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Guidelines

# Guidelines for the diagnosis of rheumatoid arthritis

## Diretrizes para o diagnóstico da artrite reumatoide

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*Description of the evidence collection method*
A review of the scientific literature was performed with the Medline database. The search for evidence was based on actual clinical scenarios and used the following Medical Subject Headings (MeSH) terms: Arthritis, Rheumatoid, Diagnosis (Delayed Diagnosis OR Delay OR Early Rheumatoid Arthritis OR VERA), Prognosis, Criteria (American College of Rheumatology/European League Against Rheumatism OR ACR/EULAR OR classification), Comparative Study, Smoking (OR tobacco use disorder), Rheumatoid Factor, Anti-cyclic Citrullinated Peptide (or anti-CCP), HLA-DRB1 OR PTPN22 OR EPITOPE, extra-articular OR extraarticular OR systemic OR ExRA, Disease Progression, Radiography OR X RAY, ULTRASONOGRAPHY, and MAGNETIC RESONANCE

*Grades of recommendation and strength of evidence*

- **A:** Most consistent experimental and observational studies.
- **B:** Less consistent experimental and observational studies.
- **C:** Case reports (uncontrolled studies).
- **D:** Opinion that is not substantiated by critical evaluation, based on consensus, physiological studies or animal models.

*Objective*
To formulate guidelines for the management of rheumatoid arthritis (RA) in Brazil, with a focus on diagnosis. The aim of the present document is to summarise the current position of the Brazilian Society of Rheumatology on this topic to orient Brazilian doctors, particularly rheumatologists, to RA diagnosis in our country.

## Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, and systemic inflammatory disease that preferentially affects the synovial membranes of joints and eventually leads to bone and cartilage destruction[1](D). RA affects 0.5%–1% of the adult population worldwide; the disease targets patients from every ethnic background[2](D) and predominately affects females (2- or 3-fold more often than males). Although RA can occur at any age, it is more frequent among individuals in the fourth to sixth decades of life[3](D).

A Brazilian multicentre study conducted with samples from the various macro-regions found a prevalence of up to 1% in Brazil's adult population[4](B), which corresponds to 1,300,000 people.

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As a chronic disease that causes irreversible joint damage, RA exacts high costs from both the patients and society at large [5](B) [6,7](D).

In recent years, significant advances have been achieved in understanding the physiopathogenesis, diagnostic methods, and therapeutic management of RA. Among these advances, the recently attributed significance of the early disease stages or so-called early RA (first 12 months with RA symptoms) stands out as an acknowledged "window of therapeutic opportunity"[8](B)[9,10](D). However, despite all advances, the currently available (clinical, laboratory, and radiological) diagnostic and prognostic indicators are of limited value to early diagnoses and individual prognoses[11](B).

The demographic and clinical features of RA vary as a function of the affected population[12](B). Most available data correspond to populations in Europe and the United States[13,14](D). Few studies have been conducted on the Brazilian population[15,16](B).

RA affects mostly individuals within the economically productive age range, and the disease eventually imposes significant limitations on their functional ability that result in the loss of work abilities. For these reasons, the indirect costs associated with RA must be included in pharmacoeconomic studies[17](B).

In Brazil and industrialised countries, the costs associated with RA are high[18](B). The impact of the expenses associated with RA is more remarkable in developing countries in which the financial resources allocated to healthcare are less robust. This situation points to the relevance of studies adapted to Brazilian conditions that assess the costs and allocation of resources for the diagnosis and treatment of RA[19](B).

RA diagnosis is based on clinical findings and complementary diagnostic tests. No single laboratory, imaging, or histopathological test alone can confirm a diagnosis.

Several illnesses that present with arthritis must be considered in the differential diagnosis of RA[20-22](D), as described in Table 1.

Diagnosis is easier when RA presents with the well-known pattern and the full range of typical symptoms. Diagnosis might be difficult in the early stages of disease because the characteristic serologic and radiological alterations are often absent[23](D).

The clinical manifestations of RA can be classified as articular and extra-articular. As RA is a systemic disease, general symptoms such as fever, asthenia, fatigue, myalgia, and weight loss can appear before or concomitantly with the onset of the articular manifestations[24](D).

## Articular manifestations

Although the articular manifestations of RA might be reversible in the early stages, persistent and uncontrolled synovitis leads to bone and cartilage destruction and irreversible tendon and ligament injuries.

The basic factor behind RA articular manifestations is synovial inflammation (synovitis), which can affect any diarthrodial joint in the body.

The clinical complaints include pain, swelling, and motion limitations of the affected joints. A physical examination will disclose the presence of pain, increased joint volume, intra-articular effusion, heat, and eventual redness. Those findings might not be evident in deep joints such as the hips and shoulders[24](D).

The characteristic features of arthritis in RA are as follows[24](D):

a) Polyarticular affection: usually involving more than four joints. Nevertheless, RA might begin and eventually remain as mono- or oligoarthritis.
b) Hand and wrist arthritis: affections of the wrist, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints are frequent from the very early disease stages. The distal interphalangeal (DIP) joints are seldom affected, a feature that distinguishes RA from other conditions such as osteoarthritis and psoriatic arthritis.
c) Symmetric arthritis: symmetric affection of joints is a common finding, although not mandatorily absolute in cases of the PIP, MCP, and metatarsophalangeal (MTP) joints.
d) Cumulative or additive arthritis: arthritis usually exhibits a cumulative pattern (progressive affection of new joints concomitant to inflammation of the previously affected ones).
e) Morning stiffness: prolonged stiffness that appears in the morning, which is accompanied by a sensation of swelling, is near-universal feature of synovial inflammation. Unlike the short-lasting (5–10 minutes, as a rule) variety observed in osteoarthritis, in inflammatory diseases, stiffness tends to last for more than 1 hour. This phenomenon is associated with immobility that occurs concomitantly to the state of sleep or rest, rather than to a particular time of the day. The duration of stiffness tends to correlate with the degree of inflammation and is an important parameter in follow-up evaluations[25](B)[26](C).

## Extra-articular manifestations

Although the articular manifestations are the most characteristic, other organs and systems can also be affected by RA.

**Table 1 – Differential diagnoses of arthritis.**

| Classes of diseases | Diseases |
|---|---|
| Infections | Viral (e.g. dengue, human immunodeficiency virus – HIV, parvovirus, cytomegalovirus, hepatitis), bacterial (e.g. N. gonorrhoeae, S. aureus), microbacterial, fungal, and others |
| Spondyloarthritis | Reactive arthritis (Chlamydia, Salmonella, Shigella, Yersinia), ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis |
| Systemic rheumatic diseases | Systemic lupus erythematosus, polymyositis/dermatomyositis, systemic sclerosis, Sjögren's syndrome, Behçet's disease, rheumatic polymyalgia, systemic vasculitis, and others |
| Microcrystalline arthritis | Gout, calcium pyrophosphate deposition disease, and others |
| Endocrine diseases | Hypothyroidism, hyperthyroidism |
| Neoplastic diseases | Metastatic neoplastic disease, lymphoma, paraneoplastic syndromes, and others |
| Others | Osteoarthritis, haemochromatosis, amyloidosis, sarcoidosis, serum sickness |

The most common extra-articular manifestations of RA include skin, eye, pleuropulmonary, heart, blood, neurological, and osteo-metabolic conditions. These occur more often in patients with severe and polyarticular disease, positive serology for the rheumatoid factor (RF) or cyclic citrullinated peptide antibodies (anti-CCP), and rheumatoid nodules[27](B)[28](D).

Brazilian studies confirmed that the initial manifestations of RA include polyarticular affection with persistent synovitis in the hands, long-lasting morning stiffness, a large number of painful and swollen joints, and fatigue[15,16](B).

## 1. Is diagnosis of RA within the first 12 months of symptoms (early RA) associated with better radiological and functional prognosis, compared to later diagnosis?

The modern differentiation of RA from other joint diseases dates from 1907. As no pathognomonic traits allow a distinction among the various types of arthritis in their early stages, the exact moment at which RA begins to progress as a separate entity from other articular illnesses is unknown[12](B).

The definition of early RA is important from both the theoretical and practical perspectives, although the terms "early" and "RA" might be addressed independently, particularly because the criteria applied to these classifications are based on established RA[13](D).

Although controversial, early RA might be defined as the initial stage of disease or a "window of therapeutic opportunity" in which adequate therapy might modify the disease progression; the prognosis in this stage is better than that of later stages[14](D).

The required symptom duration for the definition of early RA varies widely in the specialised literature. Historically, any RA of a duration less than five years has been characterised as "early"[15](B). However, together with the notion of a "window of opportunity", the original length of early RA needed to be restricted. Starting in the early 90's, early RA was consistently defined as the presence of symptoms for less than 24 months, with the main emphasis on the first 12 months of clinical manifestations[16](B).

The current indications are to assess patients with articular symptoms as soon as possible and to limit the early stage of RA to the first weeks or months of symptoms (as a rule, less than 12 months). In particular, the first 12 weeks are a critical period known as "very early" RA (VERA), while patients with more than 12 weeks but fewer than 12 months of articular symptoms are classified as so-called "late early RA" (LERA)[17](B).

The proportion of rheumatologists with opportunities to assess patients within the first six weeks of symptoms increased from 9% in 1997 to 17% in 2003; however, not every case is liable to such early assessment[18](B).

Even while admitting imprecisions in the definition of early RA, several authors have suggested that a substantial proportion of the cases with short-lasting (less than eight weeks) inflammatory arthritis exhibit spontaneous resolution, while only the few patients with persistent clinical manifestations progress into proper RA[19](B)[20-22](D). Thus, the establishment of clinical, serologic, or genetic markers that can identify patients who will progress to RA at the earliest stages and consequently will need appropriate treatments to reduce the odds of developing persistent disease and articular damage is of paramount importance.

The average time for the first visit of RA patients with a rheumatologist is 17 months, and 19 months usually elapse before the first administration of disease-modifying antirheumatic drugs (DMARDs). Factors such as education, the number of swollen joints, age, and occupation are associated with such delays[29](B).

Arthritis is characterised by articular swelling that is associated with pain or stiffness. Cases that involve more than one articulation should be referred to a rheumatologist, ideally within the first six weeks following the onset of symptoms[30](D).

For cases in which articular swelling was present only during the first year of disease, the risk of articular erosion was reduced by five years (NNT: 4), compared to those patients with joint swelling throughout the follow-up period[31](B).

RA diagnosis within the first three months of VERA was predictive of clinical (American College of Rheumatology – ACR) and radiological (Sharp score) remission[32](B).

The early identification of some factors allows clinicians to predict whether the RA lesions will exhibit radiological progression in the following 12 months. These factors include the Sharp score and modified Total Sharp Score (mTSS), the presence of autoantibodies such as RF and anti-CCP, and increased acute-phase reactants such as an erythrocyte sedimentation rate (ESR) greater than 28 mm and an average C-reactive protein (CRP) level of 10 mg/L[33](B).

The higher the erosion score at the onset of treatment, the worse the 10-year radiological prognosis (Sharp score)[34](B).

Early (within the first year) calculations of the Sharp, erosion, and reduced joint space scores permitted predictions of the radiological progression of RA patients who were followed-up for three years[35](B).

In spite of the early (three to six months from the beginning of symptoms) administration of DMARD treatment, 63.6% of the patients exhibited erosion three years later due to constitutional factors such as the presence of autoantibodies (e.g. RF or anti-CCP) and the length of disease activity (CRP, joint swelling, and response to treatment)[36](B).

The duration of RA interferes with the functional prognosis, which is measured by means of the Health Assessment Questionnaire (HAQ) and is independent of the baseline values[37](B).

When DMARD treatment was initiated within the first year of disease (average symptom duration, six months), the radiological progression (Ratingen score) was reduced at the 5-year follow-up[38](B).

In patients with symptom durations less than 12 weeks who were treated for RA, the radiological progression (Sharp-van der Heijde score, SHS) was reduced after six years of follow-up. Sustained DMARD-induced remission was 8% higher (NNT: 13) in patients with symptom durations less than 12 weeks[39](B).

DMARD treatment of RA patients within the first year of disease induced better functional (Keitel Functional Test – KFT) and clinical (joint swelling) progression at a 10-year

follow-up, compared to those who were treated one to five years after disease onset[40](B).

*Recommendation*

Diagnosis of RA with a symptom duration of less than 12 months (early RA) is of paramount importance because early diagnosis exerts beneficial effects on radiological and functional prognoses compared to later diagnosis.

## 2. Are the new 2010 ACR/European league against rheumatism (EULAR) classification criteria for RA superior to the 1987 classification criteria for the early disease stage?

RA classifications were essentially based on the criteria formulated by the ACR in 1987[41](B), which are described in Table 2. However, those criteria did not perform well in early RA cases[42](B). The ACR classification criteria for RA were based on individuals with long-standing disease and, until then, were considered to be the standard for the selection of patients for clinical studies. These criteria exhibit 91%–94% sensitivity and 89% specificity for established RA. However, some of the items, such as radiological changes (erosions) and rheumatoid nodules, do not occur often in early RA. Thus, such criteria are suboptimal for the identification of individuals with early RA (40%–90% sensitivity, and 50%–90% specificity)[43](B).

**Table 2 – 1987 American College of Rheumatology classification criteria for rheumatoid arthritis.**

| Criteria | Definition |
|---|---|
| 1.Morning stiffness | Morning stiffness lasting at least 1 hour before maximal improvement |
| 2.Arthritis of 3 or more joint areas | At least three joint areas simultaneously affected and observed by a physician. The possible areas include the right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints. |
| 3.Arthritis of hand joints | Arthritis in wrist, MCP, or PIP joint |
| 4.Symmetric arthritis | Simultaneous involvement of the same joint areas on both sides of the body. |
| 5.Rheumatoid nodules | Subcutaneous nodules over bony prominences, extensor surfaces, or in juxta-articular regions as observed by a physician |
| 6.Serum rheumatoid factor | Demonstration of abnormal amounts of serum rheumatoid factor. |
| 7.Radiographic changes | Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs showing juxta-articular bone thinning or erosions |

For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four or these seven criteria. Criteria 1 through 4 must have been present for at least six weeks. Modified from: Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.

As a result, new RA classification criteria were needed, with a special focus on the early disease stages[14](D).

The new ACR/EULAR classification criteria can be applied to any patient, provided that two basic requirements are met as follows:

1) Evidence of active clinical synovitis in at least one joint at the time of examination.
2) Synovitis cannot be better explained by another disease.

The new criteria (Table 3) are based on a score system that is calculated by direct addition. The clinical manifestations are grouped into the following four domains: joint involvement, serology, duration of symptoms, and acute-phase reactants. In questionable cases, the number of involved joints can be calculated by the use of imaging methods such as ultrasound (US) and magnetic resonance (MRI). A score > 6 is needed to classify a patient as having definite RA[44](B). These criteria can be applied both prospectively and retrospectively, provided that the data were properly recorded.

It is worth observing that whenever a patient exhibits typical erosions upon radiological examination and a clinical history compatible with RA (albeit non-documented), RA diagnosis can be directly established in a manner independent of the applicability of the classification criteria[14](D).

The new 2010 criteria were not developed for the purpose of diagnosis but rather of classification. The criteria basically serve to select homogeneous populations for studies.

Clinical RA diagnoses are extremely complex and includes multiple features that are hard to reconcile with a single scoring system[14](D). Eventually, the formal criteria might serve to guide clinical diagnoses.

Several features of the new criteria must be subjected to careful analysis before they can be universally accepted. In particular, the criteria must be validated in different populations, including Brazilian early RA cohorts.

In patients who use methotrexate and those with persistent RA, the discriminatory powers of the 2010 ACR/EULAR criteria were 76% and 87%, respectively, when the score was at least 6, and 63% and 46%, respectively, when it was < 6[45](B).

Assuming the need for methotrexate, a diagnostic gold standard, during the first year of follow-up, the 2010 ACR/EULAR criteria were able to diagnose 86% of the cases for which the score was at least 6 and 49% when it was < 6[45], compared to 87% and 41%, respectively, when the 1987 ACR criteria were used[46](B).

A comparison of the 2010 ACR/EULAR (score of at least 6) and 1987 ACR (score > 4) criteria relative to the diagnosis of patients with a disease duration of less than 12 months showed positive predictive values of 70.7% and 65.3%, respectively, and negative predictive values of 76.1% and 79.1%, respectively[47](B).

The discriminatory powers of the 2010 ACR/EULAR and 1987 ACR criteria during an 18-month follow-up period were compared and are shown in Table 4.

The application of the 2010 ACR/EULAR criteria at disease onset detected more patients who required DMARD treatment than did the 1987 ACR criteria; the values were 62% and 38%, respectively, and more particularly with regard to the use of methotrexate during the 18-month follow-up, the values were 68% versus 42%, respectively. However, the 2010 ACR/EULAR criteria were associated with a higher rate of false-positive cases (8% versus 2% for the 1987 ACR criteria)[48](B).

**Table 3 – 2010 ACR/EULAR classification criteria for rheumatoid arthritis.**

Target population (Who should be tested?) Patients who meet the following criteria:

1) Have at least 1 joint with definite clinical synovitis (swelling)*
2) Present with synovitis that is not better explained by another disease
*Differential diagnoses might include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If the relevant differential diagnoses to consider are unclear, an expert rheumatologist should be consulted.

| Joint involvement (0–5) | | Serology (0–3) | | Duration of symptoms (0–1) | | Acute-phase reactants (0–1) | |
|---|---|---|---|---|---|---|---|
| 1 large joint | 0 | Negative RF AND negative ACPA | 0 | < 6 weeks | 0 | Normal CRP AND normal ERS | 0 |
| 2–10 large joints | 1 | Low-positive RF OR low-positive ACPA | 2 | ≥ 6 weeks | 1 | Abnormal CRP OR abnormal ERS | 1 |
| 1–3 small joints (large joints are not taking into account) | 2 | High-positive RF OR high-positive ACPA | 3 | | | | |
| 4–10 small joints (large joints are not taking into account ) | 3 | | | | | | |
| > 10 joints (at least 1 small joint) | 5 | | | | | | |

A score ≥ 6 is needed for the classification of a patient with definite RA. "Joint involvement" refers to any swollen or tender joint on examination, which might be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. "Large joints" refers to the shoulders, elbows, knees, and ankles. In the category "> 10 joints" at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as joints that are not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).
In "Serology", negative refers to IU values of the rheumatoid factor or anti-citrullinated protein antibody that are less than equal to the upper limit of normal (ULN) for the laboratory and assay, low-positive refers to IU values that are higher than the ULN, but ≤ 3 times the ULN for the laboratory and assay, and high-positive refers to IU values that are ≥ 3 times the ULN for the laboratory and assay.
"Duration of symptoms" refers to patient self-reports of the duration of signs or symptoms of joint synovitis that are clinically involved at the time of assessment.
"Acute-phase reactants" (erythrocyte sedimentation rate, and C-reactive protein) are considered to be normal/abnormal according to the local laboratory standards.
Modified from: Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010; 69(9):1580-8.

**Table 4 – Positive and negative predictive values from the 1987 ACR and 2010 ACR/EULAR criteria for patients with rheumatoid arthritis who are using disease-modifying anti-rheumatic drugs at the onset of disease and 18 months later.**

| Measurement | Cohort onset | | 18 months later | |
|---|---|---|---|---|
| | 2010 ACR/EULAR | 1987 ACR | 2010 ACR/EULAR | 1987 ACR |
| + predictive value | 75% | 85% | 73% | 81% |
| - predictive value | 66% | 59% | 69% | 79% |

In cases for which the 1987 ACR criteria had been used to define RA (without radiological aid), the 2010 ACR/EULAR criteria were diagnostic of disease in 59% of the cases (positive predictive value), and ruled out the diagnosis in 93% (negative predictive value). The rate of false-positive results for the 2010 ACR/EULAR criteria was 17%. If RA was considered a chronic disease (five years of follow-up), the discriminatory power of the 2010 ACR/EULAR criteria fell to 68% when the score was at least 6 and to 61% when the score was < 6. Nevertheless, the 1987 ACR criteria identified 11.3% fewer cases as RA than did the 2010 ACR/EULAR criteria[49] (**B**).

*Recommendation*

The 2010 CR/EULAR criteria identify more patients with early RA than do the 1987 ACR criteria. However, the rate of false-positive cases is higher with the newer criteria. When follow-up criteria such as use of DMARDs or disease persistence are used, the discriminatory powers of the 2010 CR/EULAR and the 1987 ACR criteria are similar.

## 3. Is smoking associated with a poorer prognosis for articular disease in RA patients?

Smoking was found to increase the risk of non-response (ACR50) by 18.3% [number needed to harm (NNH): 6] in patients with early RA (24 weeks of symptom duration)[50] (**B**).

According to the EULAR criteria, RA patients who were smokers were less likely to achieve a good response at three months of treatment, compared to the non-smokers (NNH: 11). The patients who continued to smoke exhibited lower odds

of good treatment responses during a 5-year follow up period. That difference in good treatment responses was somewhat higher in patients who were treated with anti-tumour necrosis factor (TNF) (14%; NNH: 7)[51](B).

Smokers tend to exhibit more extra-articular manifestations of RA (pleuritic, pericarditis, interstitial lung disease, neuropathy, glomerulonephritis, vasculitis), compared to non-smokers, as well as higher average Disease Activity Score (DAS-28), and Health Assessment Questionnaire (HAQ) values [52](B).

Smoking increased the use of DMARDs in RA patients and reduced their clinical responses (ACR50) by 16% (NNH: 6), particularly in smokers of more than 20 packages/year[53](B).

The radiological progression of RA was similar in smokers and non-smokers after three years, which did not agree with the poorer clinical responses exhibited by the former[54](B).

RA patients who were smokers exhibited greater disease activity (joint pain and swelling) when compared to non-smokers after 24 months of treatment. The pain scores [(on a visual analogue scale – VAS) were also higher among the smokers. However, radiological progression did not differ between smokers and non-smokers[55](B).

Disease activity (measured as joint swelling, pain, and DAS-28) was greater in patients with an average symptom duration of seven months who were smokers when compared to non-smokers after a 5-year follow-up[56](B).

*Recommendation*

Smoking increases the disease activity of RA and reduces clinical and functional responses over time. However, there is no sufficient evidence regarding its influence on radiological disease progression.

## 4. Is measurement of the rheumatoid factor a reliable test for diagnosis and prognostic stratification in RA?

RF is an antibody that targets the Fc fragment of IgG[57](D). RF is classically associated with RA, is found in the serum of approximately 70% of RA patients, and is significantly correlated with a poorer prognosis. High RF levels are associated with aggressive disease, the presence of rheumatoid nodules, and extra-articular manifestations[58](D).

The diagnostic value of RF alone is limited because 30%–50% of patients might be seronegative during the early stage of RA[57](D). In addition to its low sensitivity, its specificity is limited. Individuals without RA might test positive for RF, and its prevalence increases with age[59](B). Patients with other medical conditions, both rheumatologic and not, might also test positive for RF[44,60](B). Therefore, negative RF serology does not rule out a diagnosis of RA, whereas the interpretation of positive results must be carefully checked against the clinical findings.

Brazilian data (incident early RA cohort) indicate a RF prevalence of approximately 50% in patients [61](B).

RF-positive patients with RA exhibited a 17% increase of mortality (NNH: 6) and cardiovascular mortality (NNH: 6) after 20 years of follow-up[62](A).

The mortality of RA patients with RF-positive serology did not differ from that of seronegative patients after 14 years of follow-up. However, when the results were analysed according to the number of expected events in the population, the mortality, and more specifically the cardiovascular mortality, was elevated in the RF-positive patients [63](B).

A 10-year follow-up study of RA patients, in which 24% of the cases tested positive for RF of the IgM and IgA isotypes, found that radiological progression was associated with and could be predicted by the serological findings (e.g. IgM or IgA)[64](B).

In a population of RA patients, 51% of whom were RF-positive, the presence of RF was predictive of radiological progression in 69% of the cases, whereas its absence ruled out progression in 83%.

RF was predictive of radiological progression (Larsen score) in RA patients after 5 years of follow-up[65](B).

RF was predictive of radiological progression (Sharp or Larsen scores)[35,66](B) and the need for biological therapy[67](B) in RA patients after three years of follow-up.

The risk of radiological progression was 24.3% (NNH: 4) higher among RF-positive patients versus RF-negative patients[68](A).

With a pre-test RA probability rate of 35%, positive RF (IgM, IgA, and IgG isotypes), measured by ELISA, increased the diagnostic probability rate to 94%, while negative serology ruled out RA with an 85% certainty rate[69](B).

In a population of patients with a 35% probability rate of RA, RF (IgM, IgA, and IgG isotypes) increased the post-test probability to 96%[70](B).

*Recommendation*

RF measurement contributes estimations of prognosis for RA patients, particularly with regard to radiological progression and mortality. Positive RF serology, particularly in populations with a pre-test probability rate of 35%, increased the diagnostic probability to 94%–96%, whereas negative RF serology ruled RA out with a post-test probability of 85%.

## 5. Is anti-CCP investigation superior to rheumatoid factor investigation for RA diagnosis?

Recently, several anti-citrullinated protein antibodies (ACPA) were shown to behave as important diagnostic tools for RA; these had a similar sensitivity and superior specificity to RF, in addition to their possible participation in disease physiopathogenesis[71](B). Their possible roles as markers of RA activity are controversial[72](B).

*Cyclic citrullinated peptide antibodies*

Among the investigated antibodies that target filaggrin-citrulline system antigens, anti-CCP exhibits the widest clinical applicability, with 70%–75% sensitivity and approximately 95% specificity. Anti-CCP analyses are particularly useful for patients with early RA and negative RF serology[73](B).

Anti-CCP measurements are also valid in investigations of undifferentiated arthritis. These antibodies are detected very early in the course of RA, and thus might be used as markers for progression and disease prognosis[41-43,74-78](B)[21,79](D).

*Other antibodies*

Other antibodies are also used to investigate RA. The aim is to develop methods with sensitivities and specificities satisfactory for early disease diagnosis, as well as more reliable markers for activity and prognosis. These antibodies include anti-mutated citrullinated vimentin (anti-MCV)[80-82](B), anti-keratin (AKA), anti-perinuclear factor (APF)[83](B), anti-filaggrin[84](B), anti-citrullinated fibrinogen (ACF)[85](B), anti-protein A2 of the heterogeneous nuclear ribonucleoprotein complex (anti-RA33)[83](B), anti-interleukin 1 (anti-IL1)[86](B), anti-1-α-enolase[87](B), and anti-advanced glycation end-product (AGE)[88](B). The specificities of these antibodies are generally satisfactory for RA diagnosis, but their sensitivities is generally lower than that of anti-CCP.

The 2010 ACR/EULAR criteria[14](D) include only RF and ACPA under the heading "autoantibodies", and the values of these antibodies are described as negative, low, or high titres. As the values of both RF and anti-CCP are expressed as international units (IU), the results are rated negative when they are equal to or higher than the upper limit of normal (ULN) in the corresponding laboratory; low-positive when they are higher than the ULN, but equal to or lower than 3 times the ULN; and high-positive when they are higher than three times the ULN.

Positive anti-CCP correlated with the MRI swelling and erosion score at a 4-year follow-up, whereas negative anti-CCP correlated with the synovitis score[89](B).

Anti-CCP was superior to RF for predictions of the progression of undifferentiated arthritis into RA (diagnostic certainties of 93% and 68%, respectively). The former also permitted better estimates of the severity of disease at a 7-year follow-up[90](B).

The risk of positive anti-CCP serology in patients with active RA is 23% higher than that of patients in the period before disease. The anti-CCP alterations did not change after seven years of follow-up[91](B).

With regard to the use of anti-CCP (second generation, anti-CCP2) and data from 15 recent RA cohorts, it was concluded that a single positive result permits a diagnosis of RA (likelihood ratio, LR+ 12.7), but that a single negative result does not rule out RA (LR– 0.45). Upon comparing RF and anti-CCP2, we found that their sensitivities are similar (56% and 58%, respectively), but the specificity of anti-CCP2 is superior (96% versus 86% for RF). The sensitivity and specificity of anti-CCP2 are higher than those of anti-CCP1. The combination of positive RF and anti-CCP2 only slightly increases the diagnostic certainty, compared to anti-CCP2 alone (LR+ 27 versus 22, respectively). An analysis of global evidence allows us to estimate the sensitivity of anti-CPP2 a 67%, and the specificity as 96%. Assuming a prevalence of 42% in RA patients according to the 1987 ACR criteria, positive anti-CCP2 serology increases the diagnostic certainty to 90%, and negative serology rules out RA with a certainty of 75%[92](B).

*Recommendation*

The sensitivity of anti-CCP is similar to that of RF, but the specificity of the former is superior, especially in the early disease stages. Anti-CCP evaluations are recommended in patients with a clinical suspicion of RA and negative RF test serology.

## 6. Are genetic markers (evaluations of HLA-DRB1 shared epitope alleles and PTPN22 genes) useful for characterisations of RA patients with poorer prognosis?

Although countless genetic markers have been described in association with RA, only the HLA-DRB1 shared epitope (SE) 10The presence of SE (HLA-DRB1) in RA patients did not correlate with radiological disease progression[105,107](B). However, according to some data, SE alleles and anti-CCP antibody levels might be associated with the severity of joint damage (erosion and radiological damage score) in RA patients[108](B). The HLA SE had no predictive value relative to radiological RA progression[109](B).

The frequency of HLA-DRB1 alleles with SE was found to be high in Latin American RA patients[110](B).

The presence of SE alleles (DRB1) might be predictive of mortality, including cardiovascular mortality, in RA patients with RA[111,112](B).

An association was found between the DRB1 genotype and RF-positive RA patients with a 3.0%–3.7% (NNH: 30) risk increase[113](B).

*Recommendation*

The PTPN22 gene polymorphism is associated with RA. Although it is not predictive of specific therapeutic responses to biological therapy, it is predictive of remission when associated with anti-CCP. Alone or in combination with HLA-DRB1 (SE), the PTPN22 polymorphism permits estimations of radiological progression or disease activity. The HLA-DRB1 allele seems to play a more important role in the prediction of poor prognosis relative to the progression, activity, severity, and mortality of RA.

## 7. Does the occurrence of extra-articular manifestations denote a more aggressive disease progression?

Although articular manifestations are the most characteristic, RA can also affect other organs and systems. The most frequent extra-articular manifestations include skin, eye, pleuropulmonary, heart, blood, neurological, and osteo-metabolic conditions. These occur more often in patients with severe and polyarticular disease, positive RF or anti-CCP serology, and rheumatoid nodules[27](B)[28](D).

The incidence of extra-articular manifestations in RA is 47.5%, which includes cardiovascular, blood, eye, and lung affections. Such manifestations are associated with a greater likelihood of the use of biological agents[114](B).

Clinically significant lung interstitial disease occurs in 10% of RA patients[115](B). Patient mortality depends on the type of lung affection and is greater when the affection is diffuse[116](B). Pulmonary fibrosis-related mortality is approximately 6%[115](B). The average survival of patients with interstitial pneumonia is 3.2 years, and thus is generally lower compared to that of other varieties of interstitial disease (6.6 years)[116](B). In RA patients with lung interstitial disease, anti-TNF drugs must be used cautiously due to the risk of increased mortality[117](B).

The mortality rate of RA patients with lung interstitial disease is 7%, and the average survival duration after diagnosis is three years. In spite of the association between interstitial lung disease and RA activity, the latter was only denoted by increased ESR in that study[118](B).

The presence of kidney dysfunction in RA patients is not associated with the activity, progression, dysfunction, or severity of the disease[119](B).

RA patients with extra-articular manifestations exhibit a 20% increase in the risk of cardiovascular events (including acute myocardial infarction, angina, coronary disease, and stroke) (NNH: 5)[120](B).

The survival of patients with extra-articular manifestations of RA (18% of cases) is lower than that of patients with exclusive articular manifestations, and the relative risk of death in the former increases by 27% after seven years of follow-up. Similar to the extra-articular manifestations, comorbidities also increase mortality, particularly cardiovascular conditions because these cause 31% of patient deaths. Increased mortality correlates with greater disease activity (RF), worse function (HAQ), and increased radiological progression[121](B).

In RA patients with extra-articular manifestations, the scores that assess disease activity, such as DAS28 and HAQ, and the Larsen radiological score tend to be poorer, thus denoting a greater disease severity. Only 4.1% of such patients achieved remission[122](B).

After 15 years of follow-up, mortality increased only in the patients with extra-articular manifestations (relative risk increase: 51%), compared to those without such conditions; pericarditis was the most significant of the manifestations[123](B).

The mortality rate of RA patients with extra-articular manifestations (7.9% prevalence) was one death per 4.3 patients per year, whereas the rate of patients without articular manifestations was one death per 11.4 patients per year[124](B).

The risk of severe gastrointestinal diseases is elevated in RA patients with extra-articular manifestations (4.6% prevalence). In such patients, the disease intensity (ACR criteria) and the signs of radiological progression are also greater[125](B).

*Recommendation*

RA progression is more severe in patients with extra-articular manifestations. These patients have more intense disease activity with reduced functional capacities, responses to treatment (less occurrence of remission), and life expectancies, compared to those with exclusive articular manifestations.

## 8. Is conventional radiography an appropriate test for RA diagnosis?

Conventional radiography is the most widely used imaging method for assessments of structural joint damage in RA. In addition to its diagnostic utility, conventional radiography plays an important role in the monitoring of disease progression, provided that it is performed at regular intervals[126](D).

The initial radiographic signs include increased amounts of soft tissues and juxta-articular osteopenia. More characteristic signs of RA, such as reduced joint space and bone erosion, appear later in the disease course.

The presence of bone erosion during the early stages of RA represents a risk factor for the development of persistent arthritis[127](B). This factor is associated with functional limitation and thus with poorer prognosis[128](B).

When erosions are identified by radiography (15% prevalence), the diagnostic probability increases to 100%. However, as negative findings do not reduce the probability (18%), they do not rule out a RA diagnosis[129](B).

In patients with strong clinical suspicion of RA but negative RF serology and radiography, the presence of anti-CCP antibodies and erosions on MRI are highly specific for RA diagnosis[130](B).

In RA patients, the sensitivity of MRI for the detection of erosions is greater than that of conventional radiography. Conventional radiography detected 89% of erosions in the MCP joint bones and 15.8% in the wrist bones; these were lower than the MRI detection rates of 100% and 69%, respectively[131](B).

The diagnostic accuracy of conventional radiography in the detection of wrist bone erosions in RA patients was 63%, whereas the accuracy of MRI was 77%[132](B).

The diagnostic sensitivity of radiography for the detection of MCP joint bone erosions in RA patients was 14%, compared to 66% with MRI[133](B).

In RA patients who were followed-up for two years, radiography identified damage progression in 40% of the cases (total Larsen score) and 15% of the MCP joint bones (Larsen score). The accuracy of plain radiography in the identification of damage progression was similar to that of MRI[134](B).

Detection of erosions by means of the E score in RA patients was lower on radiographic assessment (13.1 ± 8.3) than on MRI (28.8 ± 10.0)[135](B).

In a population of RA patients with joint erosions (95% prevalence), radiography identified 59% of the cases, compared to 95% by MRI[136](B).

Radiography of the hands of RA patients identified 50% fewer erosions than MRI, although the identification of radiological progression was similar with both methods[137](B).

In a population of RA patients with a 43% prevalence of erosions, radiography increased the diagnostic probability to 80% for cases with positive findings, and ruled out a diagnosis in 85% for those with negative findings. After a 3-year follow-up period, the identification of erosions on radiography decreased to 81% and 60%, respectively[138](B).

In a population of patients with arthritis, 36% of whom were diagnosed with RA, diagnostic radiography increased the probability of RA to 50%, but when the results were negative, the probability decreased to 33%[139](B).

Radiographic assessment of RA patients only slightly increased the probability of distinguishing between RF seropositive and seronegative cases. In a population with a 59% prevalence of RF seropositive cases, positive radiographic findings (destruction) increased the probability to 66%, and a lack of radiographic findings decreased it to 47%[140](B).

*Recommendation*

Conventional radiography must be used in diagnostic and prognostic assessments of RA. When needed and available, US and MRI should also be used.

## 9. Is ultrasound superior to conventional radiography in the diagnosis and establishment of prognosis of RA?

The sensitivity of musculoskeletal US and MRI for the detection of structural damage was superior to that of conventional radiography[141](D).

US is useful for early detection, as well as the monitoring of inflammatory activity and signs of joint destruction when performed by an operator with significant experience in musculoskeletal diseases[135](B).

Compared to MRI, the cost of US is lower, and it is not contraindicated for patients with metallic implants or claustrophobia. Additionally, US permits dynamic assessments of the joints and bilateral comparisons, as well as evaluations of other anatomical structures[134](B)[141,143](D).

The use of power and colour Doppler might provide complementary information and thus contribute to characterisations of inflammatory activity[144](D).

Positive and negative US findings, when used to identify joint inflammation in RA patients, permits definite diagnoses in 79% and 55% of the cases, respectively. These results are similar those of radiography (Sharp score) when it exhibits positive findings (74%), but superior when the radiographic findings are negative (38%)[145](B).

Using MRI as the gold-standard (as in the present study), US was superior to radiography in the detection of bone erosions in patients with recent RA, whereby the LR+ values were 31 and 20, respectively. Based on a lesion prevalence of 50%, in cases with positive findings, the diagnostic probabilities of US and radiography increase to 99% and 97%, respectively. Therefore, the utility of both methods is similar[135](B).

Relative to the detection of erosions in RA patients, when US exhibits positive findings, it achieves a diagnostic certainty of 82% and for negative findings, a certainty rate of 61%, compared to 95% and 55%, respectively, for radiography[146](B).

The sensitivity and specificity of US in the detection of inflammatory signs and interphalangeal joint destruction in RA patients were 59% and 98%, respectively, compared to 42% and 99% for radiography, respectively. The diagnostic certainties relative to US and conventional radiography were 97% and 98%, respectively, when those results were positive and 71% and 63%, respectively, when they were negative[147](B).

The sensitivity and specificity of US in the detection of MCP joint erosions in the of RA patients were 79% and 97%, respectively, compared to 32% and 98% for conventional radiography, respectively. The diagnostic certainties relative to US and conventional radiography were 96% and 94%, respectively, when those results were positive and 82% and 46%, respectively, when they were negative[148](B).

The sensitivity and specificity of US in the detection of glenohumeral joint erosions in RA patients were 74% and 75%, respectively, compared to 67% and 100% for radiography, respectively. The diagnostic certainties relative to US and conventional radiography were 75% and 100%, respectively, when those results were positive and 74% and 75%, respectively, when they were negative[149](B).

The diagnostic accuracy of US in the identification of erosions in RA patients was 84% and was thus superior to that of radiography (73%). However, when only the tests with positive findings were considered for analysis, the LR of US was lower (5 versus 13), which indicates less diagnostic certainty[150](B).

In patients with early RA, US found erosions that were not identified by radiography in 19.3% of the cases, but failed to diagnose 8.8% of the cases that were identified by radiography. The combination of both methods permitted the diagnosis of 45.6% of the lesions in that patient population[151](B).

In patients with early RA, US correlated with disease activity (DAS28) and functional capacity (HAQ) scores at 12 months of follow-up[152](B).

In patients with early RA, US increased the detection of erosions in 42.0% of the cases at the time of diagnosis and after 9 months of follow-up, compared to radiography[153](B).

The detection of joint lesions in RA patients was greater with US versus radiography; specifically, US detection was 5% greater at the time of diagnosis, and 23% greater after seven years of follow-up[154](B). However, in another study, radiography identified a larger number of erosions in RA patients, compared to US (37% and 30%, respectively). After six months, the rates were 48% and 41%, respectively[155](B).

After accounting for the number of humeral erosions (greater tuberosity, anteromedial, and posterolateral) in RA patients, the diagnostic certainties of US and radiography were 90% and 40%, respectively, when the findings were positive and 96% and 39%, respectively, when the findings were negative[152](B).

***Recommendation***

US might contribute to the diagnosis of joint erosions in RA patients, as well to the monitoring of disease progression.

## 10. Is magnetic resonance superior to conventional radiography and ultrasound for the diagnosis and establishment of prognosis of RA?

MRI is the most sensitive method with which to detect the changes associated with the early stages of RA. It permits the assessment of structural alterations of the soft tissues, bone, and cartilage, in addition to erosions at an earlier stage than conventional radiography[138](B).

In addition to the features identified by conventional radiography, MRI is further able to detect bone swelling, which was shown to be a predictor of bone erosion[135](B).

In Brazil, factors such as the high cost and lack of standardisation limit the use of MRI in clinical practice.

The results of MRI relative to RA diagnosis vary widely as a function of the applied criteria and the investigated population. Thus, the sensitivity varies from 20% to 100%, and the specificity from 0% to 100%[136,156-158](B). Additionally, the results of MRI relative to RA progression vary widely, with a sensitivity range from 18% to 100% and a specificity range from 6% to 97%[156,159-161](B). Furthermore, the use of MRI in the management of patients with recent RA does not seem to be cost-effective when compared to standard diagnostic and prognostic assessments[162](B).

In RA patients, MRI (Outcome Measures in Rheumatology – OMERACT - definition) permits the diagnosis of erosions (hands or wrists) with 35%–90% sensitivity and 35%–90% specificity, bone swelling (hands, wrists, or MCP joints) with 32.5%–65% sensitivity and 82.5%–100% specificity, and synovitis (hands or wrists) with 40-80% sensitivity and 57.7%–92.5% specificity[163](**B**).

Compared to MRI, when the findings were positive, conventional radiography could diagnose MCP and PIP joint erosions with certainty in 98%–100% of the cases, and US in 86%–7% of the cases. When the findings were negative, the rates were 84% and 93%, respectively [135,155](**B**).

The diagnostic accuracy of Doppler US for the identification of joint inflammation in RA patients was 75%, compared to MRI[164](**B**).

Using computed tomography (CT) as the gold-standard for the diagnosis of erosions in the wrists of RA patients, when the findings were positive, MRI accurately diagnosed 90% of the cases, compared to conventional radiography[138,154](**B**).

Using high-field MRI as the gold-standard for the diagnosis of erosions in the wrists and MCP joints of RA patients, when the findings were positive, limb MRI accurately diagnosed 88% to 93% of the cases, compared to conventional radiography (94%–98%) and US (82%)[165,166](**B**).

A combination of MRI synovitis, swelling, and erosion scores permitted the identification of RA patient responses to TNF-α inhibitor treatment at a 12-month follow-up[167](**B**).

As a method for long-term functional assessments in RA patients, MRI identified improvements only in 29% of the cases, compared to the functional status (assessed by doctors and patients)[168](**B**).

MRI (bone swelling) and US (inflammation) exhibited similar abilities to identify the progression of erosion in RA patients (using the Rheumatoid Arthritis MRI Scoring System – RAMRIS – as the gold standard) over a 12-month follow-up period[152](**B**).

The progression of erosion was identified by MRI (OMERACT) in 23% of patients with RA over a 5-year period, compared with 40% by conventional radiography (Larsen score)[140](**B**).

*Recommendation*

MRI is the most sensitive method with which to detect the changes associated with the early stages of RA. It permits the assessment of structural alterations of the soft tissues, bone, and cartilage, in addition to erosions at an earlier stage than conventional radiography. In Brazil, factors such as the high cost and lack of standardisation have limited the use of MRI in clinical practice.

Table 5 summarises the advantages and disadvantages of the imaging methods used to assess RA patients.

## Conclusion

The present guidelines were elaborated by the Commission of Rheumatoid Arthritis of the Brazilian Society of Rheumatology to formulate recommendations for the diagnosis and initial assessment of RA in Brazil. Due to the country's territorial extension and the diversity of its macro-regions, local differences relative to differential diagnoses and access to some (laboratory or imaging) technologies might occur.

RA diagnosis is of paramount importance, especially in the earliest stages.

Lack of diagnosis means a lack of appropriate treatment and, consequently, an increased risk of the development of persistent inflammation and progressive joint damage. Rheumatologists must be included as early as possible in assessments of patients with arthritis due to their wider experience and familiarity with the possible differential diagnoses and investigational approaches.

Despite the recent publication of guidelines for the diagnosis of RA, a revision of this subject that accounts for particular Brazilian features is relevant.

Therefore, the establishment of recommendations for RA ultimately seeks to define and provide a solid basis for Brazilian rheumatologists with data from controlled trials to promote a homogeneous approach to diagnosis within the Brazilian socioeconomic context.

**Table 5 – Advantages and disadvantages of the imaging methods used to assess patients with rheumatoid arthritis.**

| Methods | Advantages | Disadvantages |
|---|---|---|
| Conventional radiography | - Low cost<br>- Easy access | - Two-dimensional representation of 3-D lesions<br>- Exposure to ionising radiation<br>- Low sensitivity for early bone damage |
| Ultrasound | - Intermediate cost<br>- No ionising radiation<br>- Allows assessing several joints<br>- Guides diagnostic and therapeutic interventions<br>- Early detection of cartilage and bone structural damage<br>- Detection of inflammatory activity by means of power Doppler | - Operator-dependent test<br>- Poor sensitivity to detect changes in deep joints (hips) |
| Magnetic resonance | - High sensitivity<br>- No ionising radiation<br>- Complementation using contrast agents<br>- Early detection of bone swelling, cartilage and bone structural damage | - High cost<br>- Limited equipment availability<br>- Long testing time<br>- Limited to one joint per exam (e.g., knee, hand) |

Because the knowledge relative to RA increases rapidly, the corresponding recommendations should be updated on a periodic and regular basis.

## Conflicts of interest

Mota LMH: Participated in clinical and/or experimental studies sponsored by Roche and Mantecorp; was given personal or institutional grants by Abbott, AstraZeneca, MSD, Roche, and Pfizer; and was a guest lecturer at meetings and other activities sponsored by Abbott, MSD, Novartis, Roche, and Wyeth.

Cruz BA: Participated in clinical and/or experimental studies sponsored by Roche; was given personal or institutional grants by Abbott, Bristol-Myers Squibb, Mantecorp, MSD, Novartis, Roche, Wyeth, and Pfizer; and was a guest lecturer at meetings and other activities sponsored by Abbott, MSD, Mantecorp, Novartis, Roche, and Wyeth.

Brenol CV: Participated in clinical and/or experimental studies sponsored by Bristol-Myers Squibb, Pfizer, Roche, and Wyeth; was given personal or institutional grants by Abbott, Bristol-Myers Squibb, Mantecorp, MSD, Roche, and Wyeth; and was a guest lecturer at meetings and other activities sponsored by Abbott and Roche.

Pereira IA: Participated in clinical and/or experimental studies sponsored by Roche; was given personal or institutional grants by Abbott, MSD, Roche, BMS, Jansen, and Pfizer; was a guest lecturer at meetings and other activities sponsored by Abbott, MSD, BMS, Pfizer, Roche, and Janssen; is a member of the consultant or executive boards of pharmaceutical companies or the normative committees of scientific studies sponsored by Abbott, BMS, Janssen, Roche, Pfizer, and MSD.

Rezende-Fronza LS: Participated in clinical and/or experimental studies sponsored by Bristol-Myers Squibb, Pfizer, and Roche; and wrote scientific papers for journals sponsored by Pfizer.

Bertolo MB: Was a guest lecturer at meetings and other activities sponsored by Abbott, Pfizer, and Sanofi Aventis.

Freitas MVC: Was given personal or institutional grants by Abbott, MSD, Pfizer, Roche, and Wyeth; was a guest lecturer at meetings and other activities sponsored by Abbott, MSD, Pfizer, Roche, and Wyeth; is a member of the consultant or executive boards of pharmaceutical companies or the normative committees of scientific studies sponsored by AstraZeneca, MSD, and Wyeth; and wrote scientific papers for journals sponsored by Abbott, AstraZeneca, Bristol-Myers Squibb, and Wyeth.

Silva NA: Participated in clinical and/or experimental studies sponsored by Bristol-Myers Squibb and Roche; was given personal or institutional grants by Abbott, MSD, Pfizer, Roche, and Wyeth; and was a guest lecturer at meetings and other activities sponsored by Janssen, Mantecorp, MSD, and Roche.

Louzada-Junior P: Participated in clinical and/or experimental studies sponsored by Merck and Roche; was given personal or institutional grants by Abbott; and was a guest lecturer at meetings and other activities sponsored by Bristol-Meyers-Squibb, Pfizer, and Roche.

Giorgi RD: Was given personal or institutional grants by Bristol-Myers Squibb and Roche; and was a guest lecturer at meetings and other activities sponsored by Bristol-Myers Squibb and Roche.

Lima RAC: Participated in clinical and/or experimental studies sponsored by Mantecorp and Roche; was given personal or institutional grants by Acteion, Lilly, and Pfizer; and was a guest lecturer at meetings and other activities sponsored by Acteion, Lilly, and Pfizer.

Pinheiro GRC: Was given personal or institutional grants by Janssen and Roche.

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Erratum

# Erratum of Guidelines for the diagnosis of rheumatoid arthritis

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In the original article "Guidelines for the diagnosis of rheumatoid arthritis" (Rev Bras Reumatol 2013;53(2):141-157), where it reads:

*Guidelines for the diagnosis of rheumatoid arthritis*

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It should read:

*Guidelines for the diagnosis of rheumatoid arthritis*

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## Erratum

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