Atlas of Rheumatoid Arthritis

Editor
Paul Emery

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Editor biography

Professor Paul Emery is the Arthritis Research UK Professor of Rheumatology and Director of the Leeds Institute of Rheumatic and Musculoskeletal Medicine and the Director of the Leeds Musculoskeletal Biomedical Research Unit at Leeds Teaching Hospitals Trust in Leeds, United Kingdom. Professor Emery was the President of the European League Against Rheumatism (EULAR) from 2009–2011 and has served on the editorial boards major rheumatology journals including Rheumatology, Arthritis and Rheumatism, Annals of the Rheumatic Diseases, Clinical and Experimental Rheumatology, and Clinical Rheumatology. He was the inaugural President of International Extremity MRI Society (ISEMIR) and is a National Institute for Health Research (NIHR) Senior Investigator. Professor Emery is a recipient of the Roche Biennial Award for Clinical Rheumatology; the Rheumatology Hospital Doctor of the Year Award; the EULAR Prize for outstanding contribution to rheumatology research; and the Carol Nachman Prize for outstanding rheumatology research. Professor Emery's research interests center around the immunopathogenesis and immunotherapy of rheumatoid arthritis, spondyloarthritis, and connective tissue diseases. He has a special interest in the factors leading to persistent inflammation and has published over 950 peer-reviewed articles in this area.

PART ONE

Rheumatoid arthritis overview

1 Classification of rheumatoid arthritis

Daniel Aletaha

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the adult population [1]. Although there is no cure, patients may reach a state of remission, which has become an achievable goal with optimal early treatment. Early intervention in particular has made RA a less disabling disease and if treatment is instituted right from the onset, no functional impairment may occur and structural integrity may be preserved (Figures 1.1 and 1.2) [2]. Over the past decade, early intensive treatment has also been proven to change the course of later RA [2,3], and therefore, the treatment goal should be to treat RA early and persistently until remission is present [4,5].

The challenge of treating early RA is the fact that new-onset arthritis often resolves spontaneously and persistent arthritis has many differential diagnoses to be considered in addition to RA, or may even remain undifferentiated (Figure 1.3). Diagnostic algorithms have been suggested for new-onset arthritis, as there is minimal work-up needed to label the presentation as undifferentiated (Figure 1.4) [6]. Algorithms also help with the exclusion of trauma, gout, and septic arthritis; suspicion of one of the latter two requires joint fluid aspiration, which usually gives immediate diagnostic clues (Figure 1.5).

In the early treatment of RA, there are many hurdles that can cause a substantial delay in beginning treatment, including delays in patient presentation, physician referral, or diagnosis (Figure 1.6) [7]. In most clinical settings, a diagnosis will need to be established before medication can be

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instituted, including liability considerations with the use of off-label drugs. Because diagnostic criteria are not available, the diagnosis will have to be established by the rheumatologist, although he or she may decide to use a formal classification system as a basis (Figure 1.7).

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria were developed in a three-stage process (Tables 1.1 and1.2; Figures 1.8 to 1.10) to replace existing criteria, which were deemed out of date [8,9]. The 2010 ACR/EULAR criteria comprise a scoring system that considers the number and distribution of the affected joints, serology, duration of symptoms, and acute phase reactants (Table 1.3) [10]. They may be applied to patients with clinical arthritis, in whom another disease can be reasonably excluded (Figure 1.11), and may be applied prospectively or retrospectively (Figure 1.12). In addition to the direct scoring system, a tree algorithm has also been provided, the result of which is identical to the scoring system (Figure 1.13) [10]. Because the new criteria do not factor in joint erosion, which is now considered more a preventable outcome of RA rather than a classification marker, additional rules have been defined for patients who present with available X-rays of their hands and feet (Figure 1.14).

In summary, making a correct diagnosis of RA (especially early RA) remains a challenge. Because there are a large number of differential diagnoses, and the presentation of RA may be considerably heterogeneous, no formal criteria can replace the judgment and experience of the rheumatologist in the diagnostic setting. Nevertheless, classification criteria may help to guide the rheumatologist in the difficult task of establishing a diagnosis. This will allow early institution of adequate therapy and, hopefully, help to reduce the impact of this very prevalent disease on patient function and health-related quality of life.

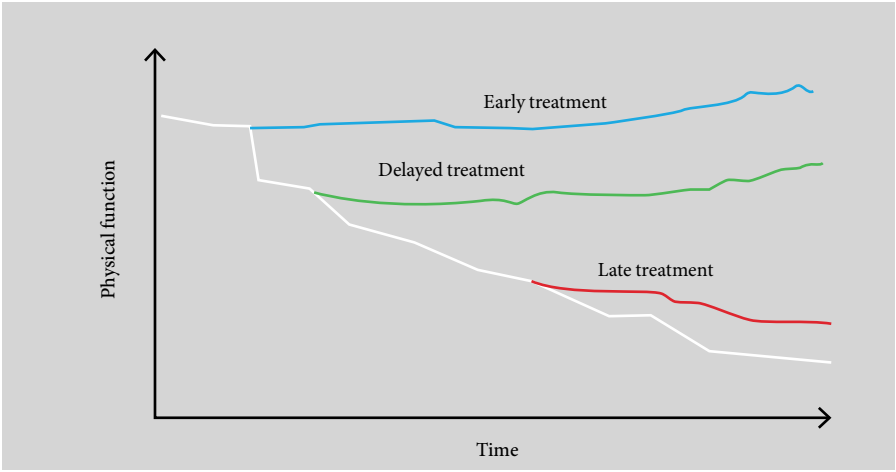

Figure 1.1 Why is early classification of rheumatoid arthritis needed? Over time, structural damage increases and physical function declines if rheumatoid arthritis (RA) is not treated effectively. While institution of therapy in late RA can improve function to only a very small extent, earlier treatment has the potential to stabilize physical function before permanent disability occurs.

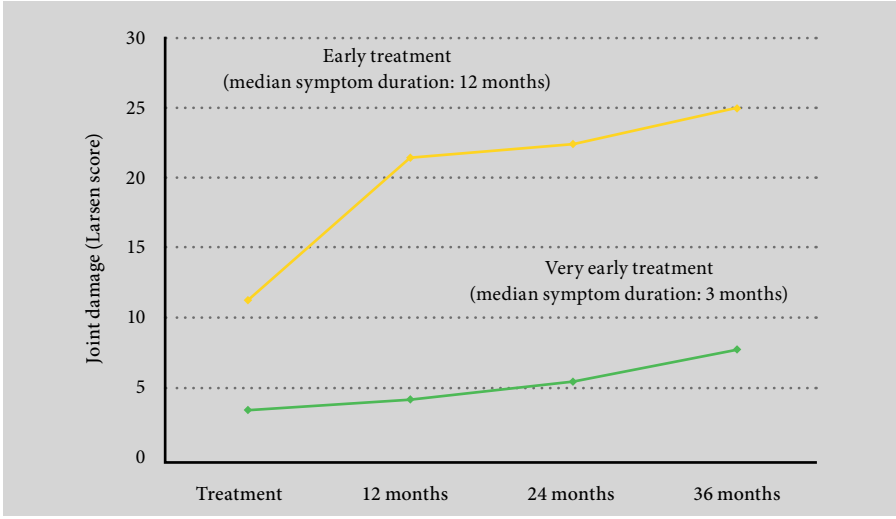

Figure 1.2 The importance of starting rheumatoid arthritis therapy very early. Even short delays in treatment initiation in patients with rheumatoid arthritis (RA) can lead to a considerable increase in structural damage over the course of 3 years. The yellow line shows that progression in Larson radiographic scores is already substantial in patients receiving early treatment initiation (ie, with a median symptom duration of only 12 months). In very early treatment initiation (ie, with a median symptom duration of 3 months, as represented by the course of the green line), the slope of progression is flattened and after 3 years, these patients did not reach the degree of structural damage that the early treatment initiation group already had at baseline despite only a 9-month delay in treatment. Adapted with permission from Nell et al [2] ©Oxford University Press.

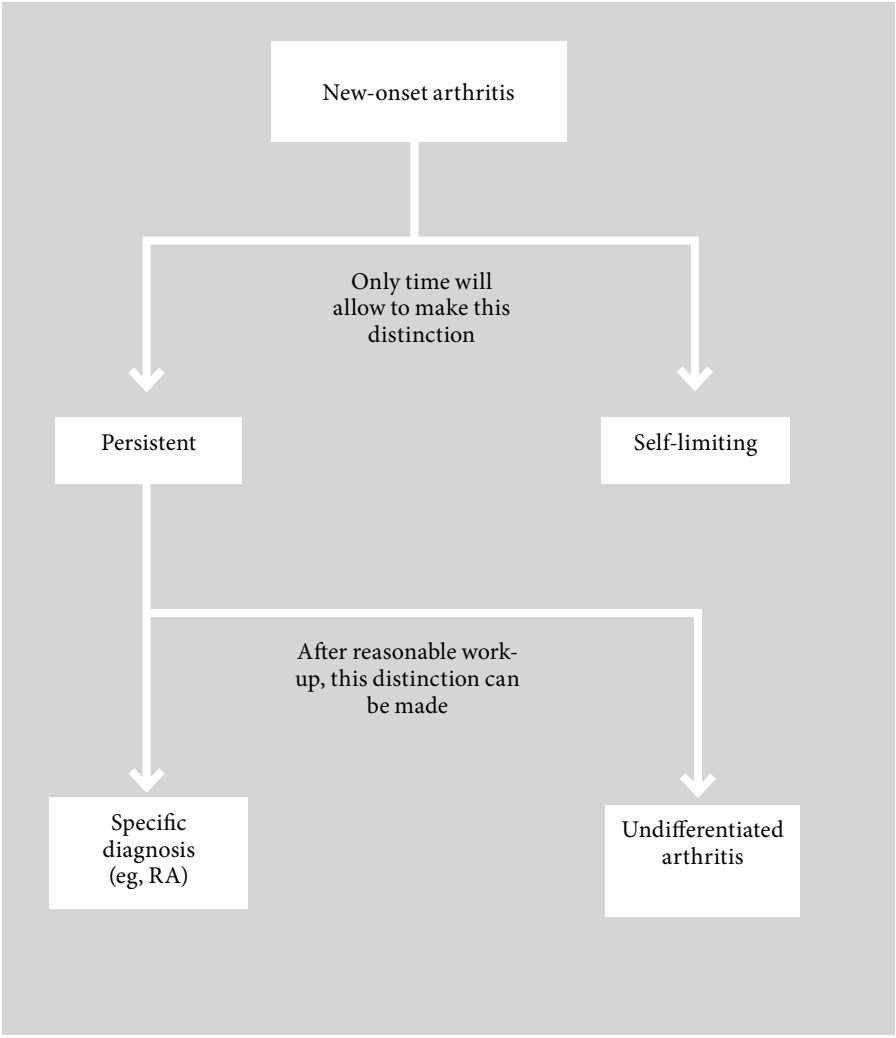

Figure 1.3 From symptom to diagnosis: rheumatoid arthritis. New-onset arthritis can have numerous causes. Only time will allow for a distinction between a self-limiting and a persistent disease. A reasonable clinical work-up needs to be done to be able to label arthritis as 'undifferentiated,' if a specific diagnosis cannot be established otherwise. RA, rheumatoid arthritis.

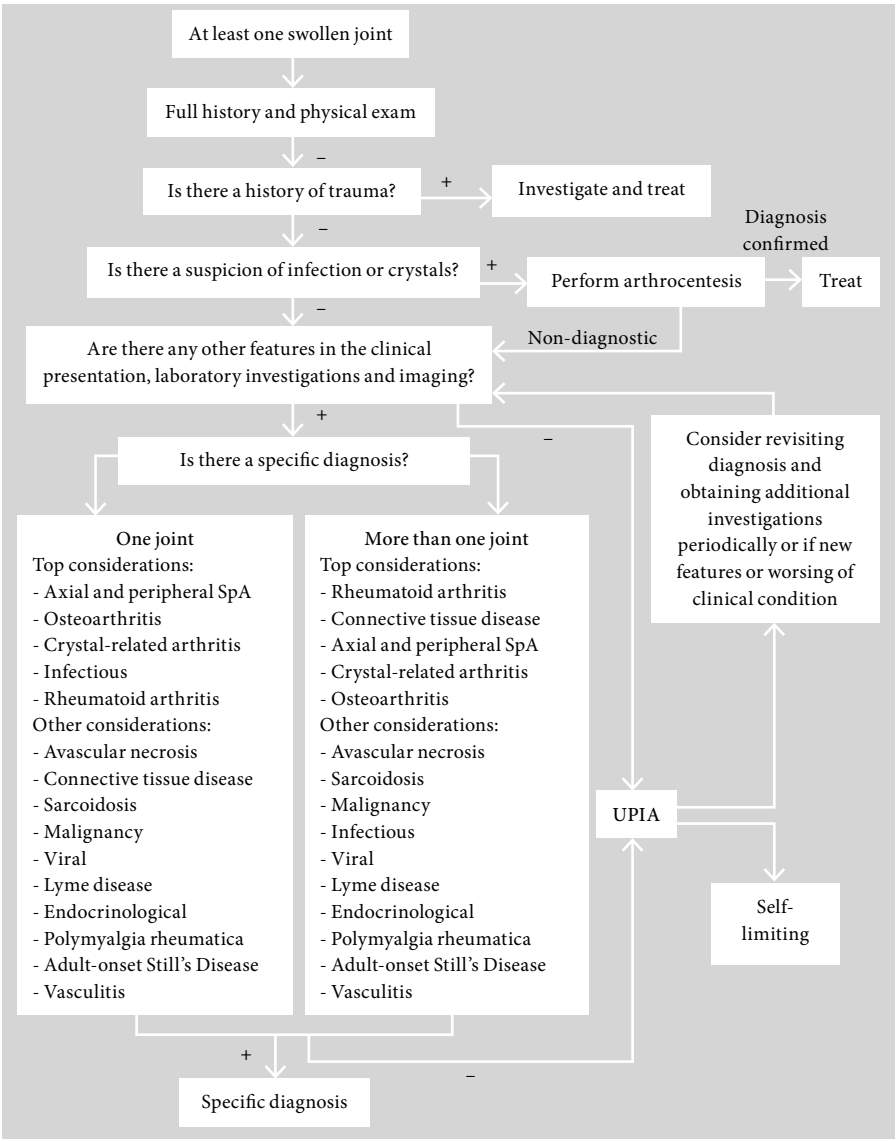

Figure 1.4 Flowchart for establishing a specific diagnosis in new onset arthritis in at least one swollen joint. Starting point in rheumatoid arthritis diagnosis is a full health history and physical examination. After exclusion of trauma and acute inflammatory events, a specific diagnosis may be established in the presence of suggestive clinical, laboratory, or imaging features, where the differential diagnoses vary according to the number of swollen joints involved. If no specific diagnosis can be established, the presentation may be labeled as 'undifferentiated arthritis' (or undifferentiated peripheral inflammatory arthritis). This status needs to be re-evaluated periodically, as undifferentiated arthritis may evolve into a specific diagnosis over time. SpA, spondyloarthritis; UPIA, undifferentiated peripheral inflammatory arthritis. Adapted with permission from Hazelwood et al [6] ©Journal of Rheumatology.

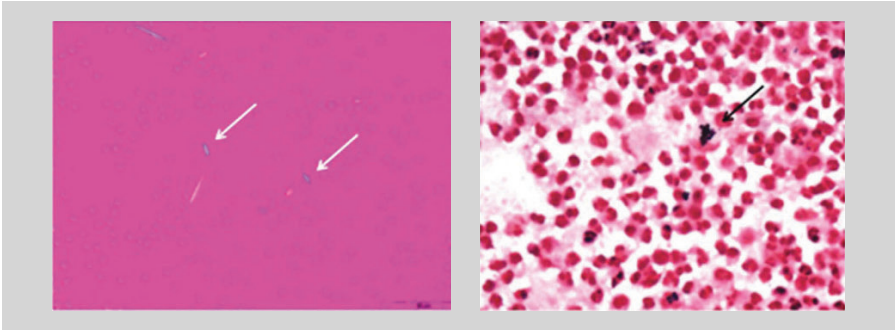

Figure 1.5 Microscopic synovial fluid analysis. Left panel: Crystal arthritis – evidence of intracellular needle shaped crystals (white arrows). Right panel: Septic arthritis showing positive Gram stain of cocci (*Staphylococcus aureus*) in typical formation (black arrow). Photo courtesy of Professor Stefan Winkler, Division of Infectious Diseases, Medical University Vienna, Austria.

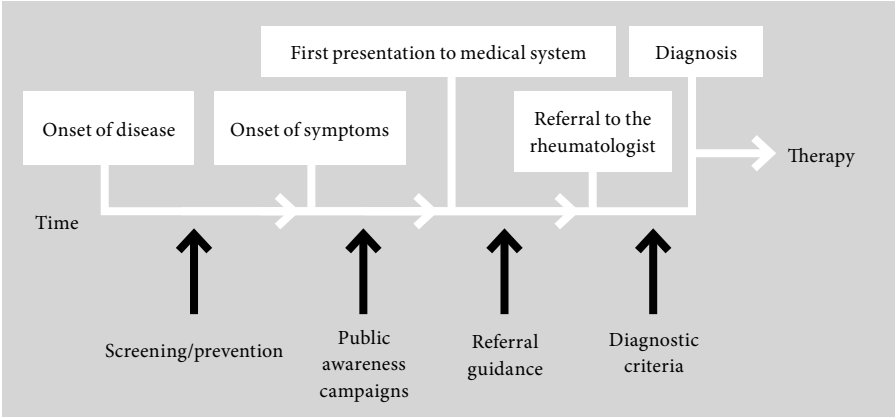

Figure 1.6 Limiting factors of early treatment. Several types of delays can occur in the course of arthritis diagnosis and treatment. First, there can be a delay between disease onset and the onset of symptoms, where screening methods (in the future) may be able to elicit preventive means. It takes varying periods of time until patients present symptoms to a medical professional, usually to a general practitioner (GP), who then may take some time before referring a patient to a rheumatologist. Greater public awareness can shorten the former, and referral guidance may be provided to GPs to shorten the latter. It may also take time until the rheumatologist has established a diagnosis. Unfortunately, no diagnostic criteria are available for rheumatoid arthritis, and this will likely not change in the future due to the complex nature of the disease. Therefore, classification criteria are often used to inform the clinical diagnosis, although their purpose is different. Adapted with permission from Aletaha and Huizinga [7] ©Elsevier.

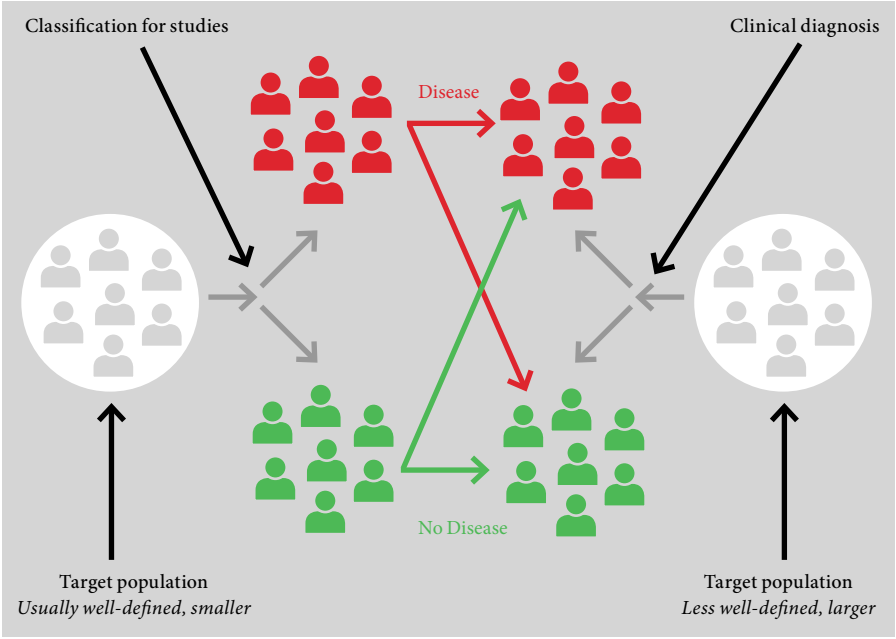

Figure 1.7 Differences between classification and diagnosis of disease. Classification criteria are developed for the purpose of identifying a homogeneous group of individuals for enrollment in clinical studies (eg, trials, observational studies, surveys). Individuals tested with classification criteria are usually well-defined. In contrast, a diagnosis has to be established by the rheumatologist and criteria are missing for most diseases. The target population for diagnosis is much wider and much more heterogeneous. Diagnostic criteria would need to be tested in various clinical settings (to patient groups with different background probabilities of disease) to understand their specific interpretation. Clinicians may adopt classification criteria to inform their diagnosis, but they will need to be aware that a classification incorporates the risk of a false-positive or false-negative, and relates to a specific (predefined) target population. In several instances, the result of the classification criteria will thus need to be overruled by the clinician.

Factor	Loading variables	Theme	Represented by
1	SJC, MCP_{SW}, $MCP_{SW\text{-}Sym}$	'MCP involvement'	MCP swelling (SW)
2	$Wrist_{SW}$, $Wrist_{TD}$, $Wrist_{SW\text{-}Sym}$	'Wrist involvement'	Wrist swelling
3	Tender joint count, MCP_{TD}, PIP_{TD}	'Hand/finger tenderness'	PIP or MCP or wrist tenderness (TD)
4	CRP, ESR	'Acute phase response'	Abnormal CRP or abnormal ESR
5	PIP_{SW}, PIP_{TD}	'PIP involvement'	PIP swelling
6	ACPA-positive, RF-positive	'Serology'	Positive for ACPA or RF

Table 1.1 Results of the data-driven Phase 1 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria: identifying variables important for classification of rheumatoid arthritis. After univariate analysis of candidate variables for prediction of methotrexate initiation, six predicting factors were determined by using principal component analysis (metacarpophalangeal joint involvement, wrist involvement, tenderness of the hand, acute phase response, proximal interphalangeal joint involvement, serology). Based on the loading of individual variables on these factors, each factor was attributed a theme. Subsequently, the most representative variable for each factor (and the most feasible) was then selected for further analysis in a multivariate model. ACPA, antibodies against citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RF, rheumatoid factor. Adapted with permission from Funovits et al [8] ©BMJ.

Representing variable	Comparison	P-value	OR (95% CI)	Weight
Swollen MCP	Present vs. absent	0.003	1.46 (1.14 to 1.88)	1.5
Swollen PIP	Present vs. absent	0.001	1.51 (1.19 to 1.91)	1.5
Swollen wrist	Present vs. absent	<0.001	1.61 (1.28 to 2.02)	1.5
Hand tenderness	Present vs. absent	<0.001	1.80 (1.33 to 2.44)	2
Acute phase	Moderate vs. normal	0.172	1.24 (0.91 to 1.70)	1
	High vs. normal	0.001	1.68 (1.23 to 2.28)	2
Serology	Moderate vs. normal	<0.001	2.22 (1.81 to 3.28)	2
	High vs. normal	<0.001	3.85 (2.96 to 5.00)	4

Table 1.2 Results of the data driven phase 1 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification project: analysis of independent contributions of important variables. The six variables representing each of the themes identified through univariate analysis and variable loading (metacarpophalangeal joint involvement, MCP, wrist involvement, tenderness of the hand, acute phase response, proximal interphalangeal joint involvement, PIP, serology) were tested in the depicted multivariate logistic regression model, using methotrexate treatment at 1 year after presentation as the reference standard. The odds ratios (ORs), refer to the independent contribution to the risk of methotrexate treatment, and the weight is based on the respective odds ratios estimated by the model. Adapted with permission from Funovits et al [8].

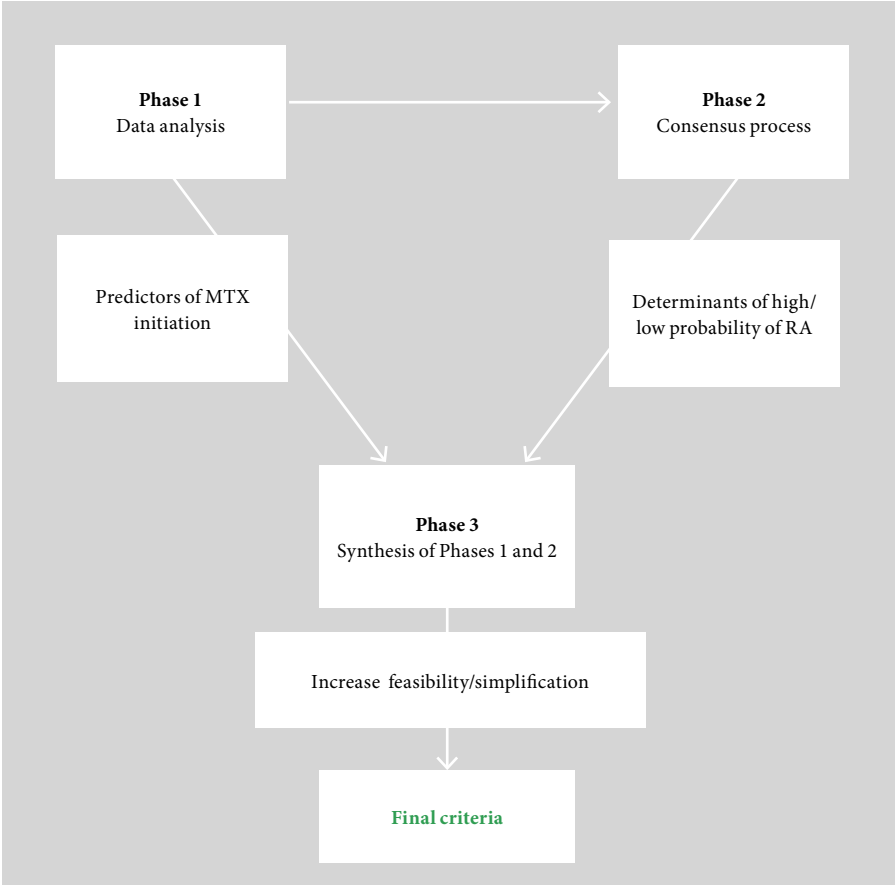

Figure 1.8 Schematic of the process to develop new classification criteria for rheumatoid arthritis. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria were derived in a three-stage process. Initially, a data analysis of several early arthritis cohorts, mostly from Europe, was used to identify the best predictors for treatment with methotrexate (MTX), which was deemed to be the best possible indicator of the physician's belief that this presentation was developing into the chronic, erosive rheumatoid arthritis (RA). During the second phase, a consensus process using conjoint decision analysis took place that fruited in the identification of determinants of a high probability of RA from the expert clinician's perspective. The results were synthetized in the last phase to increase practical usability and feasibility of the criteria in their application.

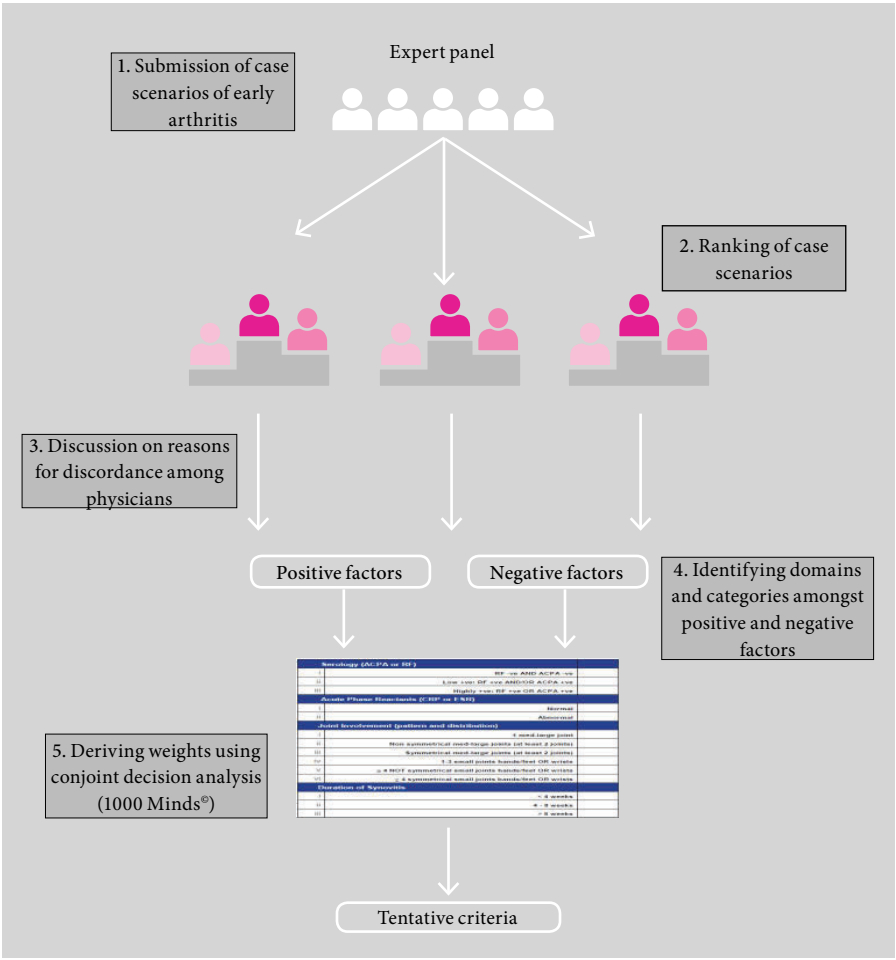

Figure 1.9 Overview of Phase 2 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. **1**. A panel of 24 international experts was established, each of whom submitted a number of case scenarios on early arthritis patients. **2.** A selection of 30 heterogeneous scenarios were then ranked by the experts for their probability of developing rheumatoid arthritis (RA). These rankings were very heterogeneous and showed a high level of discordancy across the experts. **3**. The results were then discussed to understand its reasons and causes for such discrepancy across the experts. This included possible features in the presentation that guided an expert towards choosing a higher probability ('positive factors') or lower probability ('negative factors'). **4.** Domains were identified for all positive and negative factors, and categories were defined within each domain. **5.** A computer-assisted decision analysis exercise was performed in which each category within each domain was assigned a specific weight, reflecting how strongly it affects the probability of developing RA from the perspective of expert clinicians. This led to the tentative criteria in Phase 2, which were then used to develop the final criteria set.

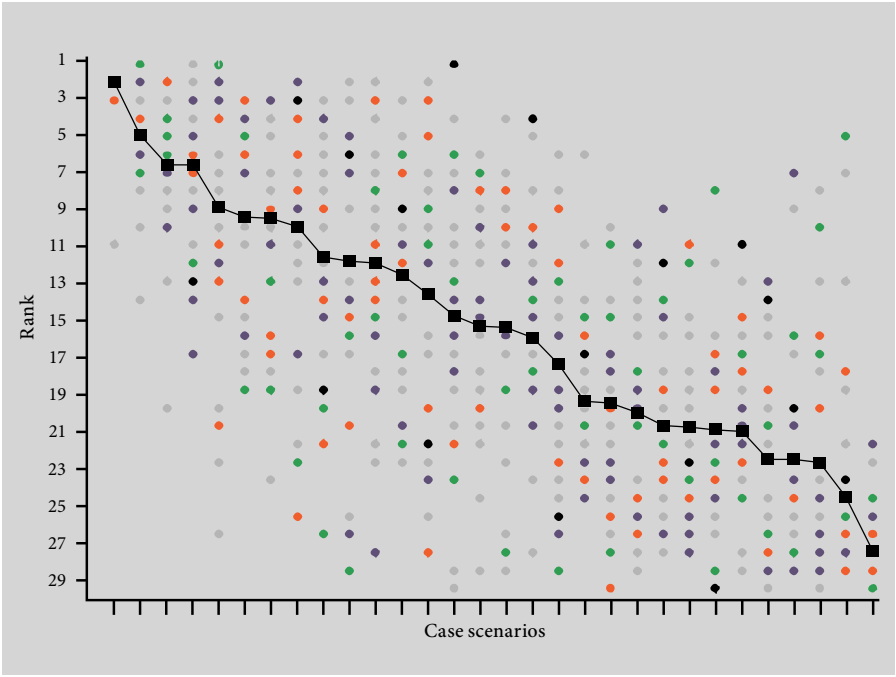

Figure 1.10 Discordance of expert clinicians in a ranking exercise of arthritis cases by their probability to develop rheumatoid arthritis. The vertical axis depicts the rank allocation (1–30) by each of the 24 experts (represented by differently colored dots) across the 30 selected case scenarios represented on the horizontal line (ordered by their average rank, from left to right; black marks and black connecting line). It can be seen that only in a few cases experts had consistent views (ie, left-most and right-most cases). All other cases showed substantial spread of rank allocations by different experts. The discussion of the reasons for discordance within these rankings led to the identification of important domains for the classification criteria from the clinical perspective. Reproduced with permission from Neogi et al [9] ©BMJ.

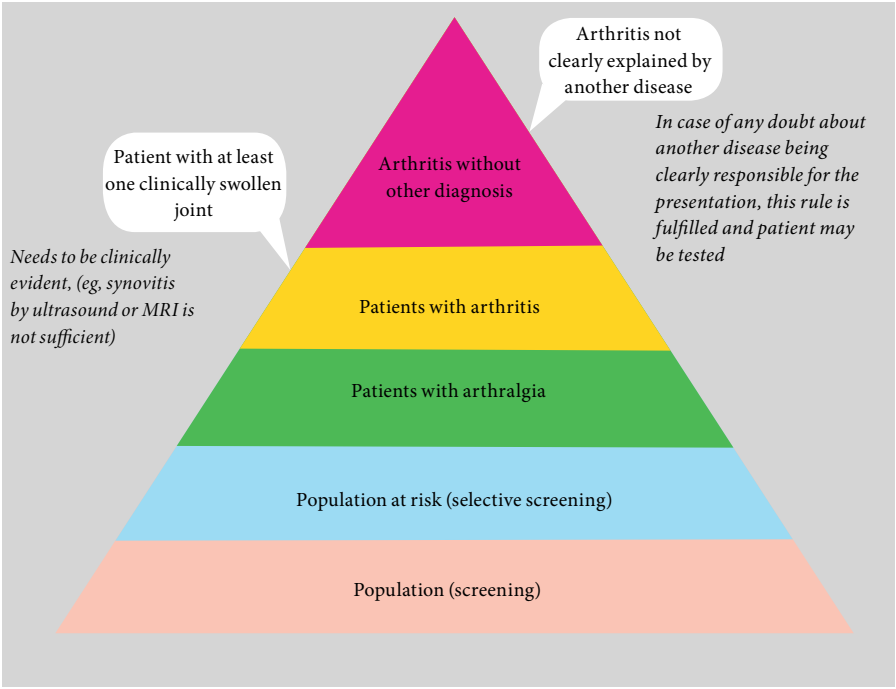

Figure 1.11 The target population for the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. The criteria may not be applied for population screening of rheumatoid arthritis (RA) or screening of individuals at risk of RA (eg, those with a positive family history of RA), nor for individuals with mere arthralgia. The requirements for patients to be tested with the criteria are (1) clinically evident arthritis (eg, joint swelling, synovitis); and (2) absence of evidence of another entity that clearly better explains the presentation (eg, acute gout attack).

Joint distribution (0–5 points)	Points
Joint involvement: Any swollen or tender joint (excluding DIP of hand and feet, 1st MTP, 1st CMC) Additional evidence from MRI/ultrasound may be used to identify additonal joints	
• 1 large joint (shoulder, elbow, hip, knee, ankles)	0
• 2–10 large joints	1
• 1–3 small joints (MCP, PIP, MTP 2–5, thumb IP, wrist); large joints not counted Does not include: DIP, 1st CMC, 1st MTP	2
• 4–10 small joints (large joints not counted)	3
• <10 joints (at least one small joint) Additional joints include: temporomandibular, sternoclavicular, acromioclavicular, and others (as reasonably expected in RA)	5
Serology (0–3 points)	
Serology: Negative: ≤ULN (for the respective lab) Low positive: >ULN but ≤3×ULN High positive: >3×ULN *Where RF is only available qualitatively, a positive result should be scored as 'low-positive' for RF*	
Negative RF *AND* negative ACPA	0
Low positive RF *OR* low positive ACPA	2
High positive RF *OR* high positive ACPA	3
Symptom duration (0–1 points)	
Symptom duration: Refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.	
<6 weeks	0
≥6 weeks	1
Acute phase reactants (0–1 points)	
Normal CRP *AND* ESR	0
Abnormal CRP *OR* abnormal ESR	1
Normal/abnormal ESR/CRP is determined by local laboratory standards	
Score ≥6 = Classification of RA TOTAL:	

Table 1.3 The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. A score of 6/10 needs to be achieved from four domains including: joint activity (0–5 points), serology (0–3 points), symptom duration (0–1 point), and acute phase response (0–1 point). ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RF, rheumatoid factor; ULN, upper limit of normal. Adapted with permission from Aletaha et al [10]©BMJ.

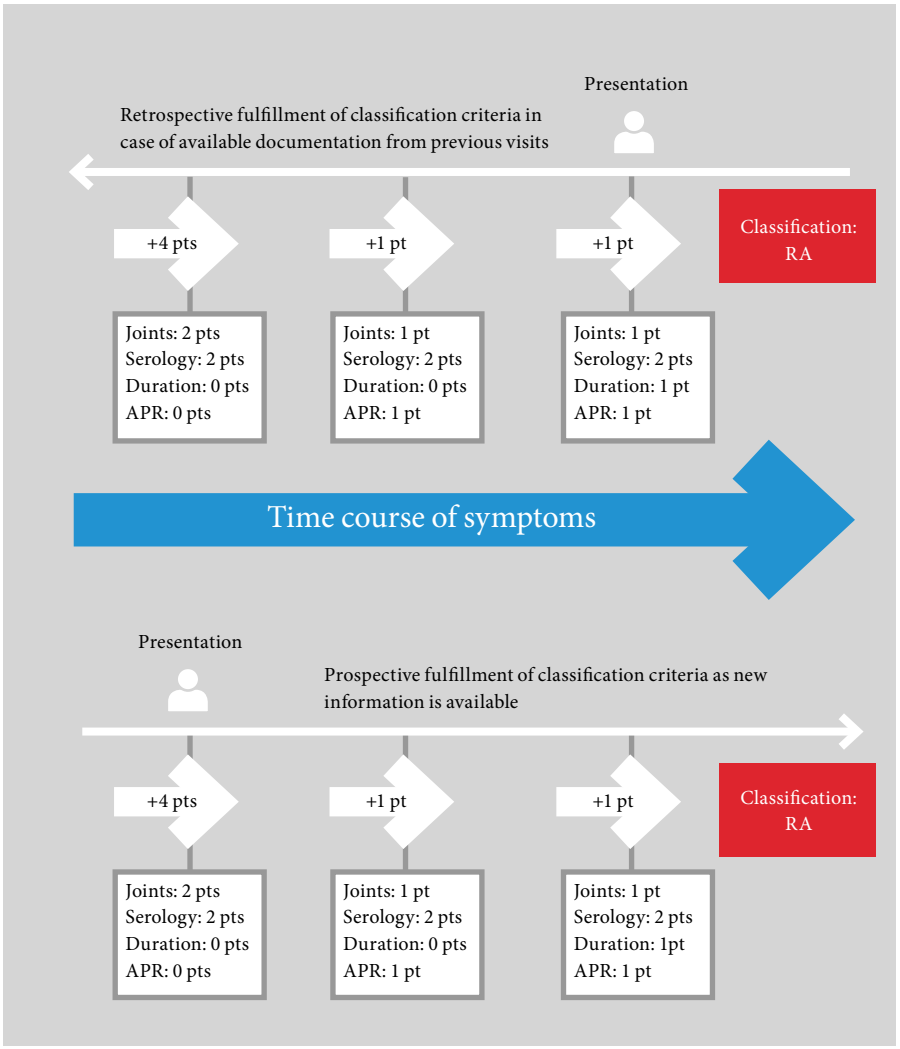

Figure 1.12 Cumulative fulfillment of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. The criteria may be fulfilled cumulatively over time, either retrospectively or prospectively. If a patient presents with a reasonable documentation on any of the domains represented in the criteria, then these can be counted towards a classification. Similarly, points in the classification system may also be collected over several prospective visits. Even if previous symptoms change, the highest score within each domain may be retained and used. APR, acute phase response; RA, rheumatoid arthritis.