifestations [25–28]. A recent study found that exposure of THP-1-derived macrophages to TNF blockers *in vitro* increases *T. whipplei* replication [18▪]. These findings suggest that host immunity, including TNF and macrophages in particular, is essential to control *T. whipplei*. However, only a subset of WD cases can be explained by treatment with TNF blockers.

TOWARD A GENETIC HYPOTHESIS FOR WHIPPLE'S DISEASE

According to the genetic theory of infectious diseases, human genetic variability largely determines the clinical features and outcome of infections [29–31]. Rare familial cases of WD have been described: brother and sister; father and daughter, brothers; grandmother and uncle [32–34]. Reinfection with another strain of *T. whipplei* in a patient with WD also provides evidence of individual lifelong genetic susceptibility [4▪▪,35]. HLA studies in patients with WD have identified no association [36]. Monogenic diseases affecting immunity are known as inborn errors or immunity or IEIs [37]. The most severe IEIs are associated with early-onset infections to a broad range of microorganisms [37]. However, some IEIs underlie susceptibility to a restricted class of microorganisms [37]. The prototypic example is Mendelian susceptibility to mycobacterial diseases (MSMD), a disorder characterized by clinical disease due to restricted susceptibility to nontuberculous mycobacteria or other intramacrophagic pathogens [38–43]. Half the patients with MSMD have germline pathogenic variants of genes encoding proteins involved in the production of IFN-γ (by lymphoid cells), or the response to IFN-γ (by myeloid cells), or both [38–43]. Inherited TNF deficiency, which is mimicked by anti-TNF therapies, can lead to WD flare-ups [25–28] and has been shown to underlie susceptibility to the more virulent *Mycobacterium tuberculosis* in two adults [44]. We therefore studied patients with WD, testing the hypothesis of an underlying IEI.

AUTOSOMAL DOMINANT IRF4 DEFICIENCY BY HAPLOINSUFFICIENCY

We first investigated a multiplex French family including four WD patients, two of whom had joint involvement [45]. The WD patients were of both sexes and belonged to two generations, with ages between 69 and 92 years. A genetic investigation was performed to test the hypothesis of autosomal dominant (AD) inheritance with incomplete penetrance. All of the patients were heterozygous for a rare missense variant (p.Arg98Trp) affecting the DNA-binding domain (DBD) of IRF4 [45]. This variant was also carried by five infected but asymptomatic individuals aged 24 –82 years from the same family. The

variant was loss-of-function in terms of DNA binding and transcriptional activity in various reporter assays [45]. The mechanism of the deficiency was haploinsufficiency. Peripheral blood mononuclear cells from the patients displayed an impaired transcriptomic response to *T. whipplei* [45]. In 2024, we identified a second French kindred with AD IRF4 deficiency in a son and his mother, presenting Whipple's arthritis at the ages of 35 and 60 years, respectively [46▪]. Both patients were heterozygous for a missense IRF4 variant (p.Arg25Ser) also affecting the DBD. In an overexpression system, this variant was hypomorphic in terms of binding to DNA and transcriptional activity. All the heterozygotes for p.Arg25Ser or p.Arg98Trp with WD identified were otherwise healthy and had never had any other history of severe infectious diseases [45,46▪]. All WD patients with AD IRF4 deficiency were successfully treated with doxycycline and chloroquine [45,46▪]. A population genetic study to estimate the prevalence of deleterious IRF4 variants was performed with the gnomAD database as a surrogate for the general population [45]. Only six of the $n = 153$ IRF4 variants from gnomAD tested were loss-of-function and only one variant was hypomorphic. These findings suggest that the prevalence of biochemically deleterious IRF4 variants in the general population is less than 4×10^{-5}, fully consistent with the prevalence of WD [45]. Two other forms of AD IRF4 deficiency have since been reported [47,48]. The variants concerned had a more profound biochemical impact, with negative dominance and the creation of a new function, and the patients had a much broader clinical phenotype at a young age. It is possible that these individuals will develop WD later in life. Overall, autosomal dominant IRF4 deficiency by haploinsufficiency is rare in the general population and underlies restricted susceptibility to WD, with an estimated penetrance across the two reported kindreds of 50% [45,46▪] (Table 1).

AUTOSOMAL RECESSIVE CD4 DEFICIENCY

In 2024, we also described a single patient with WD in a cohort of patients with autosomal recessive CD4 deficiency [49▪▪]. Rare biallelic variants of *CD4* have been identified in seven patients aged 5–61 years from five unrelated families of Colombian, Portuguese, Palestinian, and American descent [49▪▪,50,51]. Three of these patients displayed infections to human papillomaviruses (HPVs; extensive verrucous dermatitis, extensive, or recalcitrant warts), whereas various other infectious diseases were reported in single patients, including BCG-itis, tuberculosis, cryptosporidiosis, and viral pneumonia [49▪▪,50,51]. In addition, one patient was diagnosed with *bona fide* classical WD at the age of 52 years [49▪▪]. This patient was successfully treated with doxycycline and chloroquine, leading to the clearance, after 5 years, of *T. whipplei* in the feces and saliva. The seven patients were homozygous for variants of *CD4* impairing the expression of the canonical CD4 isoform [49▪▪]. They completely lacked $CD4^+$ T cells but had abnormally high counts of double-negative ($CD4^-CD8^-$) $\alpha\beta^+$ T cells. However, these cells had only a modest cell-intrinsic impairment of the ability of naive $TCR\alpha\beta^+CD8^-$ T cells to differentiate into T_H1-type, T_H17-type, and IL-9^+ effector cells [49▪▪]. They also displayed a normal response to HLA-class II antigens and were able to induce B cells. Finally, the αβ T-cell repertoire was also normal [49▪▪]. CD4 is also known to be expressed by a subset of myeloid cells that have never yet been investigated in the context of autosomal recessive CD4 deficiency [49▪▪,50,51]. These immunological investigations suggested that CD4 was redundant for most T helper functions, consistent with the lack of broad susceptibility to infections in the patients. One individual homozygous for a pathogenic CD4 variant was even completely asymptomatic. Overall, CD4 deficiency underlies susceptibility to WD, HPV, and a few other microorganisms (Table 1).

Table 1. Genetic diseases associated with Whipple's disease

Locus	*IRF4*	*CD4*
Inheritance	Autosomal dominant by haploinsufficiency	Autosomal recessive
Nb of individuals/kindreds carrying the variants	11/2	6/5
Number of reported patients/kindreds with WD	6/2	1/1
Living country of patients with WD	France	Portugal
Features of WD	Classical WD	Classical WD
Other associated clinical features of the deficiency than WD	None	Infections to HPV

HPV, human papillomavirus; WD, Whipple's disease.

CONCLUSION

WD is difficult to diagnose and treat [4▪▪]. Without antibiotic treatment, WD can be devastating, progressing to irreversible organ damage (affecting the joints and the brain in particular), or death [4▪▪,7,8]. The identification of monogenic lesions underlying WD is essential, to make it possible to develop precision medicine for patients and their families, including regular and ad hoc follow-up of patients and early screening for the disease in relative carrying potentially pathogenic variants. In addition, WD provides a unique model for studies of human intestinal immunity to a common saprophytic bacterium. Autosomal dominant IRF4 and autosomal recessive CD4 deficiencies are the only genetic diseases identified to date in patients with WD [45,46▪,49▪▪]. It is tempting to speculate that other IEI, known and unknown, may also underlie WD. There may be underreporting of such cases because patients with known IEIs, such as CD4 deficiency, are already on antibiotic treatment for other infections, have undergone hematopoietic stem cell transplantation, or die prematurely before the typical age at onset of WD [37]. There are probably also as yet unidentified IEI underlying WD, such as AD IRF4 haploinsufficiency. Several questions need to be addressed in patients with WD in the near future. First, what is the cellular basis of WD? In autosomal recessive CD4 [49▪▪] and WD IRF4 deficiency by haploinsufficiency [45,46▪] deficiencies, the pathogenesis of WD remains unclear and may involve T helper cells capable of contributing to the killing of *T. whipplei* infected myeloid cells, or myeloid cells in which *T. whipplei* can replicate [4▪▪,18▪]. The identification of new IEI in patients with WD will help us to assemble the puzzle of cellular immunity to *T. whipplei*. Second, why is there a male predominance among patients with WD [4▪▪]? The identification of genetic diseases with X-linked inheritance may provide an explanation. Third, could autoantibodies against components of host defense underlie the onset of WD? Such autoantibodies have been implicated in several infectious diseases [52]. Screening for autoantibodies against TNF may be of interest [25–28]. Fourth, why does WD onset occur in midlife, and not during childhood, even in patients with known IEI? Prospective follow-up of *T. whipplei* carriage in the presence and absence of identified IEI could shed light on the dynamics of tissue invasion by *T. whipplei*.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Pathogenesis of juvenile idiopathic arthritis

Megan M. Simonds[a] *and AnneMarie C. Brescia*[b]

Purpose of review
To provide an overview of the most recent updates in the pathogenesis of juvenile idiopathic arthritis (JIA).

Recent findings
Recent genetic studies on the pathogenesis of JIA have revolved around using *in silico* multiomic analyses to identify genetic variants that may play a role in the pathogenesis of JIA. Genome wide association studies (GWAS) have provided bulk-RNA and single cell-RNA sequencing datasets to identify groups of enhanced genes, signaling pathways, and other genetic variants. These data have led to the exploration of processes that regulate T-cell receptor signaling and T-cell differentiation, as well as genes linked to interferon-gamma signaling. Immune dysregulation is a major driver of JIA pathogenesis and neutrophil extracellular traps (NETs) are emerging as contributors to disease progression. The contribution of immune cells to the microenvironment in the inflamed joints of patients with JIA may hold the key to how inflammation is regulated and how the immune response from these cells contributes to disease progression.

Summary
This review will focus on emerging insights from large scale multiomic studies, which reveal pathways involved in JIA pathogenesis. In addition, recent studies have identified immune dysregulation, especially in the microenvironment of the inflamed joint.

Keywords
juvenile idiopathic arthritis, pathogenesis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) comprises seven subtypes in the International League of Associations for Rheumatology (ILAR) classification [1]. These subtypes are classified as systemic, oligoarticular, polyarticular rheumatoid factor negative, polyarticular rheumatoid factor positive, psoriatic, enthesitis-related, and undifferentiated arthritis. Treatment of inflammatory arthritis has been aimed at putting out fires of known upregulated inflammatory mediators. We have not been able to quite get our finger on the underlying pathologic mechanisms that result in inflammatory arthritis. It is key to understand both the genetic variations and immune system perturbations that result in inflammatory arthritis to be able to treat this disease in a more targeted and effective manner. With our advances in technology, critical steps forward have occurred in the past 18 months.

Systemic onset JIA, although included in the ILAR classification system, is considered to be an auto inflammatory disease, likely of different pathogenesis than the other subtypes of JIA. Review of this work is outside the scope of this review; however, we would suggest several recent comprehensive reviews [2▪,3▪] and original work [4▪–7▪] on this topic, published in the past 18 months.

GENETIC APPROACHES TO ELUCIDATING THE PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS

Recent genetic studies on the pathogenesis of JIA have revolved around using *in silico* multiomic analyses to identify genetic variants like single nucleotide polymorphisms (SNPs) or loci on chromosomes that may contain one or more genes that potentially play a role in the pathogenesis of JIA. Several computer-based modeling approaches have emerged as

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KEY POINTS

- Juvenile idiopathic arthritis is still of unclear etiology.
- To develop new treatment approaches we need to understand the underlying genetic variations and immune systems perturbations.
- Understanding underlying mechanisms of pathogenesis will allow individualized treatment approaches.

revolutionizing methods in precision medicine for identifying significant genes that promote and sustain disease progression. Genome wide association studies (GWAS) have provided bulk-RNA and single cell-RNA sequencing (sc-RNAseq) datasets that can be used in promising statistical analyses to identify groups of enhanced genes, signaling pathways, and other genetic variants that contribute to JIA pathogenesis.

PERIPHERAL BLOOD ANALYSIS PROVIDES GENETIC INSIGHTS INTO PATHOGENESIS

Liu *et al.* examined immune cells to determine underlying causes of JIA (Fig. 1) [8▪▪]. T-cell receptor (TCR) and B-cell receptor (BCR) repertoires were constructed from Gene Expression Omnibus (GEO) datasets for 6 JIA PBMCs and two healthy controls (HC) from bulk-RNA and single cell-RNA sequencing (sc-RNAseq) using TRUST4 algorithm [9,10]. Unique nucleotide sequences, or clonotypes were defined as small, medium, large, and hyperexpanded [8▪▪]. Data showed clonotypes with small frequencies were significantly increased in JIA when compared to HC for both TCR and BCR. This data suggests that there is less heterogeneity in TCR and BCR of JIA than HC, resulting in more specific T-cell and B-cell response that includes the rapid multiplication of immune cells in JIA [8▪▪].

Single-cell analysis on peripheral blood monocyte cells (PBMCs) from 2 HC and 6 JIA revealed CD14 monocyte-like cells were present at a significantly higher percentage than other cell types in JIA compared to HC [8▪▪]. Characterization of T-cell and B-cell subpopulations revealed differentially expressed genes (DEGs) and pathways in JIA. Increased monocyte-like phenotype could correlate with JIA disease progression. Modules created by high dimensional Weighted Correlation Network Analysis (HdWGCNA) showed significant enrichment in T-cell module three and B-cell module two, revealing functional roles in biological process, cellular component, and molecular function [8▪▪]. Cell to cell interactions in T-cell subgroups revealed a significant role for the macrophage migration inhibitory factor (MIF) signaling pathway in JIA. Monocle2 software revealed variation in cell differentiation when examining T-cells and B-cells and single-cell regulatory network inference and clustering (SCENIC) analysis demonstrated a significant role for transcription factors in naïve $CD4^+$ T cells, central memory $CD4^+$ T cells, and naïve B cells [8▪▪].

Liu *et al.* presented compelling data suggesting that TCR and BCR contain DEGs and signaling pathways, like MIF signaling, that could have significant impact on determining the pathogenesis for JIA. Their comprehensive analysis provides a formative argument for performing functional biology on the genes and pathways determined by their studies.

Pudjihartono *et al.* focused on blood-based gene regulation to identify genes that have novel causal relationships with disease traits in JIA (Fig. 1). Two sample Mendelian randomization (MR) revealed fifty-two genes reputed to have a causal relationship to JIA [11▪▪]. Of the 52 genes, 51 genes had not previously been associated with JIA. Of the 52, 44 were associated with the human leukocyte antigen (HLA) region and confirmed the role of HLA-associated genes in the pathogenesis of JIA. Authors identified shared traits with known diseases like type I diabetes, multiple sclerosis, psoriatic arthritis, Hodgkin lymphoma, and chronic lymphocyte leukemia. They also identified traits of inflammatory pathways like C-reactive protein and metabolic traits like platelet-to-lymphocyte ratio, and sphingomyelin levels. Immune dysregulation is a major driver of JIA pathogenesis; specifically, lymphotoxin A (LTA) and LTB were identified as key dysregulated genes and suggest lymphotoxin signaling could play a pivotal role in JIA pathogenesis.

LTA and LTB are members of the tumor necrosis factor superfamily. Targeting the lymphotoxin signaling pathway in JIA could provide insight into the immune response seen in patients with JIA and identify how this signaling pathway contributes to disease development and progression.

GENOME WIDE ASSOCIATION STUDIES INTEGRATE MULTI-OMIC APPROACHES TO IDENTIFY KEY CONTRIBUTORS TO JUVENILE IDIOPATHIC ARTHRITIS PATHOGENESIS

Fan *et al.* performed GWAS combining two cohorts totaling 4550 JIA genomes and 18 446 control genomes were analyzed, revealing fourteen genome-wide significant loci, four of which were novel to this analysis (Fig. 1) [12▪▪]. Integrating multiple *in silico* methods and datasets, authors identified

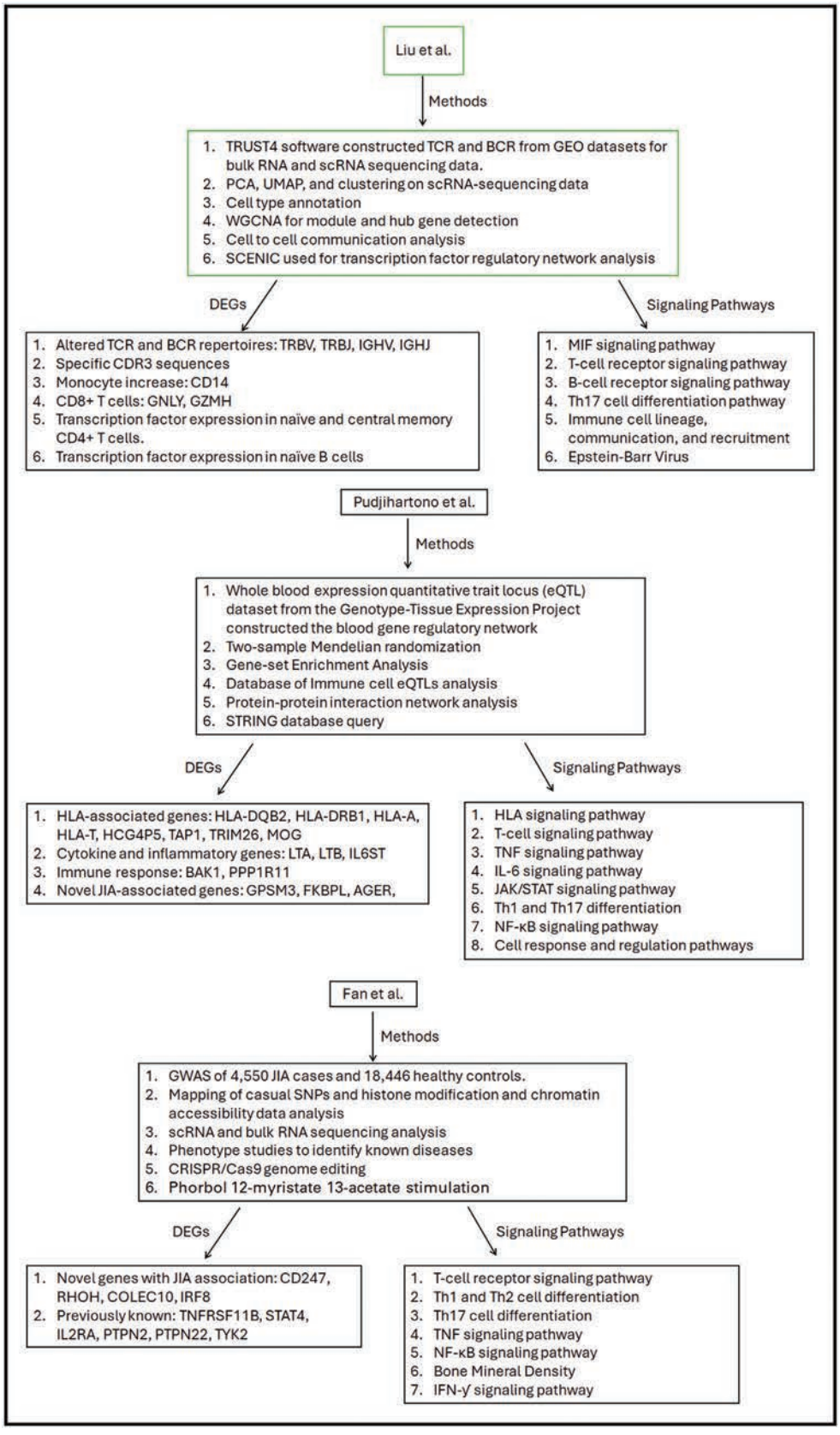

FIGURE 1. Summary flow chart of methods and major findings. Detailed illustration of methods used in multiomic genetic studies described in review. Figure describes methods used by each reviewed author and the top differentially expressed genes and signaling pathways determined by their genetic studies.

twenty-three genes within the novel loci, singling out CD247, which is part of the TCR–CD3 complex which causes T-cell proliferation, differentiation, and cytokine production and can contribute to the initiation and perpetuation of JIA. IRF8 is identified as a critical gene in JIA pathogenesis because of its role in interferon gamma signaling, a key pathway in immune regulation and inflammation.

When analyzing biological function, the four loci showed phenotypic traits of other known diseases. Two SNPs (rs2280381 and rs2450083) had significant overlap with systemic lupus erythematosus and rheumatoid arthritis. SNP rs2450083 had significant overlap with traits associated with bone mineral density (BMD). JIA patients tend to have lower BMD [13]. Authors identified COLEC10 and TNFRSF11B as having a strong genetic link between JIA and BMD [14,15]. COLEC10 is involved in the immune system and bone growth while TNFRS11B encodes osteoprotegrin, which inhibits osteoclast activity and prevents bone loss.

SNP rs13136820 was noted to influence immune signaling pathways [12▪▪]. CRISPR/Cas9 was used to delete a region of rs13136820 in K562 cells. APBB2, RHOH, and SMM14 gene expression was significantly altered by this deletion. Gene set enrichment analysis (GSEA) comparing K562 cells with the deletion and unaltered K562 cells showed that, in cells with the deletion, immune pathways like Th-cell differentiation, TNF signaling, nuclear factor (NF)-κB, and interleukin (IL)-17 signaling, were upregulated, suggesting that rs13136820 may play a critical role in immune responses in JIA.

Based on these findings, further functional studies were performed, specifically, treating K562 cells with the deletion and unaltered cells with phorbol 12-myrustate 13-acetate (PMA) to mimic an inflammatory environment. APBB2, RHOH, and SMM14 gene expression levels increased even more in K562 cells with the deletion treated with PMA. Fan *et al.* suggest a deletion in rs13136820 mimic mechanisms observed in regulatory T-cells (Tregs) of JIA patients. Authors analyzed transcriptome differences in patients with active JIA and found that RHOH was differentially expressed when comparing active JIA to healthy controls. RHOH may have a significant contribution to the pathogenesis of JIA because of its known role in T-cell receptor signaling [16,17].

Tissue enrichment analysis of integrated genomic and single-cell data identified synovial fibroblasts, T-lymphocytes, myeloid cells, ileum, oropharynx, and bones [12▪▪]. $CD4^+$ and $CD8^+$ T-cells, natural killer cells, dendritic cells, and antigen-representing B cells were most notable when analyzing single cell data [12▪▪]. These findings suggest that specific cell types play a critical role in JIA pathogenesis.

In these studies, Fan *et al.* identified key genes and critical pathways that could contribute to JIA pathogenesis. Specifically, processes that regulate TCR signaling and T-cell differentiation, as well as genes linked to interferon-gamma signaling, were identified. Novel associations with BMD suggest that bone metabolism could also be important when examining how JIA develops and progresses.

Studies such as the ones described here provide the steppingstones for future functional studies that could lead to not just elucidating the pathogenesis of JIA but also provide potential therapeutic candidates for more targeted treatment of disease.

IMMUNE PERTURBATIONS

Several immune studies have recently emerged to elucidate the pathogenesis of JIA. Specifically, immune cells have emerged as a promising topic of study in peripheral blood (PB) and synovial fluid (SF). Their contribution to the microenvironment in the inflamed joints of patients with JIA may hold the key to how inflammation is regulated and how the immune response from these cells contributes to disease progression.

T-CELLS FROM PERIPHERAL BLOOD AND SYNOVIAL FLUID IDENTIFY KEY GENES AND PATHWAYS IN PATHOGENESIS

Koutsonikoli *et al.* performed flow cytometry on $CD4^+$ and $CD8^+$ T-cells from PB and SF samples from JIA and HC to investigate programmed-cell-death-protein 1 (PD1) expression on these cell types, as well as ELISA to measure soluble PD1 (sPD1) in PB and SF samples [18▪▪]. PD1 is an immune checkpoint that regulates immune response by inhibiting apoptosis of other cell types by regulatory T-cells. $CD4^+$ and $CD8^+$ T-cells from JIA PB had higher expression of PD1 protein compared to HC and patients with active disease expressed more PD1 protein than patients with inactive disease [18▪▪]. PD1 expression on $CD4^+$ and $CD8^+$ T-cells from SF correlated to disease activity. As more joints were affected based on subtype, PD1 expression increased [18▪▪]. Interestingly, sPD1 expression was significantly elevated in SF compared to PB which suggests sPD1 is primarily localized to affected joints, but expression did not have significant differences based on disease activity [18▪▪]. This finding suggests that despite upregulation of PD1 signaling in T-cells, inflammation in affected joints persists. This pathway is worth further consideration as increased PD1 expression has been correlated with disease activity in rheumatoid arthritis (RA) [19,20].

Kozlova *et al.* measured a wide range of interleukins using ELISA in PB samples of JIA patients and

compared expression of these proteins to HC samples [21▪▪]. Pro-inflammatory interleukins were divided into three groups: IL-2 family members, IL-3 family members, and those not included into a family. They also measured anti-inflammatory interleukins IL-4, IL-10, IL-13, and IL-27. All interleukins measured have been shown previously to play a role in the pathogenesis of JIA based on literature. Overall, the findings in this study demonstrate that no single protein or family of proteins causes JIA. A more global approach to studying immune response in JIA is necessary to understand the underlying mechanisms of inflammation and disease progression. Specifically, IL-5, IL-9, IL-10, IL-15, IL-17F, and IL-27 were expressed at three times the level in JIA samples when compared to HC samples, demonstrating that no single family of interleukins is responsible for the adaptive immune response in JIA [21▪▪]. Data also suggests the anti-inflammatory interleukin expression of IL-10 and IL-27 increases in response to pro-inflammatory expression of IL-5, IL-9, IL-15, and IL-17F in JIA [21▪▪]. While many studies show that these cytokines play a role in the etiology of JIA [22–26], the mechanisms behind which these interleukins work should be investigated further to reveal the underlying causes of disease.

CREB-binding protein (CBP) and P300, a histone acetyltransferase, are well characterized proteins that function as co-activators in cell signaling and play a role in T-cell development and differentiation [27]. Studies have shown that inhibition of this signaling can suppress $CD4^+$ T-cell activation in certain cancers and other immune system disorders [28,29]. Picavet *et al.* demonstrate, through changes in both gene and protein expression in PB and SF mononuclear cells that inhibitors directed toward CBP/P300 suppresses not just $CD4^+$ T-cell activation in PB of JIA samples but also in synovial fluid mononuclear cells (SFMCs) which are found in affected joints of patients with JIA [30▪▪]. This work provides compelling evidence that CBP/P300 signaling plays a significant role in the pathogenesis of JIA through T-cell activation and that inhibiting CBP/P300 prevents downstream expression of pro-inflammatory chemokines and other inflammatory proteins expressed by T-cells which could attenuate disease progression in JIA.

NEUTROPHIL EXTRACELLULAR TRAPS PLAY A ROLE IN PATHOGENESIS

Neutrophils also have been shown to play a role in the pathogenesis of JIA. Specifically, neutrophil extracellular traps (NETs) are emerging as contributors to disease progression. While NETs are known to trap pathogens during an infection [31], studies show that they also play a role in inflammation and autoimmune diseases like RA [32]. Heshin-Bekenstein *et al.* performed a pilot study that demonstrated isolated neutrophils from oligoarticular, but not polyarticular, JIA patients have increased formation of NETs, concluding that NETs may contribute to specific disease subtype [33▪▪]. Similarly, in a larger study performed by Tang *et al.*, neutrophils isolated from oligoarticular, polyarticular, and enthesitis-related arthritis treated with either tumor necrosis factor alpha (TNFα) or PMA generated more NETs than neutrophils from HC [34▪▪]. Authors further showed that when treated with TNFα inhibitors, NET formation decreased [34▪▪]. Taken together, this data suggests that neutrophils and formation of NETs plays a role in disease development and progression in JIA.

CONCLUSION

Unraveling the pathogenesis of juvenile idiopathic arthritis is critical to discovering new therapeutic targets and even considering preventive interventions. With our newer technologies, there have been tremendous strides made in the past 18 months to reveal underlying genetic predisposition to the disease and in comprehending the immune perturbations that result in progression of disease. With the ability to analyze large datasets and integrate multiple methods, we have seen the emergence of new signaling pathways to target. The data within this manuscript provides a formative argument for performing functional biology on the genes and pathways determined by these studies.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Evolution of the axial spondyloarthritis disease activity score and uptake in clinical practice

Saad Ahmed[a] *and Pedro M. Machado*[b,c,d]

Purpose of review
This review outlines the development of the axial spondyloarthritis disease activity score (ASDAS) as a composite index to assess disease activity in axial spondyloarthritis (axSpA) and guide treatment decisions. Our review describes the iterative process by which the ASDAS was validated and its cut off values and improvement scores developed. We compare the ASDAS to the Bath ankylosing spondylitis disease activity index (BASDAI) as a tool for measuring disease activity in axSpA and how its better measurement properties have led to its widespread use in clinical and research settings.

Recent findings
Recent international guidelines have recommended the use of the ASDAS as a tool for measuring and monitoring disease activity. ASAS has changed the nomenclature so that ASDAS is based on CRP values whereas ASDAS-ESR retains its original meaning. The BASDAI can be employed as an alternative tool when using the ASDAS is not possible. The ASDAS now forms an important outcome measure in clinical trials and aiming for ASDAS remission has been shown to retard radiographic progression in axSpA.

Summary
The ASDAS demonstrates improved measurement properties, including greater validity and sensitivity to change, compared to single item variables. It offers a unified metric that enables healthcare professionals to collaborate and communicate more effectively about disease activity and treatment response to interventions in axSpA.

Keywords
axial spondyloarthritis, axial spondyloarthritis disease activity score, bath ankylosing spondylitis disease activity index, disease activity, patient reported outcomes

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton. It includes patients who have developed structural damage in the sacroiliac joints or spine (visible on radiographs), termed radiographic axSpA (r-axSpA), and those without, termed non radiographic axSpA (nr-axSpA) [1▪].

Disease activity in axSpA can be quantified by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [2] or the Axial Spondyloarthritis Disease Activity Score (ASDAS).

The ASDAS used to stand for the Ankylosing Spondylitis Disease Activity Score but the change in terminology to reflect a broader understanding of axSpA has led to it being renamed the Axial Spondyloarthritis Disease Activity Score. For the purposes of this manuscript we will refer to the ASDAS as the Axial Spondyloarthritis Disease Activity Score [3]

The ASDAS is a well validated instrument used to assess disease activity, both in r-axSpA and nr-axSpA, and is extensively used in both clinical and research settings [4,5]. The ASDAS is the recommended instrument for assessing disease activity in axSpA [6▪▪] and plays an increasingly prominent role in clinical trials assessing the efficacy and safety of new treatments.

In this review, we describe the development of the ASDAS as the most appropriate instrument for the monitoring of disease activity in axSpA and compare it to the historically used BASDAI. We

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KEY POINTS

- The axial spondyloarthritis disease activity score (ASDAS) is the most appropriate instrument to measure disease activity in axSpA and has been recommended by the 2022 ASAS-EULAR recommendations for the management of axial spondyloarthritis disease activity score (ASDAS) as a composite index to assess disease activity in axial spondyloarthritis (axSpA) update.
- The ASDAS, though easy to understand, requires the availability of CRP or ESR values and other patient reported outcomes.
- The ASDAS is often used as a reference standard for different disease activity states and has well defined cut off values. Its use is recommended to monitor changes in disease activity.
- The disease activity states and cut off values are endorsed by OMERACT and have been utilized as endpoints in observational studies and RCTs.
- Though barriers exist to the routine implementation of the ASDAS in clinical practice it is a validated outcome measure that should be employed as part of a treat to target strategy in axSpA to guide treatment decisions.

outline its incorporation into clinical trial programmes and how this led to its integration in international guidelines. We then highlight possible reasons why its widespread use in clinical practice is suboptimal and how new recommendations for a standardized disease assessment of axSpA are currently being developed by the Assessment of SpondyloArthritis international Society (ASAS).

DEVELOPMENT OF THE AXIAL SPONDYLOARTHRITIS DISEASE ACTIVITY SCORE

The ASDAS is a validated outcome measure recommended by ASAS for assessing disease activity in axSpA [7]. It is a composite five-item score that incorporates three items of the BASDAI – spinal pain, peripheral joint pain/swelling and duration of morning stiffness – along with the patient's global assessment of disease activity. An acute phase reactant, either CRP or ESR, is also included. The ASDAS therefore includes four patient reported outcomes (PROs) and a serologic marker of inflammation; the ASDAS with CRP is the preferred version. The ASDAS was developed through a Delphi process by ASAS members and only domains receiving 80% of agreement were taken forwards. The methodology was similar to that used for the development of the disease activity score (DAS) in rheumatoid arthritis (RA) with a three step statistical process including principal component, discriminant function and linear regression analysis [7]. The items selected were evaluated in a large international ankylosing spondylitis (AS) patient database (ISSAS) in which consideration of TNFi commencement was assessed [8]. The best composition of factors was then determined based on principal component and discriminant function analysis [7]. The four formula options underwent cross validation in a large independent dataset, the independent outcome assessments in AS International Study (OASIS), and showed that all four formulas performed similarly or better than the BASDAI [9]. The discriminator in OASIS was patient and physician global assessment of disease activity at baseline.

A cohort study was then conducted to evaluate the validity of four ASDAS versions against the BASDAI and its individual components and patient and physician global assessment of disease activity [10]. This showed the ASDAS to be a highly discriminative composite measure of disease activity containing items that are statistically constructed and validated as a continuous disease activity index.

Subsequent to the endorsement of the ASDAS by ASAS, clinically relevant cut off values and improvement scores were developed [5]. Data from the NORDMARD registry was used to define these cut offs and produce four disease activity states: inactive disease, moderate disease activity, high disease activity and very high disease activity.

The designation of moderate disease activity was however subsequently changed to low disease activity [11]. This reflects the wider opinions of patients and physicians about what an ASDAS value of between 1.3 and 2.1 means. Most patients within this category have mild disease activity and feel they are in a patient acceptable symptom state (PASS) – the maximum level of symptoms with which they consider themselves well [12,13].

See Fig. 1 for cut offs for disease activity states and improvement scores. Importantly the cut offs and improvement scores were endorsed by the Outcome measures in Rheumatology (OMERACT) community in 2010 [14].

ADVANTAGES OVER THE BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX

The BASDAI is a PRO measure of disease activity in axSpA and has been extensively used in clinical trials for both r-axSpA and nr-axSpA [2,15,16]. The BASDAI is reliable, easy to administer and responsive to change. However, BASDAI scores are highly dependent on patient perception as to what is related to their axSpA and scores have shown to be poorly

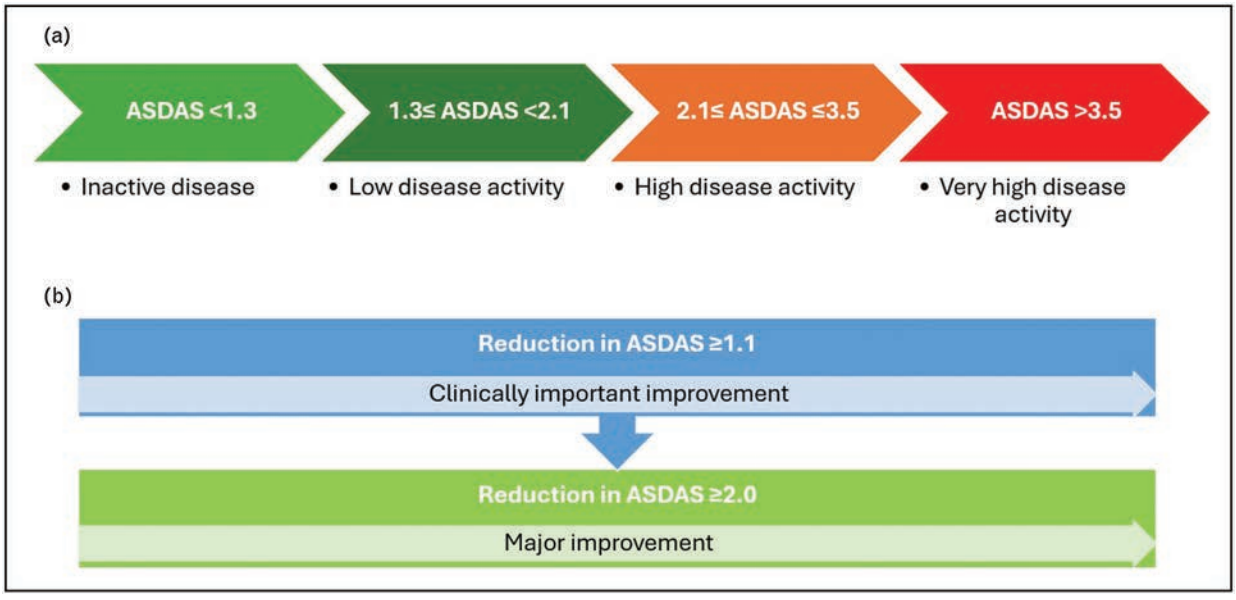

FIGURE 1. ASDAS cut offs for (a) disease activity states and (b) improvement scores.

correlated with physician global assessment [7]. Another concern is the validity of the BASDAI in measuring active inflammation given the absence of an objective marker of disease activity; as is the redundancy of the measure. Clinician familiarity and minimal administrative burden mean that use of the BASDAI is still widespread. The ASDAS however considers both subjective PROs and objective measures of inflammation and eliminates some of the redundancy of the BASDAI. Figure 2 shows the ASDAS components with a link to the online calculator.

The better measurement properties of the ASDAS, including higher discriminatory ability, superiority in assessing disease activity states and clinically significant improvements has resulted in its greater use clinically and in research.

INCORPORATION OF THE AXIAL SPONDYLOARTHRITIS DISEASE ACTIVITY SCORE IN AXIAL SPONDYLOARTHRITIS CLINICAL TRIALS

A response to treatment can be measured by response criteria and the ASAS 20 response has historically been the primary outcome measure in most drug trials in axSpA, followed by the ASAS 40 response is more recent clinical trials. It is however important to reflect the biological effects of drugs and only including PROs may not capture these.

The ASDAS and BASDAI can, in addition to ASAS defined improvement criteria, be used for defining response or improvement in trials. Importantly the ASDAS, as it includes objective inflammatory measures and not just PROs, does not share the methodological flaws of the ASAS 20, ASAS 40 or BASDAI.

ASAS has defined ASDAS based response criteria. A "clinically important improvement" is based on a change in score of at least 1.1 units and a "major improvement" involves a change of at least 2.0 units; these form the ASDAS improvement criteria [5]. ASDAS inactive disease, an ASAS defined disease activity state, refers to a value below 1.3 and is termed "inactive disease".

The major benefit of the ASDAS is its ability to assess disease activity state and disease activity change and therefore ASDAS based inclusion in randomized controlled trials (RCTs) and ASDAS based response criteria are likely to continue to become integral to drug development and clinical practice in axSpA and replace ASAS 20/40 and BASDAI based criteria.

The ASDAS has been assessed in various clinical trials which have confirmed its validity and responsiveness. The ASDAS CRP was shown to have the highest responsiveness compared to other measures, such as BASDAI, single item PROs, CRP, physician global and MRI scores in a longitudinal cohort of TNFi treated axSpA patients [17]. Importantly changes in MRI inflammation scores were also statistically correlated with changes in the ASDAS unlike BASDAI and CRP.

In another study the ASDAS CRP and ASDAS ESR were better able to discriminate between high and low disease activity compared to the BASDAI and other PRO based instruments [18]. Importantly the

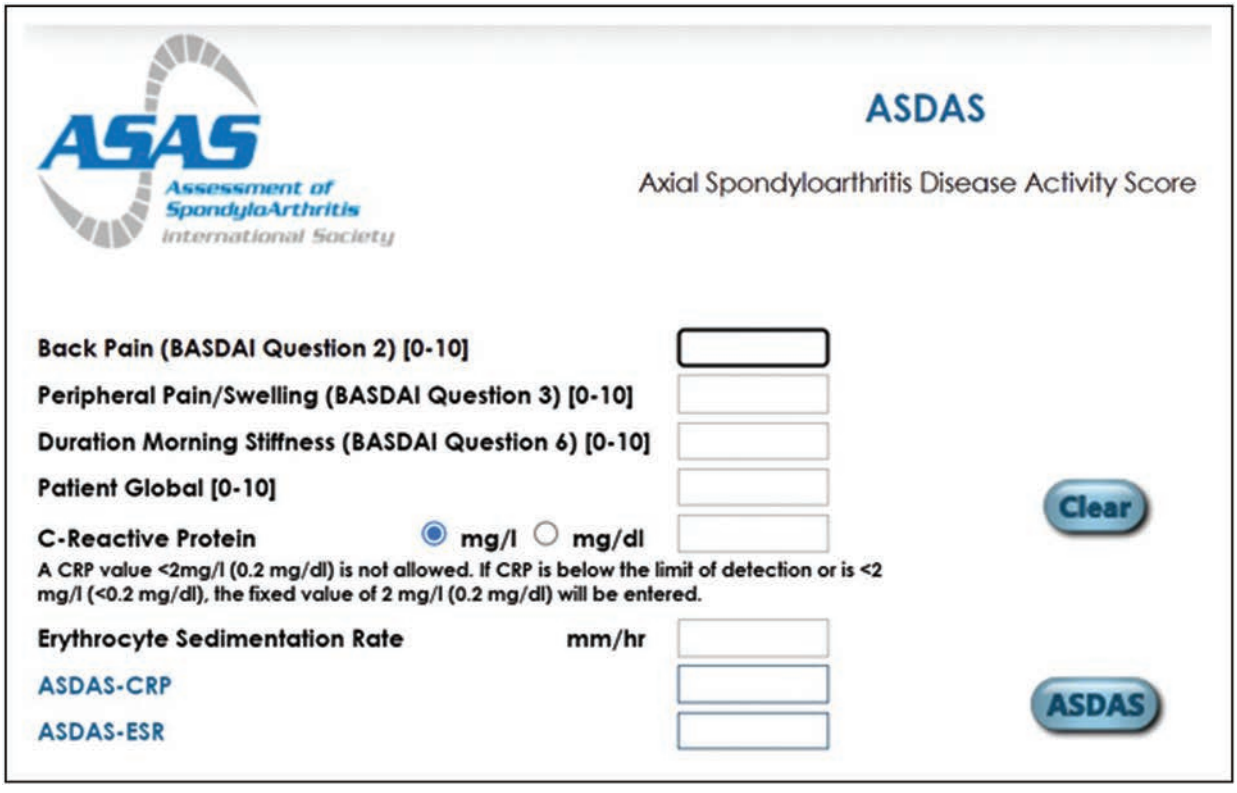

FIGURE 2. ASDAS components and online calculator available on the ASAS website (https://www.asas-group.org/instruments/asdas-calculator/). The ASAS app with an ASDAS calculator is also available from the App Store or Google Play.

results were not affected by the presence of peripheral arthritis.

A post hoc analysis looked at the comparative performance of the ASDAS CRP using RCT data from the ASCEND trial [19] which compared Etanercept with weekly Sulfasalazine and showed TNFi superiority for axial and peripheral disease. The post hoc analysis showed the ASDAS CRP to be a highly discriminatory tool for the detection of significant differences between treatments and for improvements in disease activity from baseline [20]. The BASDAI and other PROs and subjective measures showed lower discriminatory ability.

The ASDAS has been widely used in other clinical trials in patients with nr-axSpA and r-axSpA [16,21–25]. Furthermore a recent meta-analysis of sixteen RCTs has also confirmed that ASDAS based, rather than ASAS, response criteria are better able to discriminate between treatment and placebo arms in RCTs [26].

Importantly the ASDAS is now a mandatory instrument for the ASAS-OMERACT core domain set for clinical trials in axSpA [27▪]. ASAS is currently drafting expert recommendations for axSpA clinical trials including important baseline characteristics to collect and their reporting and which outcome instruments to use for monitoring disease activity, and these will include ASDAS as a key measure of disease activity.

INCORPORATION OF THE AXIAL SPONDYLOARTHRITIS DISEASE ACTIVITY SCORE INTO TREATMENT GUIDELINES AND ADOPTION IN CLINICAL PRACTICE

Recent international guidelines for the management of axSpA include those produced from The Pan American League of Associations for Rheumatology (PANLAR) and ASAS-EULAR [6▪▪,28], both of which have major international scope.

In 2022, the ASAS and EULAR updated the recommendations for the management of axSpA and showed a preference for the ASDAS as the validated outcome measure to monitor disease activity and response to treatment [6▪▪]. The taskforce acknowledged the ASDAS incorporated the patient perspective but also the addition of CRP adds an objective measure of inflammation; this is in contrast to the BASDAI. The ASDAS has been validated with a quick quantitative CRP assay [29] which may improve its uptake in clinical practice. An elevated CRP has been shown to be the strongest predictor of a good response to TNFi treatment [30] and its inclusion in the ASDAS is therefore crucial.

Structural damage progression, such as syndesmophyte formation, has also been shown to be associated with worsening ASDAS scores [31,32]. Treatment targets in axSpA also need considering and the Treat to Target principle has been suggested in axSpA [33]. An ASDAS score of <2.1, corresponding to low disease activity, was used as a target in the TICOSPA trial but failed to show superiority of tight control vs. usual care for the primary outcome [34]. The ASDAS low disease activity state was however achieved in a greater proportion of patients in the tight control arm which did show a benefit for some secondary efficacy outcomes and a 11% difference in response rates in favour of tight control. The concept of ASDAS remission and its attainment would likely prevent structural damage progression in axSpA. A 10 year observational cohort study showed that syndesmophyte production, assessed by x-rays with a 2 year interval between them, was significantly reduced in TNFi treatment patients reaching an ASDAS <1.3 [35].

The PANLAR guidelines too recommend the ASDAS for disease activity assessment but also include the SASDAS (simplified ASDAS) [36] as a simpler validated tool. Both guidelines allow the possibility of using the BASDAI in specific circumstances, such as where a CRP/ESR result isn't available.

The advantages of the ASDAS meant that the ASAS-EULAR task force decided that high disease activity should be based on an ASDAS score alone of greater than, or equal to, 2.1. The ASDAS better defines patients more likely to respond to treatment [37,38]. Importantly the assessment of high disease activity requires a holistic approach and is not limited to the calculation of the ASDAS score.

The ASAS-EULAR recommendations describe a response to treatment as a reduction in the ASDAS of at least 1.1 units. In comparison PANLAR do not provide such distinct values.

A gap often exists between the recommendations published by international task forces and their implementation in clinics. Time constraints during patient consultations are a major barrier to providing optimal care set out in recommendations.

The Simplified ASDAS (SASDAS) is an alternative to the ASDAS which is quicker and easier to use in clinical practice; it consists of the sum of the components of the ASDAS (using ESR or CRP) and has compared with the ASDAS and shown correlation when evaluating post hoc trial data [39,40,36] Further validation of the SASDAS is required.

The BASDAI remains one of the most frequently collected measures in axSpA clinics with the ASDAS reported to be collected in only 6.1% of patients in an observational cohort study [41]. The lack of electronic medical records may also mean that disease activity monitoring may not occur within defined time intervals. Moreover a paucity of studies exists which compare the BASDAI to the ASDAS in a real world setting and a recent observational cross sectional study showed substantial concordance between these two instruments in identifying disease activity thresholds and treatment responses [42]. Achieving a low ASDAS is often unrealistic for many patients and this has been reflected in trial data [43,44▪]. Non inflammatory pain, concomitant fibromyalgia and other overlapping comorbidities can often lead to inconsistent ASDAS (and BASDAI) values driven by chronic pain rather than active inflammation [45]. Finally, some national guidelines and regulatory bodies, such as those in the UK, still mandate the use of the BASDAI as the assessment tool for monitoring disease activity and determining eligibility for bDMARDs, though these are under revision [46,47]. There are however several countries that are already using the ASDAS, instead of the BASDAI, as the criterion to commence DMARDs and also to monitor treatment response [48–51].

CONCLUSION

Historically outcome assessments in axSpA were based on subjective endpoints.

The ASDAS was developed as a composite index to assess disease activity in axSpA. The ASDAS combines four PROs, three of which are also part of the BASDAI, a question on the patient's global assessment of disease activity and the CRP or ESR level. This composite measure has been shown to have superior measurement properties including being highly discriminatory in detecting treatment effects. A key feature of the ASDAS is its ability to perform well in the entire spectrum of axSpA patients, ranging from early to late disease states, r- and nr-axSpA, elevated and normal CRP, and presence or absence of peripheral arthritis. Importantly the ASDAS has been shown to correlate well with radiographic progression in axSpA [31]. Recent international treatment recommendations prioritize the use of the ASDAS compared to the BASDAI for measuring disease activity and guiding treatment decisions.

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