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# Third-Generation Anti–Cyclic Citrullinated Peptide Antibodies Improve Prediction of Clinical Arthritis in Individuals at Risk of Rheumatoid Arthritis

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**Objective.** To 1) determine the prevalence of anti–cyclic citrullinated peptide 3 (anti-CCP3) antibodies in anti-CCP2 antibody–positive (anti-CCP2+) at-risk individuals, and 2) explore the additional value of anti-CCP3 antibodies in anti-CCP2+ at-risk individuals for predicting progression to inflammatory arthritis.

**Methods.** Stored serum samples obtained from 347 anti-CCP2+ (BioPlex 2200; Bio-Rad) at-risk individuals without clinical synovitis were tested for anti-CCP3 antibodies. Anti-CCP2 titers were categorized as low or high, and anti-CCP3 titers were categorized as negative, low, or strong. Progression to inflammatory arthritis was defined as the development of clinical synovitis in ≥1 joint. Only subjects with ≥1 follow-up visit were included in the progression analysis (n = 291).

**Results.** In the 347 samples included, anti-CCP3 antibody titers tended to be either negative (n = 138 [39.7%]) or strongly positive (n =189 [54.4%]), with very few subjects showing a low titer (n = 20 [5.7%]). In contrast, for anti-CCP2 antibodies, more low titers were observed (n = 103 [29.7%]). Eighty-eight of 291 subjects (30.2%) developed inflammatory arthritis. The rate of progression to inflammatory arthritis in the low-titer anti-CCP2 group and the high-titer anti-CCP2 group fell from 7.5% to 3.3% and from 38.9% to 9.8%, respectively, when anti-CCP3 was negative. Progression in the high-titer anti-CCP2 group increased from 38.9% to 48.4% when anti-CCP3 was strongly positive. The area under the curve was 0.72 for anti-CCP2 (95% confidence interval [95% CI] 0.66, 0.78) and 0.76 for anti-CCP3 (95% CI 0.70, 0.81) for assessment of progression. In the multivariable analysis, the odds ratio for the development of inflammatory arthritis in anti-CCP3+ subjects was 1.73 (95% CI 1.20, 2.51) ($P < 0.01$).

**Conclusion.** Anti-CCP3 antibodies improve the prediction of inflammatory arthritis in anti-CCP2+ at-risk individuals. The impact of anti-CCP3 antibody status for the risk stratification of individuals with high-titer anti-CCP2 is particularly notable.

## INTRODUCTION

Anti–citrullinated protein antibodies (ACPAs) are one of the most important diagnostic biomarkers in rheumatoid arthritis (RA) (1) and a cardinal feature of the most recent American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA (2). Although ACPAs can be detected in up to 80% of patients with established RA with excellent specificity (85–99%), their prevalence in early RA is significantly lower (3–5). Moreover, ACPAs have an important prognostic value, as their presence has been associated with increased radiographic progression (6–9) and response to therapy (10–12). ACPAs can be detected in the serum of patients with RA years before the onset of the disease (13–15), and ACPA positivity, especially at high titers, confers an increased risk of developing RA in at-risk subjects (16,17).

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Several tests have been developed to identify ACPAs, with variable differences in their diagnostic profiles, but a gold standard assay for the detection of ACPAs has not been established (18). ACPAs are usually detected using second- or third-generation IgG anti–cyclic citrullinated peptide (anti-CCP2 or anti-CCP3) antibody assays. The anti-CCP2 test is the most commonly used assay in many areas, while in the US anti-CCP3 is increasingly favored. The diagnostic accuracy of anti-CCP2 and anti-CCP3 antibodies has been compared in patients with early and established RA, with no overall significant superiority of one test over the other, and similar sensitivities (68–79%) and specificities (86–96%) between the 2 tests (19–21). In 2 studies (22,23), anti-CCP3 was found to discriminate better than anti-CCP2 between RA and non-RA in patients negative for rheumatoid factor (RF). Interestingly, the combination of these 2 assays was shown to have higher specificity for the identification of RA patients than the individual assays (24,25).

In order to identify RA patients as early and accurately as possible, a critical prerequisite for disease prevention, biomarkers that can help to identify individuals at risk of future arthritis are needed. Prospective data comparing the ability of different ACPA assays, in particular the value of serum anti-CCP3 IgG in predicting the development of inflammatory arthritis in at-risk individuals, are limited (25–27).

We hypothesized that additional baseline testing for anti-CCP3 antibody would further risk stratify anti-CCP2 antibody–positive (anti-CCP2+) at-risk individuals, identifying individuals with imminent disease and those at lowest risk of progression. Based on these considerations, the aims of this study were: 1) to determine the prevalence of anti-CCP3 antibodies in anti-CCP2+ at-risk individuals, and 2) to explore the additional value of anti-CCP3 antibodies in anti-CCP2+ at-risk individuals for predicting progression to inflammatory arthritis.

## SUBJECTS AND METHODS

**Subjects and study design.** Stored baseline serum samples obtained between June 2008 and November 2018 from 347 anti-CCP2+ (BioPlex 2200 CCP2; Bio-Rad) at-risk individuals without synovitis were tested for IgG anti-CCP3 antibodies (Quanta Lite CCP3; Inova Diagnostics). Samples were from subjects in "The CCP Study: Coordinated Programme to Prevent Arthritis—Can We Identify Arthritis at a Pre-clinical Stage?" Full details of this cohort have been published previously (17,28,29). Briefly, this is a national study in which individuals ages ≥18 years with a new musculoskeletal joint symptom presenting to their primary care physician, or other health professional, were tested for anti-CCP2 antibodies. A new musculoskeletal joint symptom was defined as any new joint or musculoskeletal symptom, including (but not limited to) rotator cuff tendonitis, subacromial bursitis, carpal tunnel syndrome, tendonitis, back pain, or epicondylitis, which patients had not previously reported to their physician (29).

Individuals with a positive anti-CCP2 antibody result were invited to a dedicated research clinic at Chapel Allerton Hospital in Leeds, UK, as part of a prospective observation cohort. For each individual, the following data were collected: age, sex, smoking exposure, tenderness in the small joints of the hands on physical examination, anti-CCP2 titer, and RF status.

The thresholds for anti-CCP2 and anti-CCP3 positivity were set at >2.99 IU/ml and >20 units, respectively, according to the manufacturers' cutoffs. Anti-CCP2 titer was considered low when it was <3 times the positivity threshold and was considered high when it was ≥3 times the positivity threshold. Anti-CCP3 titer was divided into 4 categories: negative (<20 units), weak (20–40 units), moderate (40–60 units), and strong (>60 units), according to the manufacturer's cutoffs. For analysis of the results, the weak and moderate categories for anti-CCP3 were merged into a single category (low titer; 20–60 units). The threshold for RF positivity was set at ≥40 IU/ml (before February 2010) or ≥20 IU/ml (after February 2010).

Only subjects with ≥1 follow-up visit were included in the progression analysis (n = 291). Subjects who withdrew from the study and those who were lost to follow-up (including those who had only the baseline visit), were excluded from this analysis (n = 14 and n = 42, respectively). Progression to inflammatory arthritis (ever) was defined as the development of clinical synovitis (tenderness and swelling) in ≥1 joint. RA was defined according to the ACR/EULAR 2010 classification criteria (2). Moreover, 36 months was selected as a timeframe, since this represents a reasonable interval for preventive management of patients at the trajectory of developing RA and has been used in ongoing prevention trials in RA (30,31).

**Ethics approval.** This study was approved by the NHS Health Research Authority National Research Ethics Service Committee Yorkshire & the Humber–Leeds West.

**Statistical analysis.** Results are reported as the mean ± SD for quantitative variables. Data for qualitative variables are expressed as absolute frequency and as corresponding percentages. Student's *t*-test was used for the quantitative variables that had a

**Table 1.** Agreement between the anti-CCP2 and anti-CCP3 tests*

| Anti-CCP3 titer | Anti-CCP2 titer | | Total no. of subjects |
|---|---|---|---|
| | Low positive | High positive | |
| Negative | 79 (76.7) | 59 (24.2) | 138 |
| Low positive | 11 (10.7) | 9 (3.7) | 20 |
| Strong positive | 13 (12.6) | 176 (72.1) | 189 |
| Total no. of subjects | 103 | 244 | 347 |

* Except where indicated otherwise, values are the number (%) of subjects. Anti-CCP2 = anti–cyclic citrullinated peptide 2.

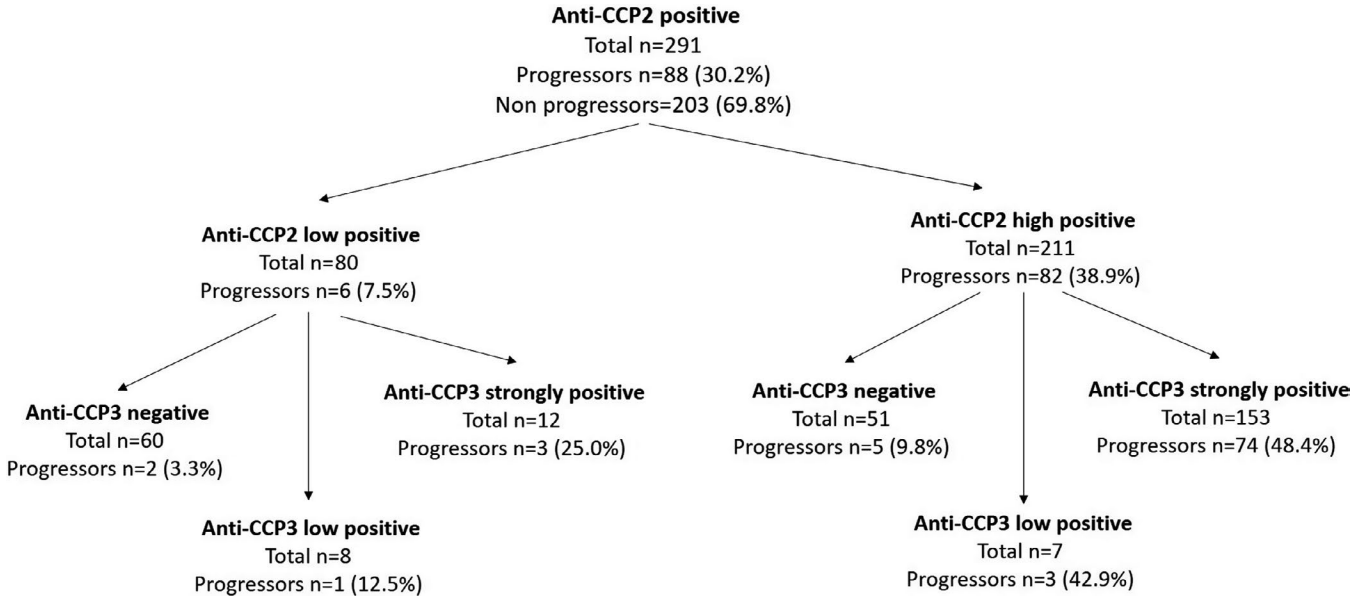


**Figure 1.** Proportions of anti–cyclic citrullinated peptide antibody–positive (anti-CCP2+) at-risk individuals progressing to inflammatory arthritis (ever), according to anti-CCP3 antibody status.

normal distribution. Receiver operating characteristic (ROC) analyses were carried out to explore the additional value of anti-CCP3 in the prediction of inflammatory arthritis in anti-CCP2+ subjects, and in subjects according to RF status. Cox proportional hazards regression was used to assess the associations between anti-CCP2 and anti-CCP3 tests and the timing of progression to inflammatory arthritis. Kaplan-Meier analysis was performed to analyze and visualize the inflammatory arthritis–free survival time for subjects according to anti-CCP3 titer, and according to anti-CCP2 and anti-CCP3 status combined. Multiple logistic regression analysis was used to define predictive values of anti-CCP3 antibodies for the development of clinical arthritis. The regression analysis was adjusted for the following confounders: age, sex, smoking exposure, tenderness in the small joints of the hands on physical examination, anti-CCP2 titer, and RF status.

## RESULTS

At inclusion, the mean ± SD age of the individuals included was 50.8 ± 13.5 years, and 70.6% were women. Of the 347 subjects, 130 (37.5%) had tenderness in the small joints of the hands on physical examination, 134 (38.6%) were RF positive, 78 (22.5%) were current smokers, and 118 (34.0%) were previous smokers. Anti-CCP3 antibodies tended to be either negative (138 [39.7%]) or strongly positive (189 [54.4%]), with very few subjects showing a low titer (20 [5.7%]). In contrast, for anti-CCP2, more low-titer results were observed (103 [29.7%]). The agreement between anti-CCP2 and anti-CCP3 tests is shown in Table 1.

Eighty-eight of 291 subjects (30.2%) developed inflammatory arthritis (mean follow-up time 16.3 ± 19.1 months), and 75 of these 88 subjects fulfilled the ACR/EULAR 2010 classification criteria for RA. Since the great majority of patients developed RA, whereas <15% continued to be classified as having inflammatory arthritis, analyses were repeated with RA instead of inflammatory arthritis, and the outcome did not change. Seventy-nine patients who had both strong anti-CCP3 and high-titer anti-CCP2 antibodies and did not progress to inflammatory arthritis were identified (mean follow-up time 31.6 ± 28.8 months).

The titer of both anti-CCP2 and anti-CCP3 antibodies was significantly higher in the individuals who progressed to inflammatory arthritis than in those who did not develop the disease (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41402/abstract). However, the presence of a significant number of outliers might have influenced this result. Moreover, the prevalence of strong positive anti-CCP3 antibodies was significantly higher in the subjects who progressed to inflammatory arthritis than in those who did not, even when only subjects with high-titer anti-CCP2 antibody were considered (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41402/abstract).

The proportions of individuals progressing to inflammatory arthritis (ever) according to anti-CCP2 and anti-CCP3 antibody status are shown in Figure 1. The hazard ratios (HRs) for high-titer anti-CCP2 and high-titer anti-CCP3 antibodies were 5.1 (95% confidence interval [95% CI] 2.2, 11.8) and 6.6 (95% CI 3.1, 14.5), respectively ($P < 0.001$). The area under the ROC curves for the anti-CCP2 and anti-CCP3 tests are shown in Figure 2.

Kaplan-Meier analysis was performed to assess inflammatory arthritis–free survival time in anti-CCP2+ at-risk individuals

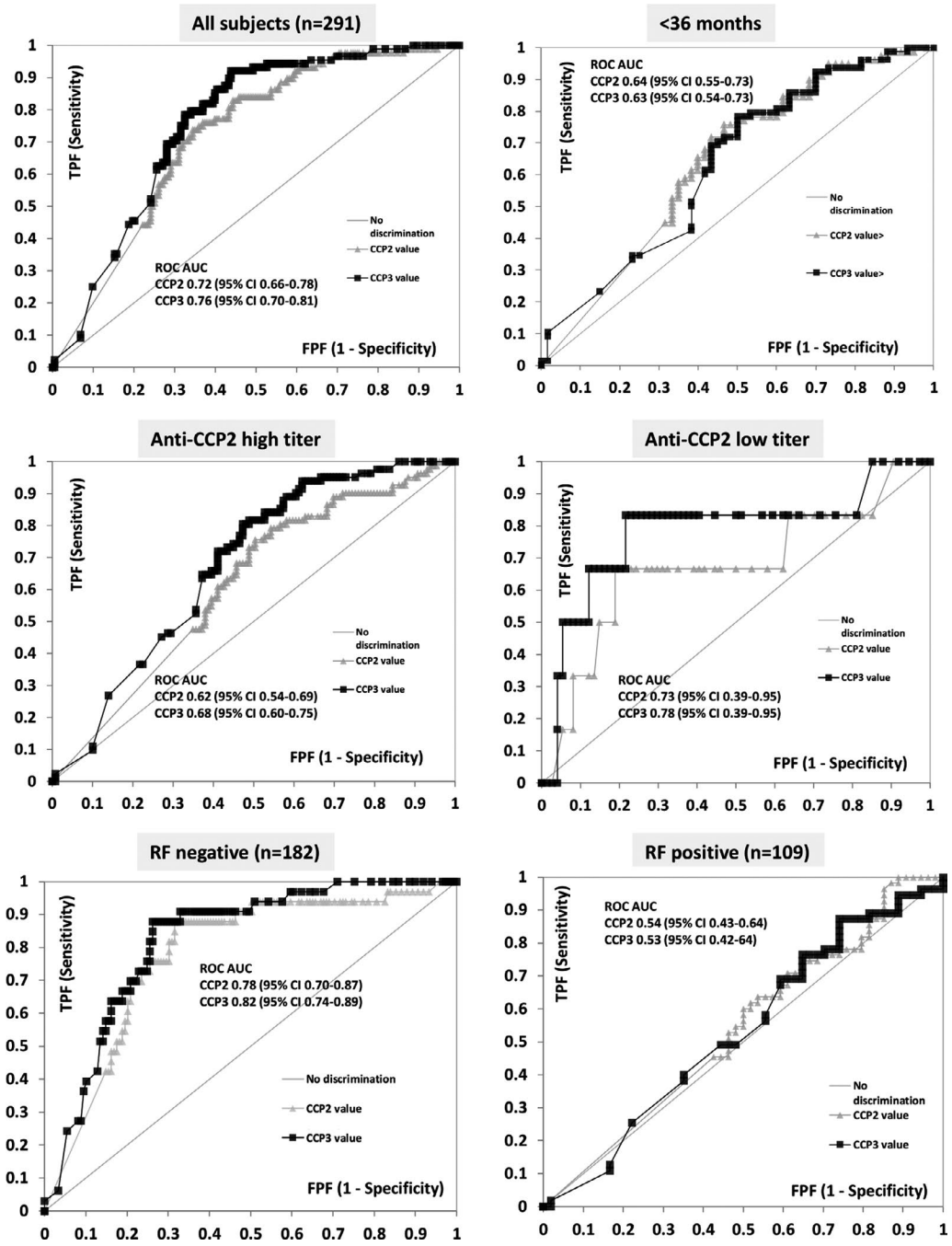


**Figure 2.** Receiver operating characteristic (ROC) analysis curves for anti–cyclic citrullinated peptide 2 (anti-CCP2) and anti-CCP3 antibodies as predictors of development of inflammatory arthritis in anti-CCP2+ at-risk individuals. ROC curves are shown for all subjects, subjects with <36 months of follow-up, subjects with high-titer anti-CCP2, subjects with low-titer anti-CCP2, rheumatoid factor (RF)–negative subjects, and RF-positive subjects. AUC = area under the curve; 95% CI = 95% confidence interval; TPF = true-positive fraction; FPF = false-positive fraction.

according to anti-CCP3 status (Figure 3). Anti-CCP3+ subjects showed a significantly reduced inflammatory arthritis–free survival rate compared to anti-CCP3– individuals. After 3 years of follow-up, ~40% of the anti-CCP3+ individuals progressed to inflammatory arthritis, compared to only 6.3% in the anti-CCP3– group ($P < 0.001$). The odds ratios for the development of inflammatory arthritis for the clinical and serologic variables included in the study are shown in Table 2.

## DISCUSSION

To the best of our knowledge, this is the first study to evaluate the incremental value of measuring serum IgG anti-CCP3 antibodies in a cohort of anti-CCP2+ individuals at risk of future development of inflammatory arthritis. Our results support a potential role for anti-CCP3 antibodies in improving the prediction of inflammatory arthritis in anti-CCP2+ at-risk subjects.

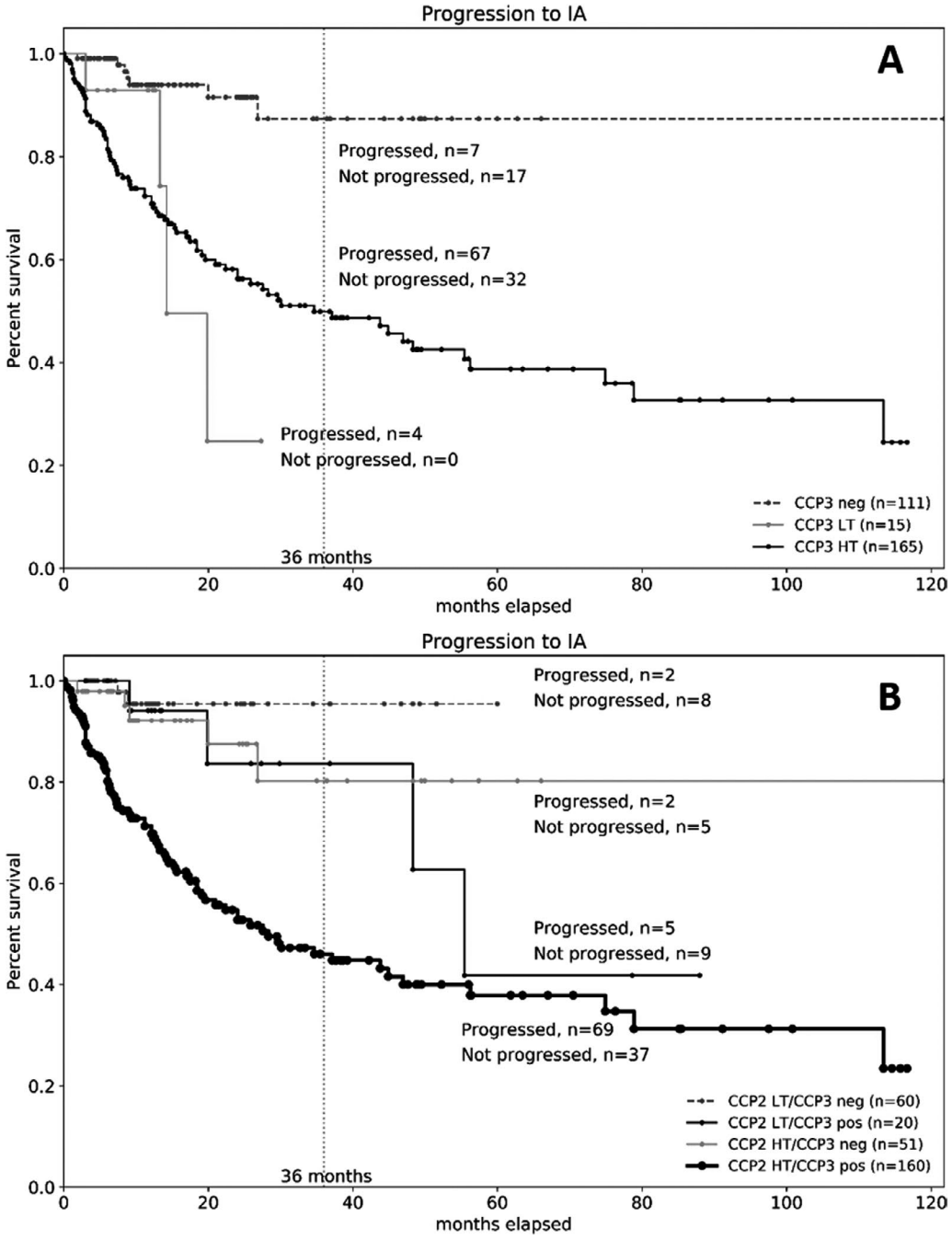


**Figure 3.** Kaplan-Meier analysis of inflammatory arthritis (IA)–free survival time according to anti–cyclic citrullinated peptide 3 (anti-CCP3) antibody status in an anti-CCP2 antibody–positive population. **A**, Significant reduction in inflammatory arthritis–free survival rate in at-risk subjects with increasing levels of anti-CCP3 antibodies. **B**, Inflammatory arthritis–free survival rate according to anti-CCP2 and anti-CCP3 titers combined. Fraction and number of nontransitioned individuals is indicated after follow-up time of 36 months (vertical line). LT = low titer; HT = high titer.

Since not all individuals with positive anti-CCP2 results develop RA (13), it is important to identify additional biomarkers that help to predict progression to inflammatory arthritis in these individuals, ideally within a clinically relevant timeframe (i.e., 36 months). Such biomarkers should identify individuals at high risk of imminent arthritis, who should be followed up closely and considered for prevention studies, while those at low risk may be followed up less intensively.

Our data suggest that levels of anti-CCP3 antibodies in anti-CCP2+ individuals can improve risk stratification and therefore inform management, including preventive approaches, such as risk factor reduction (i.e., smoking cessation), as well as consideration

**Table 2.** Multivariable logistic regression model for the development of inflammatory arthritis*

| Variable | Beta (95% CI) | OR (95% CI) | Wald statistic | *P* |
|---|---|---|---|---|
| Intercept | −1.63 (−2.34, −1.00) | 0.19 (0.10, 0.37) | −4.90 | <0.01 |
| Anti-CCP2 titer | 0.12 (−0.00, 0.24) | 1.13 (1.0, 1.27) | 1.93 | 0.05 |
| Anti-CCP3 titer | 0.55 (0.18, 0.92) | 1.73 (1.20, 2.51) | 2.91 | <0.01 |
| RF titer | 0.44 (0.09, 0.80) | 1.56 (1.09, 2.23) | 2.43 | 0.02 |
| Age | 0.05 (−0.24, 0.34) | 1.05 (0.79, 1.40) | 0.33 | 0.74 |
| Sex (male) | −0.27 (−0.90, 0.36) | 0.76 (0.41, 1.43) | −0.84 | 0.40 |
| Hand tenderness | 1.04 (0.45, 1.64) | 2.83 (1.56, 5.13) | 3.43 | <0.01 |
| Smoking (never) | −0.57 (−1.32, 0.18) | 0.57 (0.27, 1.20) | −1.49 | 0.14 |
| Smoking (previous) | 0.19 (−0.51, 0.89) | 1.21 (0.60, 2.43) | 0.53 | 0.59 |

* 95% CI = 95% of the confidence interval; OR = odds ratio; anti-CCP2 = anti–cyclic citrullinated peptide 2; RF = rheumatoid factor.

of at-risk individuals for prevention trials. Anti-CCP3 assays rely on epitopes that are not present in anti-CCP2 assays, and this may explain the additional value provided by the anti-CCP3 test in anti-CCP2+ individuals.

Importantly, the rate of progression to inflammatory arthritis in the low-titer anti-CCP2 group fell from 7.5% in anti-CCP3+ subjects to 3.3% in anti-CCP3– subjects, and the rate of progression in the high-titer anti-CCP2 group fell from 38.9% in anti-CCP3+ subjects to 9.8% in anti-CCP3– subjects. Based on these findings, a negative anti-CCP3 test in individuals with low-titer anti-CCP2 antibodies could be reassuring regarding their risk of progression to inflammatory arthritis, and lead to their re-evaluation only if symptoms change.

In contrast, progression in the high-titer anti-CCP2 group increased from 38.9% to 48.4% when anti-CCP3 was strongly positive. Therefore, a positive anti-CCP3 test in individuals with high-titer anti-CCP2 antibody further increases the risk of progression, identifying a population enriched for imminent inflammatory arthritis, with possibly a broader systemic autoimmune response (i.e., broader ACPA fine specificity), who require close follow-up and should be considered for inclusion in therapeutic trials for arthritis prevention (32,33).

The titer of both anti-CCP2 and anti-CCP3 antibodies was significantly higher in the individuals who progressed to inflammatory arthritis than in those who did not develop the disease. The area under the ROC curve, as well as the HR, was higher for anti-CCP3 antibodies compared with anti-CCP2 antibodies, indicating a higher accuracy of the anti-CCP2/anti-CCP3 combination in predicting inflammatory arthritis than anti-CCP2 antibodies alone. It is already known that in ACPA+ individuals the presence of RF improves the prediction of the development of clinical arthritis (8,34). Our results suggest that a positive anti-CCP3 result is particularly valuable in RF-negative individuals. In the multivariable analysis, only anti-CCP3 antibodies, RF, and tenderness in the small joints of the hands remained significant, whereas anti-CCP2 antibodies showed borderline results. This finding appears to be the consequence of the high prevalence of low-titer anti-CCP2 (~30%) in our population.

Only a few studies have evaluated the diagnostic value of anti-CCP3 antibodies in patients without RA. In a study conducted by Elrefaei et al (25), 2 automated anti-CCP2 assays (EliA [ThermoFisher] and ARCHITECT i200SR [Abbott Laboratories]) and a manual anti-CCP3 enzyme-linked immunosorbent assay were tested prospectively in 162 patients. The positive predictive value (PPV) of the anti-CCP2 tests appeared to be higher than that of the anti-CCP3 test (85.2% versus 72.5%, respectively). However, given the small number of RA patients (n = 41) the confidence intervals were wide, and no statistical analysis was performed to analyze whether this difference was significant. Moreover, the population included in that study was not described by the authors, which makes interpretation of the study results difficult. In addition, the follow-up time was only 6 months and there was no significant difference between the diagnostic accuracy of the anti-CCP2 and anti-CCP3 tests.

In another study (26), the authors compared the diagnostic performance of anti-CCP2 antibodies (ELiA) and anti-CCP3 antibodies (BIO-FLASH; Inova Diagnostics). Anti-CCP2 and anti-CCP3 tests were performed on samples from 127 consecutive patients for whom anti-CCP antibody and RF testing had been routinely ordered for investigation of joint disease. Retrospectively reviewed clinical data from medical records were used for the diagnosis of RA according to the ACR 1987 criteria. The anti-CCP2 test showed a higher PPV and negative predictive value (NPV) than the anti-CCP3 test (PPV 75.3% versus 69.7%, respectively, and NPV 75.9% versus 70.6%, respectively). However, there was no significant difference between the diagnostic accuracy of the 2 tests. That study showed that the combination of low-titer anti-CCP2 antibody with anti-CCP3 antibody improved the prediction of having RA, compared to using the values of anti-CCP2 alone.

A study of well characterized at (low) risk subjects (83 healthy military subjects) was carried out using anti-CCP3.1 (27), an assay that detects both IgG and IgA ACPAs. In that study, the anti-CCP2 test was significantly more specific than anti-CCP3.1 for the prediction of the future development of RA. However, the anti-CCP3.1 test was more sensitive than anti-CCP2, and consequently the differences were not significant ($P = 0.87$).

In our study, the agreement between anti-CCP2 and anti-CCP3 antibodies was poor, especially in the group with low-titer anti-CCP2 antibodies, which may be explained by the preselection of anti-CCP2+ samples. In this group, 76.7% of cases were

negative for anti-CCP3 antibodies. Surprisingly, a considerable number of subjects with high-titer anti-CCP2 antibodies (n = 59 [24.2%]) were also negative for anti-CCP3. Notably, the progression rate in the entire group with high-titer anti-CCP2 positivity (without considering anti-CCP3 status) was much higher than the progression rate in the group that had high-titer anti-CCP2+ and was negative for anti-CCP3 (38.9% versus 9.8%, respectively).

In previous studies, the agreement between the 2 tests has been evaluated almost exclusively in patients with RA, with conflicting results. In fact, some studies demonstrated good agreement between anti-CCP2 and anti-CCP3 antibodies (23,24,35–38), whereas other studies showed a significant discrepancy between the 2 tests (39,40). The lack of agreement was attributed to several factors, such as borderline results, interassay discrepancy, the fact that anti-CCP3 assays may include additional epitopes not present in the anti-CCP2 antigen sequence, and intertest variability depending on other components of the kits (i.e., standards, secondary antibody, or the cutoff used). However, these results should be interpreted cautiously, as epitope spreading would influence the agreement of testing over the disease course, and this would be different in the pre-RA versus RA period. Another important aspect that is often overlooked is the variability between different anti-CCP2 tests, which can even exceed the variability between anti-CCP2 and anti-CCP3 assays, depending on which anti-CCP2 assay is used. Interestingly, 2 studies (22,23) have shown significantly higher agreement between anti-CCP2 and anti-CCP3 tests in RF-positive RA patients.

The main limitation of the present study is that all individuals were positive for anti-CCP2. Therefore, our results can be interpreted only in the context of anti-CCP2+ at-risk individuals. Further evaluations that also include anti-CCP2– at-risk individuals are needed to allow a direct comparison of the diagnostic performances of these 2 tests in individuals at risk of developing RA. Such studies would also permit evaluation of the best screening strategy for the assessment of at-risk individuals. In support of this study, the current (European) approach is indeed to screen with anti-CCP2.

Prediction and prevention of RA has the potential to reduce health care costs in a substantial way. However, this possibility needs to be confirmed and demonstrated in health economics studies. Either financial models need to be established to allow for the testing of both anti-CCP2 and anti-CCP3, or in the case of head-to-head studies demonstrating that anti-CCP3 and RF are sufficient to predict RA development with high accuracy and precision, anti-CCP3 might be used instead. Finally, further (mechanistic) studies are needed to evaluate the potential role of anti-CCP3 antibodies in "switching" the status of individuals at risk of RA, from systemic autoimmunity to inflammation and clinical synovitis.

The opportunity to identify individuals at risk of RA, to predict evolution from an at-risk state to clinical arthritis and, ultimately, to treat these at-risk individuals in the preclinical phase in order to prevent clinical disease, represent some of the most intriguing challenges in modern rheumatology. In this context, biomarkers, which allow more precise risk stratification for RA development, become extremely important.

Our results support an important role for anti-CCP3 antibodies in improving the prediction of inflammatory arthritis in at-risk subjects who are positive for anti-CCP2 antibodies. The impact of anti-CCP3 antibody status for the risk stratification of high-titer anti-CCP2+ individuals is particularly notable. Further studies, including at-risk subjects seronegative for anti-CCP2 antibodies, are needed to compare the diagnostic performances of these 2 tests in unselected at-risk populations.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Emery had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Mankia, Mahler, Emery.

**Acquisition of data.** Di Matteo, Mankia, Duquenne, Mahler, Corscadden, Mbara, Garcia-Montoya, Nam, Emery.

**Analysis and interpretation of data.** Di Matteo, Mankia, Duquenne, Mahler, Garcia-Montoya, Nam, Emery.

## ADDITIONAL DISCLOSURES

Author Mahler is an employee of Inova Diagnostics, Inc.

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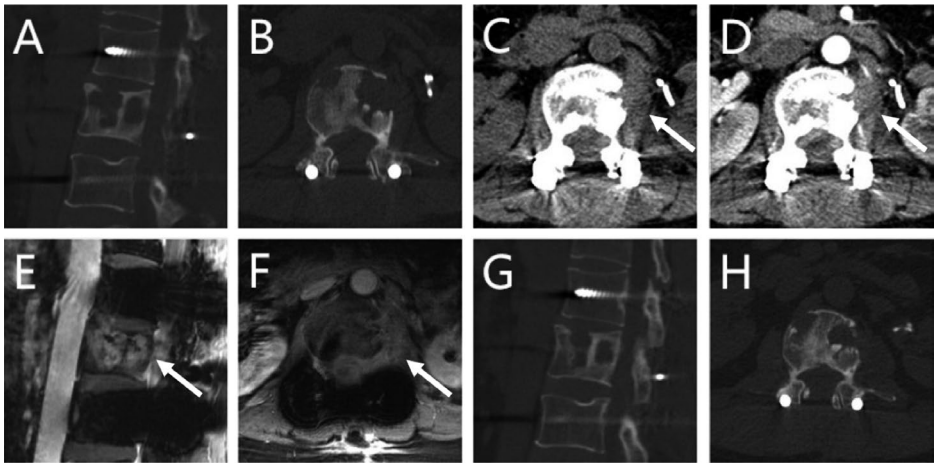
## Clinical Images: IgG4-related disease—rare presentation with spinal involvement




The patient, a 40-year-old man, presented with a 1-year history of numbness and weakness in both legs and lower back pain. Previously, computed tomography (CT) of the abdomen performed at another institution had revealed bone destruction in the L2 vertebra involving the adjacent spinal canal and spinal conus. To relieve symptoms and improve spinal stability, the patient had undergone posterior lamina decompression from L1 to L2, enlargement of the spinal canal, posterolateral bone fusion, and first to third pedicle internal fixation. Postoperative pathologic findings from L2 included fibrous tissue and collagen fiber proliferation with scattered and focal lymphoplasmacytic infiltration. Immunohistochemical analysis of the vertebral tissue for IgG and IgG4 expression had identified ~50 IgG4+ cells per high-power field, with an IgG4+:IgG+ ratio of >40%. IgG4-related disease (IgG4-RD) was suspected, and the patient was admitted to our hospital for further evaluation. During hospitalization, the patient underwent lumbar spine assessments by CT of the sagittal and axial planes and contrast-enhanced CT of the axial plane, which revealed irregular and ill-circumscribed bone destruction surrounded by increased density of the L2 vertebra (**A**–**D**) and a soft tissue–enhancing mass on the left paravertebra (**arrows** in **C** and **D**). Follow-up contrast-enhanced, fat-suppressed T1-weighted magnetic resonance imaging of the sagittal and axial planes of the lumbar spine also showed a lesion with a tissue-enhancing mass in L2 (**arrows** in **E** and **F**). CT of the chest conducted to evaluate lung involvement revealed a small nodule in the upper lobe of the right lung, which was resected upon the patient's request. Postoperative pathologic evaluation of the nodule indicated the presence of an inflammatory myofibroblastic tumor with dense lymphoplasmacytic infiltration enriched with IgG4+ plasma cells. The patient's serum IgG4 level was elevated (257 mg/dl [normal 8–140]), while antinuclear antibody and rheumatoid factor levels were within normal ranges. After considering the clinical, pathologic, radiologic, and serologic manifestations, IgG4-RD was diagnosed (1,2). The patient was treated with combination methylprednisolone and cyclophosphamide, which was successful, as 14 months later, follow-up CT of the sagittal and axial planes of the lumbar spine showed slightly decreased bone destruction (**G** and **H**), and the patient's serum IgG4 level (131 mg/dl) was within normal range.

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