# TOPIC COLLECTION:
# DIAGNOSING AND PREDICTING DEVELOPMENT OF RHEUMATOID ARTHRITIS

## Letter from the Editor

The treatment of rheumatoid arthritis is fraught with unknowns. It is not always certain how active the patient's arthritis may be, even while they are engaged in an effective treatment regimen. What factors may predict a flare of the disease and how to confirm that the patient remains in remission are unknown. Various measures of disease activity have been used, including physical exams, patient and physician assessments, inflammatory markers, and combinations of these measures.

A recent article in the *New England Journal of Medicine* offers a clue to aid definition of flares in RA and, hopefully, remissions as well. In this elegant study, longitudinal genomic analysis of RA flares revealed B-cell activation, which was followed by expansion of circulating preinflammatory mesenchymal (PRIME) cells, which are then less detectable during a flare, implying migration to the synovium from the blood, which contributes to the inflammatory process. This analysis was performed in a small number of patients. Were it possible to expand such usage more widely, genomic analysis might predict flares of RA and possibly become a nonsubjective tool for predicting disease activity, allowing us to detect flares before symptoms emerge and permitting timely therapeutic interventions.

In this collection, we present NEJM Journal Watch coverage of studies that attempt to define disease activity and treatment results. Outcomes are often hard to distinguish. In the study by Norli and colleagues of patients with an inflammatory monoarthritis, many resolved without treatment. Ford and colleagues report that while elevated levels of CCP may predict the development of RA, it is not a useful marker to predict response to medications. Finally, in another Journal Watch review of a study by Møller-Bisgaard et al., MRI exams were no better for predicting remission than the standard measures of disease outcomes.

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ORIGINAL ARTICLE

# RNA Identification of PRIME Cells Predicting Rheumatoid Arthritis Flares

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## ABSTRACT

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### BACKGROUND

Rheumatoid arthritis, like many inflammatory diseases, is characterized by episodes of quiescence and exacerbation (flares). The molecular events leading to flares are unknown.

### METHODS

We established a clinical and technical protocol for repeated home collection of blood in patients with rheumatoid arthritis to allow for longitudinal RNA sequencing (RNA-seq). Specimens were obtained from 364 time points during eight flares over a period of 4 years in our index patient, as well as from 235 time points during flares in three additional patients. We identified transcripts that were differentially expressed before flares and compared these with data from synovial single-cell RNA-seq. Flow cytometry and sorted-blood-cell RNA-seq in additional patients were used to validate the findings.

### RESULTS

Consistent changes were observed in blood transcriptional profiles 1 to 2 weeks before a rheumatoid arthritis flare. B-cell activation was followed by expansion of circulating CD45−CD31−PDPN+ preinflammatory mesenchymal, or PRIME, cells in the blood from patients with rheumatoid arthritis; these cells shared features of inflammatory synovial fibroblasts. Levels of circulating PRIME cells decreased during flares in all 4 patients, and flow cytometry and sorted-cell RNA-seq confirmed the presence of PRIME cells in 19 additional patients with rheumatoid arthritis.

### CONCLUSIONS

Longitudinal genomic analysis of rheumatoid arthritis flares revealed PRIME cells in the blood during the period before a flare and suggested a model in which these cells become activated by B cells in the weeks before a flare and subsequently migrate out of the blood into the synovium. (Funded by the National Institutes of Health and others.)

## What Is the Natural History of Recent-Onset Monoarthritis?

*During 2 years of follow-up, most cases resolved, but one quarter developed into chronic inflammatory disease.*

The differential diagnosis of recent-onset monoarthritis is broad and includes early presentation of what eventually is identifiable as chronic inflammatory rheumatic disease (CIRD), such as rheumatoid or psoriatic arthritis. In this 2-year study, Norwegian researchers aimed to identify predictors of CIRD in 347 patients who presented with monoarthritides of shorter than 16 weeks' duration; patients with crystal disease, trauma, osteoarthritis, mechanical joint abnormalities, and septic arthritis were excluded. The knee (49%), ankle (17%), and wrist (14%) were the most frequently affected joints.

During follow-up, 91 patients (26%) developed CIRD: 21 with rheumatoid arthritis, 16 with psoriatic arthritis, and 12 with chronic spondyloarthropathy, and 42 with "undifferentiated arthritis." Ten percent of patients with ankle monoarthritides, 26% of patients with knee monoarthritides, and 43% of patients with wrist monoarthritides developed CIRD. Longer duration of swelling, rheumatoid-factor positivity, or anti–cyclic citrullinated peptide positivity were independent risk factors for developing CIRD.

### COMMENT

In this 2-year study, most cases of recent-onset monoarthritides resolved, but 26% of patients developed ongoing rheumatic disorders. A large proportion of the latter group received diagnoses of undifferentiated arthritis, which could evolve over time into a more specific CIRD. In addition, some of the cases that resolved also could reappear as identifiable rheumatic diseases during longer follow-up.

**— Jonathan S. Coblyn, MD**

*Norli ES et al. Joint distribution and two-year outcome in 347 patients with monoarthritis of less than sixteen weeks' duration.* **Arthritis Care Res (Hoboken)** *2020 May; 72:705. (https://doi.org/10.1002/acr.23334)*

## Elevated Blood Levels of CCP Are Associated with Developing Rheumatoid Arthritis

*In patients with joint pain, high baseline levels of cyclic citrullinated peptide mandate close follow-up.*

Rheumatoid arthritis (RA) develops from an identifiable preclinical stage to frank disease. Previous European cohort studies have shown that patients who have arthralgia or undifferentiated arthritis and who are positive for cyclic citrullinated peptide (CCP) have excess risk for developing RA compared with CCP-negative patients. However, does the absolute level of CCP correlate with risk for RA development? In this retrospective study from a U.S. tertiary health-care system, researchers clarified this association.

Researchers identified 340 patients who tested positive for CCP between 2009 and 2016 and met study criteria (i.e., were free of RA or other systemic rheumatic disease at the time of their first positive CCP result, had at least one follow-up visit, and did not receive a diagnosis of RA within 28 days of their CCP test date). CCP testing was performed mainly to evaluate patients with joint pain. CCP positivity was quantified as low (level, 1–2 × the upper limit of normal [ULN]), medium (2–3 × ULN), or high (>3 × ULN). Medical records were reviewed through February 2018.

Mean duration of follow-up was 2.7 years, and during follow-up, 73 patients (21.5%) developed RA. Risk for RA development was higher in patients with higher baseline concentrations of CCP: The estimated progression to RA within 5 years in patients with high CCP levels was 46%. Compared with low CCP levels, the hazard ratios for medium and high CCP levels were 3.0 and 4.8, respectively (adjusted for multiple variables).

### COMMENT

This study confirms that patients with high CCP levels have substantial risk for developing RA. This mandates close follow-up for these patients and possibly supports early therapy when RA symptoms do develop. **— Jonathan S. Coblyn, MD**

*Ford JA et al. Impact of cyclic citrullinated peptide antibody level on progression to rheumatoid arthritis in clinically tested cyclic citrullinated peptide antibody-positive patients without rheumatoid arthritis.* **Arthritis Care Res (Hoboken)** *2019 Dec; 71:1583. (https://doi.org/10.1002/acr.23820)*

## Can MRI Enhance Clinical Management of Rheumatoid Arthritis?

*For patients with RA in remission, use of magnetic resonance imaging as diagnostic tool did not improve outcomes.*

Clinical remission is attainable in as many as 50% of patients with rheumatoid arthritis (RA) by using currently approved drugs and changing therapy depending on disease activity. Some experts have proposed use of magnetic resonance imaging (MRI) to define disease activity and guide therapeutic interventions — a very costly strategy. Danish researchers compared MRI versus conventional disease-activity scores to guide treatment in 200 patients with seropositive erosive RA in clinical remission. Patients were randomized to an MRI group or a conventional (control) group with evaluations in both groups every 4 months. The treatment target in the MRI group was remission, defined as absence of bone marrow edema, combined with clinical remission (according to disease-activity score and no swollen joints). The treatment target for the conventional group was clinical remission only. If signs of active disease were noted in patients from either group, treatment was escalated according to a predefined algorithm.

Treatment was intensified 173 times in the MRI-guided group versus 22 times in the conventional treatment group (73% vs. 17% of patients). At 2 years, clinical remission rates and radiographic measures of disease progression were similar in both groups.

## COMMENT

These results show that MRIs provided no benefit over standard clinical disease-activity scores for managing RA patients who already were in remission by accepted clinical criteria and suggest that MRIs should be discouraged for such patients. Use of MRIs to assess disease activity in other settings might be appropriate but should not replace standard physical exams.

— *Jonathan S. Coblyn, MD*

*Møller-Bisgaard S et al. Effect of magnetic resonance imaging vs conventional treat-to-target strategies on disease activity remission and radiographic progression in rheumatoid arthritis: The IMAGINE-RA randomized clinical trial.* **JAMA** *2019 Feb 5; 321:461. (https://doi.org/10.1001/jama.2018.21362)*

*Aletaha D and Smolen JS. Achieving clinical remission for patients with rheumatoid arthritis.* **JAMA** *2019 Feb 5; 321:457. (https://doi.org/10.1001/jama.2018.21249)*