Biological classification of childhood arthritis: roadmap to a molecular nomenclature

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Abstract

Chronic inflammatory arthritis in childhood is heterogeneous in presentation and course. Most forms exhibit clinical and genetic similarity to arthritis of adult onset, although at least one phenotype might be restricted to children. Nevertheless, paediatric and adult rheumatologists have historically addressed

disease classification separately, yielding a juvenile idiopathic arthritis (JIA) nomenclature that exhibits no terminological overlap with adult-onset arthritis. Accumulating clinical, genetic and mechanistic data reveal critical limitations in this strategy, necessitating a new approach to defining biological categories within JIA. In this Review, we provide an overview of the current evidence for biological subgroups of arthritis in children, delineate forms that seem continuous with adult-onset arthritis, and consider integrative genetic and bioinformatic strategies to identify discrete entities within inflammatory arthritis across all ages.

[H1] Introduction

Chronic inflammatory arthritis is most commonly a disease of adults. Rheumatoid arthritis (RA) affects approximately 0.6% of the population of the USA, affecting women twice as often as men and with peak incidence in the seventh decade[1,2]. Diseases in the spondyloarthritis (SpA) family affect an estimated 0.9-1.4% of adults, often beginning at an earlier age than RA and affecting men more frequently than women[3]. More rarely, adults develop a febrile arthritis termed adult-onset Still's disease (AOSD)[4]. Children also develop arthritis; prevalence worldwide ranges between 15 and 400 per 100,000 with considerable geographical variability in phenotype[5,6]. Childhood-onset arthritis peaks between the ages of 1 and 4 years, during which period girls outnumber boys by approximately 3:1. By contrast, the first year of life is relatively spared and, in adolescence, the female sex bias is less pronounced (Figure 1). These epidemiological shifts are accompanied by changes in clinical presentation, strongly suggesting that childhood-onset arthritis encompasses more than one pathophysiological entity.

The first extended description of inflammatory arthritis in children was provided by G.F. Still in 1897, who highlighted features including presentation early in life, a predilection for knee involvement and, in many children, a relentless and disabling course[7]. Characterizing this population further, in 1959 Ansell and Bywaters introduced the now traditional definition of juvenile arthritis as beginning before the 16th birthday, although they considered this threshold to be arbitrary[8-10]. Formal classification of childhood-onset arthritis developed contemporaneously in North America and Europe. In 1972, a commission of the American Rheumatism Association (now the ACR) endorsed the term 'juvenile rheumatoid arthritis', which was subsequently divided into pauciarthritis (≤4 joints involved in the first 6 months of disease), polyarthritis (≥5 joints involved in the first 6 months of disease), and systemic arthritis (with fever)[11-13]. In Europe, EULAR adopted the term 'juvenile chronic arthritis' and used terms that overlapped with

those in the American nomenclature but with distinct definitions, while also including categories for 'juvenile ankylosing spondylitis' and 'juvenile psoriatic arthritis'[14,15]. SpA in children as young as 1 year of age was recognized in 1982 as 'seronegative enthesopathy and arthropathy'[16]. An effort to unify these disparate criteria under the umbrella of 'juvenile idiopathic arthritis' (JIA) was launched in 1994 through the International League Against Rheumatism (ILAR; later the International League of Associations for Rheumatology), culminating in the current categories of systemic arthritis (sJIA), oligoarthritis (persistent or extended), rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, and enthesitis related arthritis (ERA)[17] (Figure 2).

Always regarded as provisional, the ILAR JIA nomenclature nevertheless codifies certain assumptions about how types of arthritis should be distinguished from one another. No form of JIA has the same name as any type of adult-onset arthritis, tacitly implying that childhood-onset and adult-onset arthritis are fundamentally distinct[18]. Within JIA, the number of joints affected at or near presentation is used as a marker of disease type rather than severity, whereas psoriatic JIA is distinguished categorically from ERA and recognized even in the youngest children[18-20]. These features of the ILAR classification system shape how clinicians and investigators conceptualize childhood-onset arthritis, and frame the ways in which paediatric and adult rheumatologists are able to work together (or not). In this Review, we consider the limitations of the current ILAR JIA nomenclature and discuss new strategies to produce a classification system for childhood-onset arthritis that is more securely grounded in disease biology.

[H1] Why does classification matter?

A nomenclature establishes which patients belong together and which do not. Clinical manifestations and pathogenesis both contribute, but the latter is usually prioritized where known. Within pathogenesis, a shared aetiology early in the chain of events (such as a common genetic cause) takes precedence over shared downstream pathways. Extending these principles to childhood-onset arthritis, the goal is to identify groups of patients whose disease has similar biological mechanisms.

Classification risks two kinds of error: grouping together patients with different diseases (over-lumping) and dividing patients with the same disease (over-splitting). Over-splitting is especially pernicious because it can render underlying similarities difficult to appreciate later, as exemplified by the current

chasm between paediatric and adult arthritis nomenclature (Figure 3). Over-splitting also has important practical consequences. Approval of new medications for JIA has been slowed by a requirement for randomized controlled trials to show efficacy in this population. Despite progress, this requirement poses a substantial barrier to drug access because eligible patients can be difficult to find and because the financial incentive for companies to conduct paediatric studies is modest[21]. If certain forms of arthritis were recognized as extending across the age spectrum, then paediatric drug studies could restrict their focus to pharmacokinetics, pharmacodynamics and safety, considerably accelerating drug approvals for children with JIA[22].

[H1] New classification criteria are needed

The ILAR classification criteria for JIA (Figure 3a) represented a major landmark in paediatric rheumatology, providing for the first time a worldwide language of communication about childhood-onset arthritis and serving the community well for more than 25 years[16]. More generally, the segregation of children from adult patients helped to define paediatric rheumatology as a distinct subspecialty while focusing clinical and scientific attention on children with arthritis[23,24]. Nevertheless, limitations in the ILAR nomenclature have become evident. From a practical point of view, the ILAR criteria are difficult to apply because of their complex network of inclusion and exclusion criteria, some of which have counter-intuitive implications. For example, no patient with sJIA may have a first-degree relative with psoriasis[17]. The cutoff at the age of 16 years does not correspond to the legal divide between childhood and adulthood, which is now typically at 18 years[25]. The definition of RF-positive JIA has not been updated to encompass positivity for anti-citrullinated protein antibodies (ACPAs), which are measured clinically as antibodies that recognize cyclic citrullinated peptide. Many patients with features consistent with sJIA are excluded from this category at disease onset because they lack overt arthritis, even though with early treatment, some escape joint inflammation altogether[26,27]. Such 'bookkeeping' issues are minor and easily amenable to simple textual corrections[25,28-30].

Other difficulties with the ILAR classification system are more fundamental. By considering all types of arthritis beginning before the 16th birthday to be JIA, the nomenclature provides no mechanism to recognize phenotypes that exist in both children and adults. The ILAR JIA criteria differentiate oligoarticular JIA from polyarticular JIA by the number of joints affected within 6 months of disease onset. However, neither the 5-joint threshold nor the 6-month cutoff are well supported by data. The

classification is further complicated by the limited inter-examiner reproducibility of the joint exam, the capacity of imaging to disclose inflamed joints that are not evident clinically, and the potential for early treatment to forestall progression to polyarthritis[31-34]. Further, the divide between oligoarticular and polyarticular JIA introduces the untested assumption that the number of joints and/or the speed of affected joint accrual reflects disease type rather than disease severity[19,20], an assumption that has become increasingly uncertain in light of genetic data that identify broad similarities between oligoarticular JIA and RF-negative polyarticular JIA[18,35-37]. Joint counts undervalue the importance of joint distribution in the identification of distinct forms of arthritis[38-41]. More broadly, the distinction between ERA and psoriatic JIA obscures the central role of enthesitis in psoriatic arthritis[42]. Furthermore, although there is no gold standard test to identify children whose arthritis manifests a psoriatic diathesis, some evidence suggest that current ILAR criteria distribute nearly 60% of such children into other JIA categories[40,43].

Taken together, these limitations highlight the emerging need to replace the ILAR JIA classification criteria with a nomenclature that is based on disease biology. This "next generation" nomenclature should be informed by the growing understanding of arthritis mechanisms as well as by a big-picture view of joint inflammation as it occurs across all ages.

[H1] Differentiation of arthritis subtypes

Much of the biological data on arthritis subtypes comes from research into adult-onset arthritis. RA was first distinguished from gout in the 19th century[44-46]. The discovery of RF in 1939 enabled the further subdivision of RA into RF-positive and RF-negative subtypes[47,48]. In 1956, RF-negative RA was differentiated from a family of diseases subsequently termed SpA, which includes psoriatic arthritis and ankylosing spondylitis[49,50]. These divisions have since been sharpened by the identification of distinct genetic associations for RF-positive RA, RF-negative RA, and SpA; by the recognition of enthesitis as a prominent feature of SpA; and by the discovery of citrullinated peptides as antigenic targets within RF-positive RA, such that seropositive RA now encompasses disease accompanied by either RF or ACPAs[3,50-57] (Figure 3b).

Studies in animal models show that arthritis can arise via several distinct mechanisms[57]. Although human arthritis might be more complex than arthritis in animals, compelling data suggest the existence

of what one might term 'biological fault lines' in human disease, providing a useful guide to the ways in which types of arthritis diverge from one another (Figure 4).

[H2] Synovitis versus enthesitis. The synovium is composed of fibroblasts, macrophages and other cells that reside within a loose connective tissue substructure. In RA, synovitis is the primary factor that underlies musculoskeletal pathology. In SpA, arthritis often involves (or might even begin with) inflammation of the entheses, specialized sites where ligaments, tendons and joint capsules insert into bone[58,59]. Mechanisms of enthesitis differ from those that cause synovitis. Mouse models of disease show that enthesis-resident T cells programmed to produce cytokines associated with T helper 17 cell responses cause florid enthesitis when triggered by IL-23, an effect that might be magnified by mechanical stress[60-62]. Correspondingly, whereas RA affects mainly synovium-rich diarthrodial joints, SpA affects the Achilles and patellar tendon insertions, as well as locations rich in ligamentous attachments such as the spine and sacroiliac joints. Enthesitis contributes to dactylitis (sausage-like digital swelling) through the swelling of ligaments, pullies and joint capsules in the fingers and toes, accounting for the high specificity of this clinical feature for psoriatic arthritis in adults[42,63-65]. While the proximity of entheses to synovial tissues (including synovium-lined tendon sheaths) means that the distinction is rarely absolute, the difference between synovitis and enthesitis provides a useful conceptual framework to differentiate RA and related arthritides from SpA (Figure 4a).

[H2] Autoantibody-related versus autoantibody-independent synovitis. In mice, many, but not all, models of experimental synovitis are mediated through pathogenic autoantibodies[57]. These antibodies typically trigger arthritis in the form of immune complexes, formed in the blood in response to a circulating antigen or within the joint in response to an antigen that is either intrinsically local (such as collagen) or deposited from the circulation (such as glucose-6-phosphate isomerase). Joints might be uniquely susceptible to immune complex-mediated disease because the cartilage surface is acellular and lacks both intrinsic clearance mechanisms and membrane-bound complement inhibitors[57]. However, arthritis in mice can also arise in an autoantibody-independent manner, through pathogenic T cells or other mechanisms[66,67]. Human arthritis probably exhibits a parallel divergence. In RA, seropositive patients have immune complexes embedded in their cartilage and synovium, accompanied by complement fixation products in the synovial fluid[57,68,69]. By contrast, joints from patients with seronegative RA or SpA typically lack both immunoglobulin deposition and complement fixation,

suggesting that immune complexes have little or no pathogenic role in these diseases. Correspondingly, T peripheral helper (T_{PH}) cells, T helper cells that promote antibody formation by B cells outside of lymph nodes, are abundant in joints from patients with RF-positive RA (and potentially in patients with the proposed subset of antinuclear antibody (ANA)-positive early-onset JIA, see section on A juvenile-only form of arthritis?) but are rare in patients with RF-negative RA[70,71]. The distinction between seropositive RA and seronegative RA thus reflects, at least in part, a divide between arthritis with and without joint-deposited autoantibodies (Figure 4b). Importantly, RA develops through several phases, including an asymptomatic preclinical period characterized by high titres of autoantibodies without synovitis[72]. What distinguishes pathogenic from 'bystander' autoantibodies and whether the role of autoantibodies varies over the course of the disease are currently unknown[73].

[H2] Autoimmunity versus autoinflammation. Autoimmune diseases arise from misrecognition of self-antigens as a result of a break in immune tolerance. By contrast, autoinflammatory diseases reflect the antigen-independent hyperactivation of immune pathways, most commonly from defects within innate immunity[74]. RA seems to be primarily autoimmune in aetiology, as reflected by the associations with specific HLA alleles for both seropositive and seronegative forms. By contrast, AOSD and sJIA exhibit features suggestive of autoinflammation, including fever, rash and an often rapid response to IL-1 blockade, although an HLA class II genetic linkage complicates the straightforward categorization of these conditions as autoinflammatory[75,76]. Diseases in the SpA family probably also exhibit a prominent autoinflammatory component, reflecting the tendency of HLA-B27 to fold and traffic aberrantly, provoking an unfolded protein response that is exacerbated by mechanical stress at the entheses[77]. Autoimmunity and autoinflammation are not mutually exclusive, and polygenic inflammatory diseases commonly have elements of each[78] (Figure 4c).

[H1] Arthritis in children and adults

Many diseases exhibit phenotypic variance as a function of age at onset, reflecting factors such as genetic load, physiological maturation and/or senescence, and environmental exposures (Box 1)[79-81]. For inflammatory arthritis, accumulating data indicate that most forms affect both adults and children.

[H2] Seropositive arthritis. Childhood-onset seropositive arthritis typically first appears in late childhood, rarely before age 8 years and typically in early adolescence[82]. As with seropositive RA in

adults, the disease usually affects many joints, is often both RF-positive and ACPA-positive, can be accompanied by rheumatoid nodules, requires sustained and often aggressive disease-modifying therapy, and is associated with HLA class II alleles that share specific citrulline-binding residues in the antigen-binding pocket, as well as with shared non-HLA risk loci[36,83,84]. To all intents and purposes, RF-positive polyarticular JIA and seropositive RA are the same disease[18,25,36,84].

[H2] Spondyloarthritis. Adults with ankylosing spondylitis often report the onset of symptoms as teenagers[85]. Typical sacroiliitis is well documented in adolescents[86], whereas in younger children SpA commonly presents in a less differentiated form, characterized by enthesitis, arthritis and prominent arthralgia, often without sacroiliitis[16]. Gathered together under the ILAR classification of ERA, HLA alleles associated with SpA in children overlap with those of ankylosing spondylitis, supporting the idea of continuity in SpA across the age spectrum[36,87]. Psoriatic arthritis in children is more controversial. Definitive identification is often challenging because skin disease can lag behind arthritis by a decade or more[39,88]. Some of these children closely resemble the phenotype for the proposed early-onset ANA-positive subset of JIA (see section on A juvenile-only form of arthritis?), rendering a unique psoriatic identity uncertain[19,89]. However, classic adult-type psoriatic arthritis is readily observed in adolescents with overt psoriasis vulgaris, and associated enthesitis of the dactylitic digit has been confirmed by imaging and histology[64]. Furthermore, the prevalence of psoriatic JIA (5-20% of JIA, varying with population and criteria employed) greatly exceeds the expected chance association of JIA with psoriasis, which has a prevalence of psoriasis among children of 1-2%[39,43,89,90].

[H2] Seronegative arthritis. Seronegative arthritis appears to be a heterogeneous mixture of conditions in both adults and children. Evidence for this suggestion includes substantial patient-to-patient clinical variation, a lower heritability than seropositive RA in adults, and the abundance of pathways that can lead to autoantibody-independent arthritis in animal models[20,57,79]. Studies of childhood seronegative arthritis have been insufficient to determine the role of autoantibodies and immune complexes. However, clinical similarities have been noted between patients with early-onset oligoarticular JIA and a subset of patients with RF-negative polyarticular JIA[19,20,91,92]. HLA associations are shared among oligoarticular JIA, RF-negative polyarticular JIA, and adult seronegative RA[36]. Beyond HLA, less is known about genetic associations, but available data similarly suggest shared genetic associations across the age spectrum, further supported by familial aggregation of seronegative RA with JIA[93,94]. Together, these

considerations favour continuity between children and adults in at least some forms of seronegative arthritis.

[H2] Systemic JIA and adult-onset Still's disease. The febrile arthritis designated sJIA is highly distinctive within the JIA family. Current definitions segregate sJIA from AOSD by age of onset, a requirement for overt arthritis, and several other minor differences[17,95]. However, E.G. Bywaters's original description of AOSD in 1971 explicitly considered adult patients to have the paediatric disease[96]. Similarities between sJIA and AOSD include the ubiquity of fever, a characteristic rash, a generally even male-to-female ratio, high concentrations of ferritin and D-dimer, high concentrations of circulating IL-18, and a characteristic, rapid response to IL-1 blockade or IL-6 blockade[4,18,97-99]. The rash is more common in children than in adults, whereas sore throat is reported less frequently; by contrast, progression to chronic arthritis might occur somewhat less commonly in adults than in children[4]. Importantly, heterogeneity is present even within sJIA, reflected in phenotypic variation age at onset, differing patterns of circulating cytokines, and variation in response to therapy[100-102]. As such, it has been suggested that a rapid and complete response to IL-1 inhibitors might be used to identify a subset of patients with sJIA who have predominantly autoinflammatory features[102].

[H1] A juvenile-only form of arthritis?

The most remarkable feature of the epidemiology of arthritis in children is a peak in incidence during early childhood, typically between the ages of 1 and 4 years (Figure 1). Most patients in this early peak present with an oligoarticular phenotype, many of whom have only a single swollen knee. These patients are negative for RF and ACPAs but are commonly positive for ANAs, albeit typically at a modest titer (≤1:320). This population is also at highest risk for chronic anterior uveitis, an indolent but destructive disease distinct from the acute anterior uveitis observed in both adult and paediatric SpA and which has no counterpart in adult-onset arthritis. Up to 50% of patients with this early-onset childhood arthritis enter long-term drug-free remission, an outcome rarely observed in adult arthritis[103,104]. Corroborating studies suggest that HLA associations and peripheral blood transcriptomic signatures differ between in children who present with arthritis at age 6 years and below compared with those who present at an older age[37,105,106]. However, the optimal way to delimit this distinctive paediatric population remains undefined.

The Paediatric Rheumatology International Trials Organisation (PRINTO) has proposed a form of arthritis termed 'early-onset ANA-positive JIA' that encompasses children with arthritis beginning at ≤ 6 years of age with at least two ANA titers of ≥ 1:160 and without another recognizable form of JIA[25]. This proposal was formed on the basis of a literature review[19] and two studies that found that children with JIA who met the specified ANA threshold typically had a younger age of onset (80% under 6 years), fewer affected joints, and more uveitis than patients in the oligoarticular, RF-negative polyarticular and psoriatic JIA categories who had never tested positive for ANAs[19,91,92]. One study found that synovial tissue from patients with JIA who had a positive ANA (at any titre) had an excess of lymphoid aggregates, although it is not clear that synovial tissue from patients with untreated JIA echoes this finding[107,108]. Some evidence suggests that patients within the ANA-positive early-onset group may exhibit an abundance of synovial fluid T_{PH} cells, potentially implicating pathogenic autoantibodies[71]. Unresolved questions include the sensitivity and specificity of the presence of an ANA at the level proposed, and whether ANA positivity predicts clinical features independent of age, although interestingly the abundance of synovial fluid T_{PH}-like cells was not explained by early onset alone[18,71,106,109,110].

Although data supporting the existence of a unique form of arthritis in young children are compelling, they are not yet conclusive. Differences in anatomy, immunology, and environmental exposures — collectively the 'substrate' in which a disease occurs — could potentially translate into phenotypic differences between younger and older patients with the same disease (Box 1). Fine-mapping failed to identify a unique set of HLA associations for persistent oligoarticular JIA, the closest fit for the proposed new phenotype among the existing JIA categories[36]. The chronic anterior uveitis that is so characteristic of these patients can also occur in young children without arthritis, raising the possibility that this hallmark feature reflects the paediatric substrate rather than a unique arthritis-associated biology[111]. The features considered characteristic of the ANA-positive early-onset subgroup are seen as well in early-onset ANA-negative children with arthritis[40]. sJIA, which is genetically unrelated to oligoarticular and polyarticular JIA, also peaks in younger children, as do other immune-mediated conditions such as Kawasaki disease, type 1 diabetes and dermatomyositis, highlighting a possibly pivotal role for the immunologic milieu of early childhood[4,112]. Further investigation will be required before it can be concluded that early-onset JIA – ANA positive or not – represents a distinct disease of childhood.

[H1] Moving towards a new classification

Segregating childhood-onset arthritis from adult-onset disease produced several benefits. Not only did it help to distinguish paediatric rheumatology as a field, but it also drew the attention of regulators, funding agencies, and pharmaceutical companies to types of arthritis that affect children[23,24,30]. In this sense, the ILAR JIA classification terminology served the field better than did 'juvenile rheumatoid arthritis', with its tacit implication that childhood-onset arthritis might simply be 'baby rheumatoid'. A distinct nomenclature helped to support the development of research organizations with specialized expertise in paediatric rheumatology, including the Pediatric Rheumatology Collaborative Study Group (PRCSG), PRINTO, and the Childhood Arthritis and Rheumatology Research Alliance (CARRA), as well as organizations for parents and other advocates for children with arthritis. Collectively, these organizations have drawn considerable funding into paediatric rheumatology research, revolutionizing the understanding of disease phenotypes, disease course and treatments, and leading to the regulatory approval of a broad range of medications for JIA.

A further benefit has been to underscore the particular needs of children. Developing joints are highly vulnerable to arthritis-mediated injury and deformity, including the temporomandibular joint[113]. Similarly, linear growth of the skeleton is easily impaired by systemic inflammation or glucocorticoid therapy[114]. Children with arthritis require screening for chronic anterior uveitis[115]. Drug dosing must be adjusted by age and weight. In addition, children and their families must be managed in a manner that is developmentally appropriate, with attention given to issues such as school performance, body image, pregnancy risk, vocational aspirations and the transition to adulthood. The use of a unique terminology for childhood-onset arthritis has helped to ensure that children with arthritis are not managed simply as little adults.

These advantages are real but irrelevant to the question of whether childhood arthritis is biologically unique enough to merit its own terminology. As previously noted, the demarcation at age 16 years was never intended to reflect (or worse, to create) a fundamental difference between paediatric and adult-onset arthritis[9,116]. No other specialty in medicine has found it useful to segregate a whole category of disease by a hard age cutoff; even within rheumatology, only arthritis is treated in this way, whereas systemic lupus erythematosus, vasculitis, myositis, systemic sclerosis and other conditions are largely recognized as existing on a paediatric-adult continuum.

The authors of this Review agree upon four conclusions derived from the considerations summarized in the previous sections. First, the categorical divide between childhood-onset arthritis and adult-onset arthritis was an unintended consequence of the historical processes used to develop the current ILAR nomenclature and is at odds with emerging data. Second, the traditional division between oligoarticular and polyarticular JIA is unlikely to represent an important distinguishing feature between different types of arthritis. Third, most arthritis phenotypes extend across the age spectrum, including seropositive RA, seronegative RA, SpA and sJIA (AOSD). And fourth, early-onset JIA might represent a distinct disease, although its pathophysiological uniqueness and boundaries remain to be established. These conclusions represent the starting point for ongoing studies into disease classification.

Two models have so far been proposed that incorporate the biological insights discussed in this Review into the classification of primary idiopathic arthritis: the PRINTO model and the four-cluster model. Arthritis that is secondary to a distinct process, for example familial Mediterranean fever or Blau syndrome, is not considered further here.

[H2] The PRINTO model. In 2015, PRINTO embarked upon a multi-step effort to define disease entities within childhood-onset arthritis (defined for this purpose as onset <18 years) that are homogeneous from a clinical and laboratory perspective. A web Delphi process was used to revise the current ILAR JIA categories, followed by the use of nominal group technique at a consensus conference to achieve provisional criteria for new arthritis categories. Four principal forms were identified, entitled systemic JIA, RF-positive JIA, enthesitis/spondylitis-related JIA, and early-onset ANA-positive JIA[25] (Figure 5a). Psoriatic arthritis was not included because consensus was not reached on its definition. Childhood-onset arthritis outside of these categories is considered to be either 'other JIA' (fits criteria for no definition) or 'unclassified JIA' (fits the criteria for more than one definition)[25]. These definitions are considered to be provisional and an effort is underway to collect data from over 1,000 children with new-onset arthritis, including clinical descriptors, routine laboratory test results and, where possible, biological samples. The resulting data will be analyzed to see if clustering of clinical and laboratory descriptors enables the identification of homogeneous entities (including psoriatic arthritis) in the group of patients provisionally included in the 'other JIA' category, and a further process using nominal group technique will be organized to discuss the data and to provide evidence-based validation of the

provisional criteria[25]. Strengths of the PRINTO approach are its rigorous methodology and focus on the use of clinical measures readily available to clinicians at the point of care. Limitations include the restriction of patients analyzed to children and the possibility that not all features relevant for biological categorization will be evident in the data available.

[H2] Four-cluster model. A four-cluster model has been proposed for arthritis in both adults and children based on the 'biological fault lines' of autoantibody-related versus autoantibody-independent, synovitis versus enthesitis, and autoimmune versus autoinflammatory disease[18] (Figure 5b). These categories are not operationalized as inclusion and exclusion criteria, but instead are drawn as Venn diagrams to highlight mechanistic overlap, recognizing that, for example, many genetic risk loci are shared between seropositive and seronegative arthritis, such that a family history of either type of arthritis confers a genetic risk for the other[18,79,93,94]. This model emphasizes lumping over splitting and allows each category to remain internally heterogeneous. Pending the development of stronger evidence, early-onset JIA remains within the seronegative arthritis category, although some evidence hints at a potential role for B cells and T_{PH} cells, and therefore potentially autoantibodies, despite a lack of RF in these children[71,106]. Strengths of the four-cluster model are its pathophysiologic foundations and the fact that it encompasses both children and adults. However, unlike the PRINTO model, it is not directly applicable to the clinic, serving a guide for concept generation and research rather than practice.

[H1] Strategies for biological phenotyping

Understanding childhood-onset arthritis will require collaborative effort. In March 2016, an international group of clinicians, clinical trial experts, translational researchers and basic researchers gathered in London, UK seeking to speed progress in personalized medicine for children with rheumatic disorders. Participants endorsed a statement of principles, termed the London Declaration, "to improve care and ultimately cure childhood rheumatic disorders through worldwide collaboration"[117]. Signatories to this group included PRINTO, CARRA, the Understanding Childhood Arthritis Network (UCAN), and the CLUSTER Consortium. UCAN is a federation of research networks focused on translational research in childhood arthritis that represents more than 50 countries and 300 sites in a 'hub and spoke' model, with centres in Utrecht, Netherlands (UCAN-U), Toronto, Canada (UCAN-CAN) and Singapore (UCAN-A)[118]. UCAN aims to use harmonized procedures for collection, processing, transfer, storage, and access

to clinical and biologic data to enable the use of computational biology and machine learning to discover genetic, biologic and phenotypic markers that provide diagnostic and prognostic information to caregivers at the bedside. The CLUSTER Consortium is a UK-based network that aims to study approximately 5,000 children and young people with JIA to enable biomarker-driven stratified medicine for individuals with childhood-onset arthritis and associated uveitis. Parallel efforts are underway to understand adult arthritis through detailed analysis of joint tissues, including the US National Institutes of Health-sponsored Accelerating Medicines Partnership and the UK Pathobiology of Early Arthritis Cohort[119,120].

An important goal of the childhood-onset arthritis research being carried out by such collaborative consortia and networks in the next decade will be to identify biologically homogeneous subgroups, in the expectation that discovery of distinct biological signatures will enable the partition of patients into groups amenable to mechanism-based intervention. Identifying entities that are clinically homogeneous will not be sufficient, because a similar phenotype can emerge from distinct aetiologies. However, it will be important to seek characteristic clinical hallmarks, both for application in the clinic and to simplify downstream mechanistic studies. These efforts will be critical for the integration of paediatric-onset arthritis research into ongoing disease prevention research for RA and psoriatic arthritis[72,121].

[H2] Genetic approaches to disease clustering. Genetic studies have the major advantage that an individual's primary DNA sequence is not modified by disease activity or treatment. Furthermore, genes reside at the origin of the aetiopathogenic sequence, eliminating the possibility that a genetic association reflects a disease effect or epiphenomenon rather than a cause.

In rare cases, a single-gene defect can give rise to arthritis. Examples include mutations in *LACC1* and *MYD88*[122,123]. However, most arthritis requires input from both genes and the environment, as exemplified by imperfect concordance between siblings and even between identical twins[124-126]. Genome wide association studies (GWAS) have been used to identify ~30 loci with strong evidence of genetic association with oligoarticular JIA and RF-negative polyarticular JIA[35,127]. The effect of each variant is small, with odds ratios ranging from 6 for the HLA region to 1.1-1.6 for other loci; these odds ratios reflect the effect of the common variants amenable to study by GWAS, and should not be interpreted as a reflection of the importance of particular genes[18,35]. Genetic associations provide critical

information at the population level, helping to establish the fundamental differences between seropositive RA, seronegative RA, and SpA in adults[18]. HLA associations support the identity of seropositive RA and RF-positive polyarticular JIA, the continuity between ankylosing spondylitis and ERA, and the similarity among seronegative forms of arthritis across the age spectrum[36,84]. Variants outside the HLA region are also highly informative. sJIA does not overlap with non-systemic forms of JIA at any non-HLA loci, and thus is likely to be biologically distinct[75,112]. By contrast, non-HLA variants are shared across seropositive forms of arthritis irrespective of age of onset, consistent with the continuity of this condition across the age spectrum[84]. Too little is known about seronegative RA to draw conclusions, but the available data on associations beyond the HLA region suggest overlap between oligoarticular JIA and RF-negative polyarticular JIA[93].

Genetics alone will not produce a definitive arthritis subclassification system, because fundamental immunoregulatory mechanisms are often shared across autoimmune diseases[128]. However, similarity of HLA and non-HLA associations is strong evidence of identity between types of arthritis, whereas dissimilarity is strong evidence to the contrary, enabling genetics to serve as a touchstone of correct subset identification. The introduction of advanced methodologies to define the causal non-coding variants will provide an opportunity to genetically 'fingerprint' arthritis across the age spectrum[129]. Genetics and epidemiology could then further inform understanding of mechanisms. For example, synergy between HLA alleles and smoking led to the hypothesis that seropositive RA could begin in the lung, and studies that defined associations between HLA alleles and specific autoantibodies have suggested new ways in which the seropositive–seronegative division within RA might be further refined[130,131]. Of first importance will be a closer analysis of the early-onset JIA subset in children. Broadly speaking, oligoarticular JIA shares HLA associations with RF-negative polyarticular JIA and seronegative RA[36]. However, certain HLA alleles to carry risk or protection only within age-specific windows; for early-onset JIA, *HLA-A2*, *HLA-DRB1*03*, *HLA-DRB1*05* (later refined to *HLA-DRB1*11*), *HLA-DRB1*06* (later refined to *HLA-DRB1*13*) and *HLA-DRB1*08* conferred susceptibility and *HLA-DRB1*04* and *HLA-B27* conferred protection[37,105]. Confirming these results and testing whether they vary with ANA status will be highly informative with respect to identifying whether there is in fact a distinct arthritis in early childhood.

[H2] Big data and machine learning for disease clustering. Technical and computational advances provide new ways to characterize biological phenotypes and to identify patterns within the resulting datasets. The range of methodologies of potential relevance for arthritis is large and includes genomic strategies (such as whole genome sequencing, transcriptional profiling at the bulk, cell subpopulation or single-cell level, and epigenetic analysis), cell profiling (such as flow cytometry with DNA-tagged antibodies for single-cell surface or transcriptomic studies, mass cytometry, phosphoprotein assessment, and functional assays), autoantibody arrays, proteomics, lipidomics, and advanced histological methods (such as quantitative immunostaining and spatial transcriptomics). Analysis methods include any of a diverse range of clustering strategies and supervised or unsupervised machine learning.

Unsupervised machine learning aims to be 'data-driven' for the discovery of underlying patterns and clusters. It is important to remember, however, that such studies are never fully hypothesis-independent because they reflect investigator choices with respect to input sample, biological assays and analytical assumptions. Given the propensity to find patterns in almost any dataset, machine learning needs to be informed by an understanding of pathogenesis. Putative disease clusters can be assessed for plausibility by examining a number of specific queries (Box 2).

Early categorization efforts illustrate both the promise and the challenges of subgroup identification in JIA[41,132,133]. In one study, children with recent-onset non-systemic JIA, untreated except for NSAIDs, were divided into a derivation cohort (n=157) and a validation cohort (n=102)[132]. Using principal components analysis, patients in the derivation cohort were clustered based on demographic features, clinical and laboratory data, and a panel of cytokines and chemokines measured in plasma. The five resulting groups were distinct from the ILAR JIA categories and were replicated in the validation cohort, exhibiting relatively homogeneous joint trajectories[132]. A related study employed a wider range of biomarkers, analyzing patients both at diagnosis and after 6 months of treatment, arriving at a different set of clusters (three at baseline and five at follow-up)[133]. Another study assessed joint trajectories in 640 new-onset patients with JIA and found seven distinct patterns of joint involvement[41]. These studies demonstrate the power of dimensionality reduction strategies to identify patterns. However, to the extent that the patterns found in these studies did not align with each other, they illustrate the influence of the choice of input data on the results, highlighting the need for orthogonal, longitudinal,

and biologically-informed approaches to ensure that the clusters recognized correspond to distinct pathophysiologic groups.

[H1] Conclusions

Defining biological subtypes within childhood-onset arthritis remains a dauntingly complex task. In this Review, we outline a roadmap forward based on advances in arthritis biology, genetics, and clinical science that have been made since the ILAR JIA categories were first proposed more than 20 years ago. Reclassification of disease has risks as well as advantages. Practical concerns notwithstanding, certain ingrained assumptions are no longer tenable, most fundamentally that of a categorical difference between childhood-onset and adult-onset arthritis, offering the prospect of fruitful collaboration between pediatric and adult rheumatologists in coming years. Approaches that take advantage of new opportunities in clinical and biological phenotyping, interpreted cautiously and through the lens of pathogenesis, promise to accelerate progress toward the personalized management of children with arthritis.

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. *Arthritis and rheumatism.* 2010;62(6):1576-1582.
2. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. *Arthritis Care Res (Hoboken).* 2013;65(6):870-878.
3. Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. *The New England journal of medicine.* 2016;374(26):2563-2574.
4. Nigrovic PA, Schneider R. Systemic Juvenile Idiopathic Arthritis and Adult Onset Still Disease. In: Hashkes PJ, Laxer RM, Simon A, eds. *Textbook of Autoinflammation.* Cham, Switzerland: Springer Nature Switzerland AG; 2019:587-616.
5. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2007;369(9563):767-778.
6. Consolaro A, Giancane G, Alongi A, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health.* 2019;3(4):255-263.
7. Still GF. On a Form of Chronic Joint Disease in Children. *Med Chir Trans.* 1897;80:47-60.
8. Ansell BM, Bywaters EG. Prognosis in Still's disease. *Bull Rheum Dis.* 1959;9(9):189-192.
9. Bywaters EG. Heberden oration, 1966. Categorization in medicine: a survey of Still's disease. *Annals of the rheumatic diseases.* 1967;26(3):185-193.
10. Ansell BM. Heberden Oration, 1977. Chronic arthritis in childhood. *Annals of the rheumatic diseases.* 1978;37(2):107-120.
11. Criteria for the classification of juvenile rheumatoid arthritis. *Bull Rheum Dis.* 1972;23(5):712-719.

12. Brewer EJ, Jr., Bass J, Baum J, et al. Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. *Arthritis and rheumatism.* 1977;20(2 Suppl):195-199.
13. Cassidy JT, Levinson JE, Bass JC, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis and rheumatism.* 1986;29(2):274-281.
14. Wood PHN. Special meeting on nomenclature and classification of arthritis in children. In: Munthe E, ed. *The Care of Rheumatic Children.* Basel: EULAR Publishers; 1978:47-50.
15. Woo P, Wedderburn LR. Juvenile chronic arthritis. *Lancet.* 1998;351(9107):969-973.
16. Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis and rheumatism.* 1982;25(9):1041-1047.
17. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *The Journal of rheumatology.* 2004;31(2):390-392.
18. Nigrovic PA, Raychaudhuri S, Thompson SD. Genetics and the classification of arthritis in adults and children. *Arthritis Rheumatol.* 2018;70(1):7-17.
19. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? *The Journal of rheumatology.* 2003;30(9):1900-1903.
20. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. *Annals of the rheumatic diseases.* 2012;71(9):1437-1439.
21. Council RftCttEPat. State of Paediatric Medicines in the EU: 10 years of the EU Paediatric Regulation. In:2017.
22. Ruperto N, Martini A. Current and future perspectives in the management of juvenile idiopathic arthritis. *Lancet Child Adolesc Health.* 2018;2(5):360-370.
23. Schaller JG. The history of pediatric rheumatology. *Pediatr Res.* 2005;58(5):997-1007.
24. Beukelman T, Nigrovic PA. Juvenile Idiopathic Arthritis: An Idea Whose Time Has Gone? *The Journal of rheumatology.* 2019;46(2):124-126.
25. Martini A, Ravelli A, Avcin T, et al. Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. *The Journal of rheumatology.* 2019;46(2):190-197.
26. Nigrovic PA, Mannion M, Prince FH, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis and rheumatism.* 2011;63(2):545-555.
27. Ter Haar NM, van Dijkhuizen EHP, Swart JF, et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. *Arthritis Rheumatol.* 2019;71(7):1163-1173.
28. Behrens EM, Beukelman T, Cron RQ. Juvenile idiopathic arthritis classification criteria: loopholes and diagnosis software. *The Journal of rheumatology.* 2007;34(1):234; author reply 234-235.
29. DeWitt EM, Kimura Y, Beukelman T, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2012;64(7):1001-1010.
30. Rumsey DG, Laxer RM. The Challenges and Opportunities of Classifying Childhood Arthritis. *Curr Rheumatol Rep.* 2020;22(1):4.
31. Guzman J, Burgos-Vargas R, Duarte-Salazar C, Gomez-Mora P. Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. *The Journal of rheumatology.* 1995;22(12):2331-2336.

32. van Gulik EC, Welsink-Karssies MM, van den Berg JM, et al. Juvenile idiopathic arthritis: magnetic resonance imaging of the clinically unaffected knee. *Pediatric radiology.* 2018;48(3):333-340.
33. Magni-Manzoni S, Scire CA, Ravelli A, et al. Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. *Annals of the rheumatic diseases.* 2013;72(2):223-228.
34. Al-Matar MJ, Petty RE, Tucker LB, Malleson PN, Schroeder ML, Cabral DA. The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. *Arthritis and rheumatism.* 2002;46(10):2708-2715.
35. Hinks A, Cobb J, Marion MC, et al. Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. *Nat Genet.* 2013;45(6):664-669.
36. Hinks A, Bowes J, Cobb J, et al. Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases. *Annals of the rheumatic diseases.* 2017;76(4):765-772.
37. Hollenbach JA, Thompson SD, Bugawan TL, et al. Juvenile idiopathic arthritis and HLA class I and class II interactions and age-at-onset effects. *Arthritis and rheumatism.* 2010;62(6):1781-1791.
38. Huemer C, Malleson PN, Cabral DA, et al. Patterns of joint involvement at onset differentiate oligoarticular juvenile psoriatic arthritis from pauciarticular juvenile rheumatoid arthritis. *The Journal of rheumatology.* 2002;29(7):1531-1535.
39. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis and rheumatism.* 2006;54(11):3564-3572.
40. Stoll ML, Nigrovic PA, Gotte AC, Punaro M. Clinical comparison of early-onset psoriatic and non-psoriatic oligoarticular juvenile idiopathic arthritis. *Clinical and experimental rheumatology.* 2011;29(3):582-588.
41. Eng SWM, Aeschlimann FA, van Veenendaal M, et al. Patterns of joint involvement in juvenile idiopathic arthritis and prediction of disease course: A prospective study with multilayer non-negative matrix factorization. *PLoS medicine.* 2019;16(2):e1002750.
42. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. *The New England journal of medicine.* 2017;376(10):957-970.
43. Stoll ML, Lio P, Sundel RP, Nigrovic PA. Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. *Arthritis and rheumatism.* 2008;59(1):51-58.
44. Landré-Bouvais AJ. *Doit-on admettre une nouvelle espèce de goutte sous la dénomination d goutte asthenique primitive?* Paris: École de Médecine de Paris 1800.
45. Garrod AB. On gout and rheumatism: The differential diagnosis, and the nature of the so-called rheumatic gout. . *Med Chir Trans* 1854;37:181–220.
46. Garrod AE. *A treatise on rheumatism and rheumatoid arthritis. .* London: Charles Griffin & Co.; 1890.
47. Waaler E. On the occurrence of a factor in human serum activating the specific agglutination of sheep blood corpuscles. *Acta Pathol Microbiol Scand.* 1940;17:172-188.
48. Rose HM, Ragan C, et al. Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc Soc Exp Biol Med.* 1948;68(1):1-6.
49. Wright V. Psoriasis and arthritis. *Annals of the rheumatic diseases.* 1956;15(4):348-356.

50. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore).* 1974;53(5):343-364.
51. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High association of an HL-A antigen, W27, with ankylosing spondylitis. *The New England journal of medicine.* 1973;288(14):704-706.
52. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *The New England journal of medicine.* 1978;298(16):869-871.
53. Ball J. Enthesopathy of rheumatoid and ankylosing spondylitis. *Annals of the rheumatic diseases.* 1971;30(3):213-223.
54. Nienhuis RL, Mandema E. A New Serum Factor in Patients with Rheumatoid Arthritis; the Antiperinuclear Factor. *Annals of the rheumatic diseases.* 1964;23:302-305.
55. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *The Journal of clinical investigation.* 1998;101(1):273-281.
56. Klareskog L, Ronnelid J, Lundberg K, Padyukov L, Alfredsson L. Immunity to citrullinated proteins in rheumatoid arthritis. *Annual review of immunology.* 2008;26:651-675.
57. Chang MH, Nigrovic PA. Antibody-dependent and -independent mechanisms of inflammatory arthritis. *JCI insight.* 2019;4(5).
58. Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol.* 2017;13(12):731-741.
59. Simon D, Tascilar K, Kleyer A, et al. Structural entheseal lesions in patients with psoriasis are associated with an increased risk of progression to psoriatic arthritis. *Arthritis Rheumatol.* 2020.
60. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. *Nature medicine.* 2012;18(7):1069-1076.
61. Cuthbert RJ, Fragkakis EM, Dunsmuir R, et al. Brief Report: Group 3 Innate Lymphoid Cells in Human Enthesis. *Arthritis Rheumatol.* 2017;69(9):1816-1822.
62. Gracey E, Burssens A, Cambre I, et al. Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. *Nat Rev Rheumatol.* 2020;16(4):193-207.
63. Healy PJ, Groves C, Chandramohan M, Helliwell PS. MRI changes in psoriatic dactylitis--extent of pathology, relationship to tenderness and correlation with clinical indices. *Rheumatology (Oxford, England).* 2008;47(1):92-95.
64. Tuttle KS, Vargas SO, Callahan MJ, Bae DS, Nigrovic PA. Enthesitis as a component of dactylitis in psoriatic juvenile idiopathic arthritis: histology of an established clinical entity. *Pediatric rheumatology online journal.* 2015;13:7.
65. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis and rheumatism.* 2006;54(8):2665-2673.
66. Horai R, Saijo S, Tanioka H, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. *The Journal of experimental medicine.* 2000;191(2):313-320.
67. Sakaguchi N, Takahashi T, Hata H, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. *Nature.* 2003;426(6965):454-460.
68. Pekin TJ, Jr., Zvaifler NJ. Hemolytic Complement in Synovial Fluid. *The Journal of clinical investigation.* 1964;43:1372-1382.

69. Ruddy S, Austen KF. The complement system in rheumatoid synovitis. I. An analysis of complement component activities in rheumatoid synovial fluids. *Arthritis and rheumatism.* 1970;13(6):713-723.
70. Rao DA, Gurish MF, Marshall JL, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature.* 2017;542(7639):110-114.
71. Fischer J, Dirks J, Haase G, et al. IL-21(+) CD4(+) T helper cells co-expressing IFN-gamma and TNF-alpha accumulate in the joints of antinuclear antibody positive patients with juvenile idiopathic arthritis. *Clinical immunology (Orlando, Fla.* 2020:108484.
72. Holers VM, Demoruelle MK, Kuhn KA, et al. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. *Nat Rev Rheumatol.* 2018;14(9):542-557.
73. Trouw LA, Rispens T, Toes REM. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. *Nat Rev Rheumatol.* 2017;13(6):331-339.
74. Nigrovic PA, Lee PY, Hoffman HM. Monogenic autoinflammatory disorders: Conceptual overview, phenotype, and clinical approach. *The Journal of allergy and clinical immunology.* 2020;146(5):925-937.
75. Ombrello MJ, Remmers EF, Tachmazidou I, et al. HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. *Proc Natl Acad Sci U S A.* 2015;112(52):15970-15975.
76. Nigrovic PA. Autoinflammation and autoimmunity in systemic juvenile idiopathic arthritis. *Proc Natl Acad Sci U S A.* 2015;112(52):15785-15786.
77. Colbert RA, Navid F, Gill T. The role of HLA-B*27 in spondyloarthritis. *Best practice & research Clinical rheumatology.* 2017;31(6):797-815.
78. Nigrovic PA, Lee PY, Hoffman HM. Monogenic autoinflammatory disorders: conceptual overview, phenotype, and clinical approach. *The Journal of allergy and clinical immunology.* 2020 in press.
79. Frisell T, Holmqvist M, Kallberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. *Arthritis and rheumatism.* 2013;65(11):2773-2782.
80. Langefeld CD, Ainsworth HC, Cunninghame Graham DS, et al. Transancestral mapping and genetic load in systemic lupus erythematosus. *Nature communications.* 2017;8:16021.
81. Gensler LS, Ward MM, Reveille JD, Learch TJ, Weisman MH, Davis JC, Jr. Clinical, radiographic and functional differences between juvenile-onset and adult-onset ankylosing spondylitis: results from the PSOAS cohort. *Annals of the rheumatic diseases.* 2008;67(2):233-237.
82. Prahalad S, Thompson SD, Conneely KN, et al. Hierarchy of risk of childhood-onset rheumatoid arthritis conferred by HLA-DRB1 alleles encoding the shared epitope. *Arthritis and rheumatism.* 2012;64(3):925-930.
83. Ferucci ED, Majka DS, Parrish LA, et al. Antibodies against cyclic citrullinated peptide are associated with HLA-DR4 in simplex and multiplex polyarticular-onset juvenile rheumatoid arthritis. *Arthritis and rheumatism.* 2005;52(1):239-246.
84. Hinks A, Marion MC, Cobb J, et al. Brief Report: The Genetic Profile of Rheumatoid Factor-Positive Polyarticular Juvenile Idiopathic Arthritis Resembles That of Adult Rheumatoid Arthritis. *Arthritis Rheumatol.* 2018;70(6):957-962.
85. Nigrovic PA, White PH. Care of the adult with juvenile rheumatoid arthritis. *Arthritis and rheumatism.* 2006;55(2):208-216.

86. Weiss PF, Xiao R, Biko DM, Chauvin NA. Assessment of Sacroiliitis at Diagnosis of Juvenile Spondyloarthritis by Radiography, Magnetic Resonance Imaging, and Clinical Examination. *Arthritis Care Res (Hoboken).* 2016;68(2):187-194.
87. Colbert RA. Classification of juvenile spondyloarthritis: Enthesitis-related arthritis and beyond. *Nat Rev Rheumatol.* 2010;6(8):477-485.
88. Southwood TR, Petty RE, Malleson PN, et al. Psoriatic arthritis in children. *Arthritis and rheumatism.* 1989;32(8):1007-1013.
89. Nigrovic PA. Juvenile psoriatic arthritis: bathwater or baby? *The Journal of rheumatology.* 2009;36(9):1861-1863.
90. Stoll ML, Mellins ED. Psoriatic arthritis in childhood: A commentary on the controversy. *Clinical immunology (Orlando, Fla.* 2020;214:108396.
91. Ravelli A, Felici E, Magni-Manzoni S, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis and rheumatism.* 2005;52(3):826-832.
92. Ravelli A, Varnier GC, Oliveira S, et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis and rheumatism.* 2011;63(1):267-275.
93. Nigrovic PA, Martinez-Bonet M, Thompson SD. Implications of juvenile idiopathic arthritis genetic risk variants for disease pathogenesis and classification. *Current opinion in rheumatology.* 2019;31(5):401-410.
94. Frisell T, Hellgren K, Alfredsson L, Raychaudhuri S, Klareskog L, Askling J. Familial aggregation of arthritis-related diseases in seropositive and seronegative rheumatoid arthritis: a register-based case-control study in Sweden. *Annals of the rheumatic diseases.* 2016;75(1):183-189.
95. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *The Journal of rheumatology.* 1992;19(3):424-430.
96. Bywaters EG. Still's disease in the adult. *Annals of the rheumatic diseases.* 1971;30(2):121-133.
97. Vastert SJ, Jamilloux Y, Quartier P, et al. Anakinra in children and adults with Still's disease. *Rheumatology (Oxford, England).* 2019;58(Suppl 6):vi9-vi22.
98. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *The New England journal of medicine.* 2012;367(25):2385-2395.
99. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *The New England journal of medicine.* 2012;367(25):2396-2406.
100. Russo RA, Katsicas MM. Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. *The Journal of rheumatology.* 2013;40(3):329-334.
101. Shimizu M, Nakagishi Y, Yachie A. Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles. *Cytokine.* 2013;61(2):345-348.
102. Gattorno M, Piccini A, Lasiglie D, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis and rheumatism.* 2008;58(5):1505-1515.
103. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *The Journal of rheumatology.* 2002;29(9):1989-1999.
104. Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. *The Journal of rheumatology.* 2003;30(3):579-584.

105. Murray KJ, Moroldo MB, Donnelly P, et al. Age-specific effects of juvenile rheumatoid arthritis-associated HLA alleles. *Arthritis and rheumatism.* 1999;42(9):1843-1853.
106. Barnes MG, Grom AA, Thompson SD, et al. Biologic similarities based on age at onset in oligoarticular and polyarticular subtypes of juvenile idiopathic arthritis. *Arthritis and rheumatism.* 2010;62(11):3249-3258.
107. Gregorio A, Gambini C, Gerloni V, et al. Lymphoid neogenesis in juvenile idiopathic arthritis correlates with ANA positivity and plasma cells infiltration. *Rheumatology (Oxford, England).* 2007;46(2):308-313.
108. Finnegan S, Clarke S, Gibson D, McAllister C, Rooney M. Synovial membrane immunohistology in early untreated juvenile idiopathic arthritis: differences between clinical subgroups. *Annals of the rheumatic diseases.* 2011;70(10):1842-1850.
109. Albers HM, Brinkman DM, Kamphuis SS, et al. Clinical course and prognostic value of disease activity in the first two years in different subtypes of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2010;62(2):204-212.
110. Guzman J, Henrey A, Loughin T, et al. Predicting Which Children with Juvenile Idiopathic Arthritis Will Have a Severe Disease Course: Results from the ReACCh-Out Cohort. *The Journal of rheumatology.* 2017;44(2):230-240.
111. Heiligenhaus A, Klotsche J, Niewerth M, et al. Similarities in clinical course and outcome between juvenile idiopathic arthritis (JIA)-associated and ANA-positive idiopathic anterior uveitis: data from a population-based nationwide study in Germany. *Arthritis research & therapy.* 2020;22(1):81.
112. Ombrello MJ, Arthur VL, Remmers EF, et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. *Annals of the rheumatic diseases.* 2017;76(5):906-913.
113. Cannizzaro E, Schroeder S, Muller LM, Kellenberger CJ, Saurenmann RK. Temporomandibular joint involvement in children with juvenile idiopathic arthritis. *The Journal of rheumatology.* 2011;38(3):510-515.
114. MacRae VE, Farquharson C, Ahmed SF. The pathophysiology of the growth plate in juvenile idiopathic arthritis. *Rheumatology (Oxford, England).* 2006;45(1):11-19.
115. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Rheumatol.* 2019;71(6):864-877.
116. Cassidy JT, Levinson JE, Brewer EJ, Jr. The development of classification criteria for children with juvenile rheumatoid arthritis. *Bull Rheum Dis.* 1989;38(6):1-7.
117. Robinson E, Albani S, Beresford MW, et al. Towards stratified medicine in juvenile idiopathic arthritis. *Pediatric rheumatology online journal.* 2017;15(37):53-54.
118. Yeung RS, Albani S, Feldman BM, Mellins E, Prakken B, Wedderburn LR. Enhancing translational research in paediatric rheumatology through standardization. *Nat Rev Rheumatol.* 2016;12(11):684-690.
119. Zhang F, Wei K, Slowikowski K, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nat Immunol.* 2019;20(7):928-942.
120. Lewis MJ, Barnes MR, Blighe K, et al. Molecular Portraits of Early Rheumatoid Arthritis Identify Clinical and Treatment Response Phenotypes. *Cell Rep.* 2019;28(9):2455-2470 e2455.
121. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol.* 2019;15(3):153-166.

122. Sikora KA, Bennett JR, Vyncke L, et al. Germline gain-of-function myeloid differentiation primary response gene-88 (MYD88) mutation in a child with severe arthritis. *The Journal of allergy and clinical immunology.* 2018;141(5):1943-1947 e1949.
123. Wakil SM, Monies DM, Abouelhoda M, et al. Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol.* 2015;67(1):288-295.
124. Moroldo MB, Tague BL, Shear ES, Glass DN, Giannini EH. Juvenile rheumatoid arthritis in affected sibpairs. *Arthritis and rheumatism.* 1997;40(11):1962-1966.
125. Moroldo MB, Chaudhari M, Shear E, Thompson SD, Glass DN, Giannini EH. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. *Arthritis and rheumatism.* 2004;50(6):1928-1934.
126. Prahalad S, Ryan MH, Shear ES, Thompson SD, Glass DN, Giannini EH. Twins concordant for juvenile rheumatoid arthritis. *Arthritis and rheumatism.* 2000;43(11):2611-2612.
127. McIntosh LA, Marion MC, Sudman M, et al. Genome-wide association meta-analysis reveals novel juvenile idiopathic arthritis susceptibility loci. *Arthritis Rheumatol.* 2017.
128. Kirino Y, Remmers EF. Genetic architectures of seropositive and seronegative rheumatic diseases. *Nat Rev Rheumatol.* 2015;11(7):401-414.
129. Li G, Martinez-Bonet M, Wu D, et al. High-throughput identification of noncoding functional SNPs via type IIS enzyme restriction. *Nat Genet.* 2018;50(8):1180-1188.
130. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis and rheumatism.* 2006;54(1):38-46.
131. Terao C, Brynedal B, Chen Z, et al. Distinct HLA Associations with Rheumatoid Arthritis Subsets Defined by Serological Subphenotype. *American journal of human genetics.* 2019;105(3):616-624.
132. Eng SW, Duong TT, Rosenberg AM, Morris Q, Yeung RS. The biologic basis of clinical heterogeneity in juvenile idiopathic arthritis. *Arthritis Rheumatol.* 2014;66(12):3463-3475.
133. Rezaei E, Hogan D, Trost B, et al. Associations of clinical and inflammatory biomarker clusters with juvenile idiopathic arthritis categories. *Rheumatology (Oxford, England).* 2020;59(5):1066-1075.
134. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Arthritis and rheumatism.* 2010;62(6):1824-1828.
135. Qiu J, Soderlund-Venermo M, Young NS. Human Parvoviruses. *Clin Microbiol Rev.* 2017;30(1):43-113.
136. Jadon DR, Shaddick G, Jobling A, Ramanan AV, Sengupta R. Clinical outcomes and progression to orthopedic surgery in juvenile- versus adult-onset ankylosing spondylitis. *Arthritis Care Res (Hoboken).* 2015;67(5):651-657.
137. Webb R, Kelly JA, Somers EC, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. *Annals of the rheumatic diseases.* 2011;70(1):151-156.
138. Webber D, Cao J, Dominguez D, et al. Association of systemic lupus erythematosus (SLE) genetic susceptibility loci with lupus nephritis in childhood-onset and adult-onset SLE. *Rheumatology (Oxford, England).* 2020;59(1):90-98.
139. Scott IC, Seegobin SD, Steer S, et al. Predicting the risk of rheumatoid arthritis and its age of onset through modelling genetic risk variants with smoking. *PLoS genetics.* 2013;9(9):e1003808.

140. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci.* 2015;282(1821):20143085.
141. Ercan A, Kohrt WM, Cui J, et al. Estrogens regulate glycosylation of IgG in women and men. *JCI insight.* 2017;2(4):e89703.
142. Laver-Rudich Z, Silbermann M. Cartilage surface charge. A possible determinant in aging and osteoarthritic processes. *Arthritis and rheumatism.* 1985;28(6):660-670.
143. Alpizar-Rodriguez D, Finckh A. Environmental factors and hormones in the development of rheumatoid arthritis. *Seminars in immunopathology.* 2017;39(4):461-468.
144. Prisco LC, Martin LW, Sparks JA. Inhalants other than personal cigarette smoking and risk for developing rheumatoid arthritis. *Current opinion in rheumatology.* 2020;32(3):279-288.
145. Derrien M, Alvarez AS, de Vos WM. The Gut Microbiota in the First Decade of Life. *Trends Microbiol.* 2019;27(12):997-1010.
146. Horton DB, Scott FI, Haynes K, et al. Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case-Control Study. *Pediatrics.* 2015;136(2):e333-343.
147. Arvonen M, Virta LJ, Pokka T, Kroger L, Vahasalo P. Repeated exposure to antibiotics in infancy: a predisposing factor for juvenile idiopathic arthritis or a sign of this group's greater susceptibility to infections? *The Journal of rheumatology.* 2015;42(3):521-526.

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Figure 1. The epidemiology of juvenile idiopathic arthritis.

Age of onset in 1,081 children with arthritis was evaluated in the Pediatric Rheumatology Clinic at The Hospital for Sick Children, Toronto, Canada. Note the paucity of juvenile idiopathic arthritis onset in the first year of life, the incidence peak in girls between the ages of 1 and 4 and the relatively balanced sex ratio of arthritis that begins in adolescence. Adapted from ref [134].

Figure 2. The evolution of classification criteria for childhood-onset arthritis.

Since 1959, juvenile-onset and adult-onset arthritis have been distinguished by an age cutoff at the 16th birthday. Nomenclature has evolved from the American Rheumatism Association criteria for 'juvenile rheumatoid arthritis' (JRA) and the EULAR criteria for 'juvenile chronic arthritis' (JCA) to the current International League of Associations for Rheumatology (ILAR) juvenile idiopathic arthritis (JIA) system, for which a provisional revision has been proposed by the Paediatric Rheumatology International Trials Organisation (PRINTO). ANA, antinuclear antibody; AS, ankylosing spondylitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.

Figure 3. Current arthritis classification in children and adults.

a | The major diagnostic categories of idiopathic inflammatory arthritis beginning in childhood (before the 16th birthday) according to the International League of Associations for Rheumatology nomenclature[16]. **b** | The major diagnostic categories of idiopathic inflammatory arthritis beginning in adulthood (age 16 and onward)[3]. IBD, inflammatory bowel disease; RF, rheumatoid factor.

Figure 4. Biological fault lines in arthritis.

Studies in murine models of arthritis and in humans have revealed three central dichotomies in arthritis biology: synovitis versus enthesitis, autoantibody-related versus autoantibody-independent, and autoimmune versus autoinflammatory. Distinct forms of arthritis can be characterized by understanding where they reside on each spectrum. AOSD, adult-onset Still's disease; sJIA, systemic juvenile idiopathic arthritis; SpA, spondyloarthritis; RA, rheumatoid arthritis.

Figure 5. Proposed subdivisions within arthritis: PRINTO and the four-cluster model.

The provisional Paediatric Rheumatology International Trials Organisation (PRINTO) juvenile idiopathic arthritis (JIA) categories for childhood-onset arthritis[25] (**a**) and the four-cluster model defining mechanistic subgroups within arthritis across the age spectrum (**b**). These two models represent hypotheses with differing methodology and purposes. The PRINTO model reflects an ongoing effort based on consensus methodology to provide preliminary criteria defining clinically homogeneous entities in JIA to enable structured validation studies and biological research. The four-cluster model integrates clinical and biological data to define groups with arthritis that exhibit pathophysiologic

similarity, irrespective of age of onset. These models resemble each other more than they differ, with both recognizing seropositive arthritis, spondyloarthritis, and systemic JIA (adult-onset Still's disease) as distinct entities. Children with early-onset JIA (potentially distinguished further by the presence of antinuclear antibody (ANA)) may form a distinct subset within seronegative arthritis. Part **b** adapted from ref [18].

Box 1. Age of onset effects in arthritis.

Diseases that share a common pathophysiology can still manifest differently because of factors that vary with age. A familiar example is parvovirus B19 infection, which presents in children as the so-called 'fifth disease' (slapped-cheek exanthema), in adult women as joint inflammation or miscarriage, and in patients with sickle cell disease as aplastic crisis[135]. Phenotypic variation with age is similarly evident in arthritis. For example, spondyloarthritis beginning in childhood is associated with a higher risk of joint replacement than adult-onset disease, whereas systemic juvenile idiopathic arthritis (JIA) presenting in very early childhood exhibits more macrophage activation syndrome and a worse prognosis than sJIA presenting later in childhood[100,136]. Age-dependent variation can arise through pathways including differences in genetic loading, organic substrate, and environment. These mechanisms probably result in continuous rather than dichotomized variation, a difficulty intrinsic to any effort to assigning a specific age cutoff to a form of arthritis for classification purposes.

[bH1] Genetic loading

Within a polygenic disease, earlier onset often reflects a stronger genetic predisposition. For example, in systemic lupus erythematosus, patients with more genetic risk variants tend to present earlier in life and to more frequently develop nephritis[80,137,138]. In rheumatoid arthritis (RA), the presence of HLA risk alleles predicts a lower age at onset, and presentation before 40 years of age confers an elevated risk of developing RA for family members[79,139].

[bH1] Substrate differences

Children and adults differ anatomically and physiologically in ways that are relevant to arthritis. Immune function changes with age, including under the influence of sex hormones[140,141]. Developing tissues, such as joints or eyes, might theoretically expose antigens that are lacking in adult joints or otherwise exhibit differential vulnerability to disease. For example, JIA beginning before age 6 years is associated with an especially high risk for chronic anterior uveitis, but a similar condition also affects young children

without arthritis[111]. Conversely, ageing cartilage might be less resistant to complement fixation and therefore favour immune complex-mediated arthritis[57,142].

[bH1] Environment

The environment to which an individual is exposed varies with age. The risk of RA increases with smoking, occupational silica inhalation, and obesity, all more prevalent in adults than in children[143,144]. By contrast, children experience an evolving gut microbiome, recurrent viral infections and, in some cases, frequent antibiotic treatments, all with immunological consequences[145-147].

Box 2. Queries for any proposed subtype of chronic inflammatory arthritis.

[b1] Is the subtype consistent with, or convincingly overturn, established understanding of arthritis biology?

[b1] Does the subtype display substantial genetic coherence, as reflected in internal homogeneity and differences from other types of arthritis?

[b1] Does the subtype include all patients with sufficiently similar disease biology, or are many closely related cases excluded?

[b1] Does the subtype distinguish disease type from disease severity?

[b1] Does the subtype distinguish disease type from variation owing to age of onset?

[b1] Has the subtype been validated using approaches distinct from those used for its derivation?