REVIEW

Which patients presenting with arthralgia eventually develop rheumatoid arthritis? The current state of the art

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ABSTRACT

Early initiation of treatment in patients with inflammatory arthritis at risk of persistence and/or erosive progression is important because it is associated with a reduced rate of progression of joint damage and functional disability. It has been proposed that a window of opportunity exists, during which disease processes are less matured and disease modification can be more effective. The phase of arthralgia preceding clinical arthritis is likely to be an important part of this window of opportunity, during which treatment might prevent progression to clinical arthritis. Several proof-of-concept trials in individuals with arthralgia are now evaluating this hypothesis. Central to such trials is the ability to identify groups at high risk of rheumatoid arthritis (RA) in whom preventive treatment can be tested. This review describes the relevance of adequate prediction making, as well as the accuracy of different types of predictors (including imaging and serological markers) with their value in predicting the progression of arthralgia to arthritis. Despite promising results, studies have been performed in heterogeneous patient populations and most findings have not been validated in independent studies. Future observational or preventive studies should be conducted with homogeneous patient groups (eg, patients fulfilling the European League Against Rheumatism criteria for arthralgia at risk of RA) in order to increase interstudy comparability and to allow result validation.

THE RELEVANCE OF ADEQUATE PREDICTION MAKING

Research into the earliest phases of rheumatoid arthritis (RA) is important because early treatment is associated with better outcomes. To facilitate this research the European League Against Rheumatism (EULAR) study group of risk factors for RA has defined several stages of RA development: genetic risk factors for RA, environmental risk factors for RA, systemic autoimmunity associated with RA, symptoms without clinical arthritis and unclassified arthritis (UA).1 These stages are based on the presumed order in which different risk factors exert their effects. Individuals in the first three stages are generally asymptomatic.

Over time symptoms may develop—initially often in the absence of clinically evident arthritis. In patients with established RA, the different phases may be identified retrospectively. However, it is clinically important to be able to predict with accuracy and confidence the future development of RA during its prearthritis stages. During recent years the phase of arthralgia has gained increasing interest as the risk of progression to RA is (in most cases) likely to be higher in symptomatic than in asymptomatic ‘at risk’ individuals. In addition, this is the way individuals typically present to medical care.

The phase of arthralgia is likely to be an important part of the so-called window of opportunity. Studies in patients with classified RA have revealed that an earlier start of treatment is associated with better outcomes.2,3 Because at presentation with clinical arthritis most patients will have a chronic disease, it is hypothesised that the period preceding clinical arthritis might be important. Within this prearthritides phase, disease processes might

Key messages

What is already known about this subject?

► Adequate risk prediction in patients with arthralgia is crucial for the development of clinically meaningful preventive trials and for implementation of positive trial results.

What does this study add?

► Predictors for progression to arthritis in arthralgia patients were reviewed; except for ACPA, none are replicated, which is partly due to heterogeneity in patient selection.

How might this impact on clinical practice?

► Before using these predictors in prognostication, results should be validated and studied in homogeneous groups of patients with arthralgia.
be less matured, making patients more susceptible to DMARDs. A review of murine studies suggested that DMARD initiation (e.g., methotrexate and abatacept) prior to clinical arthritis was effective. Several ongoing proof-of-concept trials in individuals with arthralgia are evaluating the hypothesis that DMARD initiation can prevent progression to clinically evident arthritis. Results of two randomised controlled trials have been published; the first included 83 patients with anti- 

trullinated protein antibodies (ACPA)-positive and/or rheumatoid factor (RF)-positive arthralgia who were treated with dexamethasone or placebo, and the second included 82 patients with ACPA-positive and RF-positive arthralgia with C reactive protein (CRP) levels $\geq 3 \text{mg/L}$ and/or subclinical synovitis on ultrasound (US) or MRI of the hands, who were treated with a single infusion of rituximab or placebo. Although a decrease in ACPA levels and a delay in arthritis onset were reported, neither intervention prevented the development of RA. This failure to prevent RA development may indicate that (1) the hypothesis is false (i.e., that the disease is not more modifiable in its arthralgia phase compared with its arthritis phase), or (2) the wrong drugs were tested, or (3) the studies included too few patients with a high risk of progression to RA, making it less easy to observe a preventive effect.

The importance of including patients with a high risk of progression to RA was illustrated in a recent post-hoc analysis of data from the Probable Rheumatoid Arthritis: Methotrexate versus Placebo Treatment (PROMPT) trial, in which patients with UA were treated with methotrexate with the aim of preventing progression to RA. The risk of progression to RA was $\sim 30\%$, and without further stratification, methotrexate did not modify this risk. However when only patients with a high (>80%) 1-year predicted risk of progression to RA were evaluated, methotrexate was highly effective in preventing RA development. In addition, methotrexate was also associated with disease-modifying antirheumatic-drug (DMARD)-free remission in this high-risk group (36% vs 0% in the placebo group). Although these post-hoc analyses were based on small sample sizes, these data demonstrate the relevance of including patients with a sufficiently high risk in preventive trials. The results of ongoing proof-of-concept trials in arthralgia are awaited over the next decade.

Not all of the ongoing preventive trials have fulfilment of the 2010 classification criteria for RA as primary outcome. This is supported by the fact that the presence of persistent clinical arthritis or a clinical diagnosis of RA is an outcome that fits with daily clinical practice.

Before implementing potential positive findings of preventive trials in daily rheumatological practice, we need to know which patients with arthralgia would otherwise develop RA and should be offered treatment, and conversely which patients should be reassured that disease progression is unlikely (figure 1).

**Figures**

**Figure 1** Adequate risk prediction is crucial for the design of informative preventive trials and for implementation of positive trial results.

**Figure 2** Predictors of rheumatoid arthritis development belong to different categories. A predictor of disease might directly reflect the underlying biological process, it can be a biological bystander of disease, or it might have no relation at all with the underlying biology and is a phenotypic marker.

**Types of Predictors**

Optimally performing biomarkers are often causally related to the underlying biological process. Examples include the combination of increased free thyroxine (FT4) and decreased serum thyrotropin (TSH) levels, which are pathognomonic for hyperthyroidism, and the urinary human chorionic gonadotropin (HCG)-based pregnancy test, which is seldom negative in pregnant women and high HCG levels are rarely present in settings other than pregnancy. Predictors can also be bystanders, markers that are side products of the biological process but characteristic of the disease. Other predictors are phenotypic in nature (figure 2). RA has a complex aetiopathology and its development is not easily reflected by a single marker. The presence of ACPA within RA is strongly predictive of erosive progression and may be causally related to the development of bone erosions, but its role in the development of RA is unclear and its presence is not 1:1 related to disease development. Furthermore, it has become clear that in addition to RF and ACPA, several other autoantibodies are present in RA. These different sets of autoantibodies may thus be considered as bystanders, although very useful in the diagnostic process. In the absence of pathognomonic markers, multiple biomarkers should be combined to predict which patients with arthralgia will progress to RA.

**Differentiating Arthralgia Suspicious for Progression to RA from Other Arthralgias**

Before reviewing the accuracy of different types of predictors, appreciation of the population studied is important. Arthralgia is a non-specific symptom and the biological nature of joint pain is diverse. Consequently, the risk to
Clinical expertise of GPs and rheumatologists in differentiating patients with arthralgia. This figure is constructed based on the following references: The clinical expertise of GPs and rheumatologists is effective in differentiating patients with arthralgia; of all patients with MSK symptoms visiting their GPs (~300/1000/year), only a small subset is suspected for arthritis (~3/1000/year). Of all patients with any MSK symptoms visiting secondary care (~8/1000/year), only 7% were identified as CSA. The incidence of any MSK symptom in secondary care is higher than the incidence of patients with suspected arthritis in primary care, as GPs also refer patients with MSK symptoms in whom they did not suspect arthritis to be present. 74% of patients with CSA had a positive EULAR definition. CSA, clinically suspect arthralgia; GP, general practitioner; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; MSK, musculoskeletal symptoms.

Altogether, patients with arthralgia in secondary care who are considered as CSA and fulfil the EULAR definition of arthralgia suspicious for progression to RA (clinically suspect arthralgia, CSA). Importantly, for patients with CSA, the odds for progression to RA were 55 times larger than the odds for patients with unexplained arthralgia. The rheumatologists’ clinical expertise had a high accuracy (93%), sensitivity (80%) and specificity (93%) for future RA. Although these data support the use of the rheumatologist’s clinical experience in identifying patients with arthralgia who are at risk of RA, a drawback is that this approach is subjective. This is a particular problem for research studies, where homogeneous groups of patients should be included. A EULAR task force has recently explicated this clinical expertise in clinical items that are measurable. A sensitive definition requires the presence of at least three items and a specific definition requires the presence of at least four items. AUC, area under the curve; EULAR, European League Against Rheumatism; MCP, metacarpophalangeal; RA, rheumatoid arthritis; sens, sensitivity; spec, specificity; UA, undifferentiated arthritis.

**Figure 3** Clinical expertise of GPs and rheumatologists in differentiating patients with arthralgia in different settings.

Musculoskeletal (MSK) symptoms are very prevalent in primary care. Primary care data from the Netherlands suggest an annual incidence of non-traumatic MSK symptoms of ~300/1000. In other words, almost one-third of the population visits the general practitioner (GP) at least once a year with an MSK symptom. The vast majority of these patients have explanations for their joint symptoms other than the beginning of a systemic inflammatory arthritis, and inflammatory arthritis is considered by GPs in only a minority of patients (figure 3). A separate Dutch GP study recorded an incidence of suspected arthritis of ~3/1000/year; most patients had a monoarthritis, and 60% had self-limiting symptoms. A small proportion of patients had suspected oligoarthritis or polyarthritis, and symptom persistence was more common in this group. These data support the notion that GPs are able to differentiate inflammatory from non-inflammatory cases of MSK symptoms and that the incidence of suspected inflammatory arthritis in primary care is low.

A similar observation has been made in secondary care. Most patients with arthralgia referred to rheumatologists have a diagnosis other than (imminent) RA. In addition, of patients presenting with arthralgia of uncertain cause, the large majority are not considered to be at risk of RA by their rheumatologists. A recent study revealed that only 7% of these patients with arthralgia were identified as clinically suspicious for progression to RA by their rheumatologists. A recent study revealed that only 7% of these patients with arthralgia were identified as clinically suspicious for progression to RA by their rheumatologists.
optimised selection of patients with arthralgia will result in an increased risk of RA in the population, and—as a result of Bayes’ theorem—this will also result in higher post-test chances when performing additional tests, such as laboratory or imaging tests, in this subset of patients with arthralgia.

SEARCH STRATEGY

The accuracy of different types of laboratory or imaging markers for predicting RA development is reviewed below. With the assistance of a medical librarian, we searched in the medical literature databases PubMed, Embase (Ovid version), Web of Science and Cochrane Library up to June 2017. Central terms in our search strategy were arthralgia, arthritis, autoantibodies, serological markers and imaging. In total 145 references on autoantibodies, 117 on serological markers and 310 on imaging markers were extracted. Reference lists of the identified articles were hand-searched for additional articles. From the total list of references, we selected the studies on patients with arthralgia with a longitudinal cohort design.

THE PREDICTIVE ACCURACY OF AUTOANTIBODY TESTING IN ARTHRALGIA

Nested case–control studies have shown that autoantibodies can be present years before the disease becomes manifest.20 21 Such studies use blood samples collected historically from patients known at the time of the study to have RA. Since, for patients presenting with arthralgia, it is relevant to know absolute risks for development of arthritis, this review focused on longitudinal studies. Most cohort studies that investigated the presence of autoantibodies have studied seropositive (ACPA and/or RF) patients in clinically ill-defined groups; one cohort study evaluated patients with CSA (table 1). In agreement with previous nested case–control studies, several longitudinal cohort studies have shown that the presence of ACPA associated with the development of clinical arthritis.22–26 The value of the level of ACPA (within ACPA-positive patients) in predicting arthritis development is unclear. While two studies, reporting on the same cohort, found an association between ACPA level and arthritis development,22 23 two other studies did not.26 27 Although these three cohorts selected ACPA-positive patients with arthralgia using different inclusion criteria (seropositive arthralgia, CSA or ACPA-positive persons with non-specific MSK symptoms) in different settings (primary and/or secondary care), the contrasting results are not yet explained. In addition to ACPA level, other ACPA characteristics have also been studied. The number of epitopes recognised by ACPA was associated with arthritis development in several studies in ACPA-positive patients with arthralgia.28–30 In addition, a decrease in galactosylation and an increase in core fucosylation of serum ACPA IgG1, indicating a change towards a more inflammatory phenotype of these autoantibodies, have been observed prior to the onset of RA.31

The value of RF in the preclinical phase of RA has also been studied.22–24 26 32 Two studies, on the same cohort, performed stratified analyses and observed that within ACPA-positive patients, the additive presence of RF associated with arthritis development.22 25 These studies did not contain ACPA-negative patients; hence, no information could be provided on the single presence of RF. Two studies, on the same cohort, did contain an RF-negative group and showed in univariable analyses that the presence of RF conferred a higher risk of arthritis; however, after adjusting for the concomitant presence of ACPA, this association was lost.24 26 Therefore it remains to be determined if the single presence of RF in arthralgia is a true predictor, although one study suggested that high levels of RF are a predictor in contrast to low levels of RF.26

Finally the presence of anticyclic citrullinated peptide (anti-CarP) antibodies in the preclinical phase of RA was studied. One study in autoantibody-positive individuals observed an association between anti-CarP antibodies and the development of arthritis,33 whereas another study in patients with CSA did not observe an additive value of anti-CarP when ACPA and RF status is known.26

In conclusion, the presence of ACPA is associated with arthritis development while this is less clear for RF and anti-CarP antibodies. A disadvantage of most current studies is that patients are selected based on autoantibodies; thus, there is no autoantibody-negative reference group. In addition, as inclusion of patients in these cohorts was driven largely by ACPA positivity, these patients would not necessarily have been defined as CSA and would not necessarily have fulfilled the EULAR definition of arthralgia. Furthermore as noted above, some of the available data are based on analyses of the same patient cohorts (studies in table 1 reported on six cohorts). Finally, in clinical practice where patients present with arthralgia, it is important to estimate absolute risks for progression to arthritis, but many studies did not provide these risks. Studies that did determine positive predictive values (PPVs) observed that the PPV of ACPA (independent of RF) ranged between 16% and 50%.22 26 This broad range can be explained by differences in patient settings, since PPVs are dependent on the prior risks of arthritis development, which varied in the different settings that were studied.

THE PREDICTIVE ACCURACY OF NON-ANTIBODY SEROLOGICAL MARKERS IN ARTHRALGIA

Various acute phase reactants, cytokines, chemokines and other systemic markers have been studied in the preclinical phase of RA (table 2). Results of studies evaluating CRP and erythrocyte sedimentation rate (ESR) are conflicting. Some studies have identified an association between CRP or ESR and arthritis development,22 27 30 34–36 while others have not.22 27 30 34–36 The only study showing an association between CRP level at study entry and development of arthritis included patients with CSA and did
| Author, Year          | Cohort                                                                 | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors                                           | Main result                                                                                     |
|----------------------|------------------------------------------------------------------------|-----------|------------------------------|--------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| de Bois et al., 1996 | Arthralgia (secondary care)                                            | 52†       | 10 (21)                      | NP                                                                       | 12                                         | Presence of IgM-RF                                         | RF predicts development of RA; PPV 50%, NPV 100%. Factors associated with arthritis development: ¬within all patients: ACPA (HR 6.0, 95% CI 1.8 to 20), but not RF ¬within ACPA+ patients: RF (HR 3.0, 95% CI 1.4 to 6.9) and high ACPA levels (HR 1.7, 95% CI 1.1 to 2.5). PPV for arthritis development within 2 years: ACPA-RF+ 6%, ACPA+RF+ 16%, ACPA+RF+ 40%. |
| Bos et al., 2010     | ACPA+ and/or RF+ arthralgia (secondary care)                          | 147       | 29 (20)                      | 11 (5–17)                                                               | 28 (19–39)                                  | Presence and level of IgM-RF and ACPA                      | Anti-CRP antibodies, but not anti-CRP levels, predicted progression to RA, independent of ACPA and RF (HR 1.6, 95% CI 1.1 to 2.3). PPV for arthritis development: ACPA+ anti-CRP− 40%, ACPA+anti-CRP+ 58%. |
| van de Stadt et al., 2011 | ACPA+ and/or RF+ arthralgia (secondary care)                        | 244       | 69 (28)                      | 11 (5–20)                                                               | 36 (18–60)                                  | Reactivity of ACPA to five citrullinated peptides          | Anti-CRP antibodies, but not anti-CRP levels, predicted progression to RA, independent of ACPA and RF (HR 1.6, 95% CI 1.1 to 2.3). PPV for arthritis development: ACPA+ anti-CRP− 40%, ACPA+anti-CRP+ 58%. |
| Shi et al., 2013     | ACPA+ and/or RF+ arthralgia (secondary care)                          | 340       | 129 (38)                     | 12 (6–24)                                                               | 36 (20–52)                                  | Presence and level of anti-CarP IgG antibodies              | Anti-CRP antibodies, but not anti-CRP levels, predicted progression to RA, independent of ACPA and RF (HR 1.6, 95% CI 1.1 to 2.3). PPV for arthritis development: ACPA+ anti-CRP− 40%, ACPA+anti-CRP+ 58%. |
| Van de Stadt et al., 2013 | ACPA+ and/or RF+ arthralgia (secondary care)                        | 374       | 131 (35)                     | 12 (6–23)                                                               | 32 (13–48)                                  | Presence and level of IgM-RF and ACPA                      | Anti-CRP antibodies, but not anti-CRP levels, predicted progression to RA, independent of ACPA and RF (HR 1.6, 95% CI 1.1 to 2.3). PPV for arthritis development: ACPA+ anti-CRP− 40%, ACPA+anti-CRP+ 58%. |
| de Hair et al., 2014  | ACPA+ and/or RF+ individuals at risk for RA (secondary care and public fairs) | 55‡       | 15 (27)                      | 13 (6–27)                                                               | 24 (14–47)                                  | Presence and level of IgG ACPA and reactivity to 10 citrullinated peptides | Total number of citrullinated peptides recognised by ACPA was associated with arthritis development (HR 1.2, 95% CI 1.0 to 1.4). Proportion of ACPA+ patients and ACPA level was not different in patients with and without progression to arthritis. |
| Rakieh et al., 2015  | ACPA+ persons with aspecific musculoskeletal symptoms (primary and secondary care) | 100       | 50 (50)                      | 7.9 (0.1–52)                                                            | 20 (0.1–69)                                  | IgM-RF and ACPA levels                                     | A measurement combining high level of RF and/or ACPA was not associated with arthritis development (HR 1.5, 95% CI 0.5 to 4.5, independent of tenderness of small joints, morning stiffness, PD signal and SE). |
| Rombouts et al., 2015 | ACPA+ arthralgia (secondary care)                                      | 183§      | 105 (57)                     | 12 (6–24)                                                               | 35 (21–52)                                  | Fc glycosylation pattern of ACPA-IgG1 and total IgG1       | ACPA display decreased Fc galactosylation and increased fucosylation prior to the onset of RA. |

Continued
| Author, Year | Cohort | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result |
|-------------|--------|-----------|-------------------------------|-------------------------------------------------|---------------------------------|-----------------|-------------|
| Janssen et al, 2016<sup>30</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 34 | 14 (41) | 17 (5–35) | 40 (24–43) | Total Ig-RF and IgG-ACP levels and ACPA reactivity to four citrullinated peptides | Within those who developed RA, ACPA and RF levels were not increased at time of diagnosis compared with 6 months before diagnosis. Patients with progression to arthritis had a broader IgG ACPA repertoire and more IgA reactivity for Fib1. |
| van Steenbergen et al, 2016<sup>24</sup> | Clinically suspect arthralgia (secondary care) | 150* | 30 (20) | 1.7 (0.8–4.1) | 17 (9–24) | IgM-RF and ACPA presence | In univariable analyses both ACPA and RF were associated with arthritis development (ACPA: HR 10, 95% CI 4.9 to 21; RF: HR 6.9, 95% CI 3.3 to 14). PPV for arthritis development within 1 year: ACPA 63%. |
| Nam et al, 2016<sup>25</sup> | Persons with aspecific musculoskeletal symptoms (primary care) | 2028 | 47 (2.3) | ACPA+ 1.8 (1.0–4.3) ACPA− 5.1 (2.9–14) | ACPA+ 12 (1.5–28) ACPA− 14 (13–22) | ACPA presence | RR for developing RA within 12 months in ACPA+ group was 67 (95% CI 32 to 138) and for IA it was 46 (95% CI 25 to 82). PPV of ACPA for development of RA was 42% and of IA 47%. |
| Ten Brinck et al, 2017<sup>26</sup> | Clinically suspect arthralgia (secondary care) | 241 | 44 (18) | 3.6 (1.2–4.8) | 103 (81–114) | IgM-RF, ACPA, anti-CarP presence and ACPA and IgM-RF level | ACPA, RF and anti-CarP were associated with arthritis development, but only ACPA was independently associated (HR 5.3, 95% CI 2.0 to 14). RF levels but not ACPA levels were associated with progression to arthritis. PPV for arthritis development within 2 years: ACPA-RF+ 38%, ACPA+RF− 50%, ACPA+RF+ 67%. |

Patients in refs 22 23 28 29 31 33 and in refs 24 26 are derived from the same cohort. Studies depicted in grey have provided absolute risks.* One patient who developed gout during follow-up was excluded from analyses. † Five patients were lost to follow-up. In this study there was no correction for the presence of ACPA. ‡ IgM-RF-positive and/or ACPA-positive individuals with arthralgia (n=34) or with a first-degree relative with RA with or without arthralgia (n=16). Information on family history of RA was missing for five patients in whom no arthritis developed. § Patients in this study were selected based on high ACPA serum level (median 419 U/mL, IQR 131.0–1216.0). ACPA, anticitrullinated protein antibodies; anti-CarP, anticarbamylated protein; IA, inflammatory arthritis; NP, not provided; NPV, negative predictive value; PD, power Doppler; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.
### Table 2 Non-antibody serological markers in the preclinical phase of RA

| Author, Year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result |
|--------------|------------------|-----------|------------------------------|---------------------------------------------------------------------|------------------------------------------|------------------|-------------|
| **Proteins** |                  |           |                              |                                                                     |                                          |                  |             |
| Bos et al, 2010 | ACPA+ and/or RF+ arthralgia (secondary care) | 147       | 29 (20)                      | 11 (5–17)                                                           | 28 (19–39)                               | CRP levels       | CRP levels were similar in patients with and without arthritis development (3.0, IQR 1.1–4.7; and 2.3, IQR 0.9–5.0; P=0.81, respectively). |
| Limper et al, 2012 | ACPA+ and/or RF+ arthralgia (secondary care) | 137       | 35 (26)                      | 11 (3.7–18)                                                        | 21 (6–48)                                | hsCRP, PCT and SPLA2 levels, and TNF-α, IL-6, IL-12p70, IL-10 and IFN-γ | Biomarker levels were not significantly different in patients with and without progression to arthritis during follow-up. |
| van de Stadt et al, 2012 | ACPA+ and/or RF+ arthralgia (secondary care) | 348       | 116 (33)                     | 12 (6–23)                                                           | 24 (14–49)                               | Total cholesterol, HDLc, LDLc, triglycerides, apoA1 and apoB | After correction for ACPA only ApoA1 was predictive of arthritis development (HR 0.5, 95% CI 0.3 to 0.9). For HDLc, a trend was observed (HR first vs second and third tertiles 0.7, 95% CI 0.5 to 1.0). |
| de Smit et al, 2014 | ACPA+ and/or RF+ arthralgia (secondary care) | 289       | 94 (33)                      | 12 (6–20)                                                           | 30 (13–49)                               | IgA, IgG and IgM antibody levels against Porphyromonas gingivalis | Anti-P. gingivalis antibody levels at baseline were not elevated in patients with progression to arthritis compared with patients without progression. |
| Rakieh et al, 2015 | ACPA+ persons with aspecific musculoskeletal symptoms (primary and secondary care) | 100       | 50 (50)                      | 7.9 (0.1–52)                                                       | 20 (0.1–69)                              | hsCRP levels     | CRP level at baseline was not associated with arthritis development (uncorrected HR 1.3, 95% CI 0.7 to 2.4). PPV for arthritis development: 56%. |
| Rombouts et al, 2015 | ACPA+ arthralgia (secondary care) | 183§      | 105 (57)                     | 12 (6–24)                                                           | 35 (21–52)                               | ESR              | ESR was increased prior to the diagnosis of RA (arthralgia at baseline: median 15.0 mm/hour (IQR 7.0–25); RA at diagnosis: 25 mm/hour (IQR 19–33)). |

Continued
| Author, Year       | Study population                      | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result                                                                                                                                 |
|-------------------|---------------------------------------|-----------|------------------------------|--------------------------------------------------------------------------|--------------------------------------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Janssen et al, 2016<sup>30</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 34        | 14 (41)                      | 17 (5–35)                                                                | 40 (24–43)                                 | CRP levels and ESR | At study entry CRP levels and ESR were comparable between patients with and without progression to arthritis. |
| van Steenbergen et al, 2016<sup>34</sup> | Clinically suspect arthralgia (secondary care) | 150*      | 30 (20)                      | 1.7 (0.8–4.1)                                                           | 17 (9–24)                                 | CRP levels            | CRP level was associated with arthritis development, independent of other clinical factors and MRI-detected inflammation (HR 1.1, 95% CI 1.0 to 1.1). PPV for arthritis development: 32%. |
| van Beers-Tas et al, 2016<sup>34</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 144       | 43 (30)                      | 15 (0–60)                                                                | 60 (1–60)                                 | 14-3-3η           | 14-3-3η was associated with arthritis development in patients with seropositive arthralgia, but when corrected for ACPA and RF 14-3-3η did not predict onset of arthritis. PPV of 14-3-3-η for arthritis development: 86%. |
| Chalan et al, 2016<sup>34</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 27        | 11 (41)                      | 8 (1–32)                                                                | Patients with non-progressing arthralgia: 26 (6-33) | 25 serum immune markers: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, IFN-α, IFN-γ, GM-CSF, TNF-α, IL-1RA, IL-2 R, Eotaxin (CCL11), IL-8, IP-10 (CXCL10), MCP-1 (CCL2), MIG (CXCL9), MIP-1α (CCL3), MIP-1β (CCL4), Rantes (CCL5) | Trends for increase in IL-5, MIP-1β, IL-1RA and IL-12 in patients with arthralgia with progression to arthritis. AUC for IL-5 was 0.8 (95% CI 0.6 to 1.0). ESR and CRP were not significantly different in patients with and without progression to RA. |

Continued
### Table 2  Continued

| Author, Year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result |
|--------------|------------------|-----------|-------------------------------|------------------------------------------------------------------------|-------------------------------------------|------------------|-------------|
| Zufferey et al., 2017  | RF and ACPA polyarthritis of >6weeks' duration (secondary care) | 80 | 9 (11) | NP | 18 (7)† | CRP levels | CRP level was not predictive of RA in univariable or multivariable regression analysis (OR 3.0, 95% CI 0.4 to 24, corrected for gender and US score). PPV of CRP for development of arthritis: 22% |

### PBMCs and expression of cell surface markers

| Author, Year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result |
|--------------|------------------|-----------|-------------------------------|------------------------------------------------------------------------|-------------------------------------------|------------------|-------------|
| Janssen et al., 2016 | ACPA+ and/or RF+ arthralgia (secondary care) | 34 | 14 (41) | 17 (5–35) | 40 (24–43) | Treg number and subsets | Treg number and subsets were comparable in patients with and without progression to arthritis during follow-up. |
| Lübbers et al., 2015 | ACPA+ and/or RF+ arthralgia (secondary care) | 155 | 44 (38) | 8 (5–13) | 23 (12–30) | B cell signature, comprising CD19, CD20, CD79α, CD79β | Combination of low B cell score and high type I IFN signature predicts arthritis development in seropositive arthralgia. AUC for B cell score combined with ACPA and RF was 0.9 (95% CI 0.8 to 1.0) in IFN<sup>high</sup> group and 0.7 (95% CI 0.6 to 0.8) in IFN<sup>low</sup> group. PPV of IFN<sup>high</sup>Bcell<sup>low</sup> score for development of arthritis: 60%. |
| Lübbers et al., 2016 | ACPA+ and/or RF+ arthralgia (secondary care) | 113 | 40 (35) | 13 (7.4–22) | 27 (19–42) | Absolute number of CD14<sup>+</sup> monocytes, CD4<sup>+</sup>, CD8<sup>+</sup>, CD56<sup>+</sup> T cells (CD3<sup>+</sup>), CD80<sup>+</sup>, CXCR3<sup>+</sup>, CD27<sup>+</sup> B cells (CD19<sup>+</sup>) and CD16<sup>+</sup>CD56<sup>+</sup>CD3<sup>−</sup>NK cells | Decreased CD8<sup>+</sup> T cells and memory B cells in patients who developed arthritis. |
### Table 2

| Author, Year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | Measured factors | Main result |
|--------------|------------------|----------|-------------------------------|----------------------------------------------------------------|------------------------------------------|-----------------|-------------|
| Hunt et al., 2016<sup>48</sup> | ACPA+ persons with aspecific musculoskeletal symptoms (primary and secondary care) | 103 | 48 (47) | 63% progressed within 12 months | 18 (0.1–80)<sup>‡</sup> | Naïve T cells, inflammation-related cells and Tregs | T cell subset dysregulation in ACPA+ individuals predates the onset of inflammatory arthritis, predicts risk and faster progression to inflammatory arthritis. PPV for T cell subset combined with clinical factors was 60%. PPV of clinical model alone was 50%. |
| van Baarsen et al., 2010<sup>50</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 109 | 20 (18) | 7 (4–15) | 30 (22–39) | Gene expression profile | Signatures associated with arthritis development were involved in IFN-γ-mediated immunity, haematopoiesis and chemokine/cytokine activity. |
| Limper et al., 2012<sup>50</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 137 | 35 (26) | 11 (3.7–18) | 21 (6–48) | mRNA expression levels of 21 inflammatory genes | Biomarker levels were not significantly different in patients with and without progression to arthritis during follow-up. |
| Lübbers et al., 2013<sup>50</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 115 | 44 (38) | 8 (5–13) | 23 (12–30) | Expression level of 7 type I IFN response genes: IFI44L, IFI6, IFIT1, MXA, OAS3, RSAD2, EPSTI | HR for development of arthritis was 2.4 (95% CI 1.3 to 4.5) for IFN<sup>hig</sup> individuals, corrected for ACPA and RF: AUC for IFN-score combined with ACPA and RF was 0.8 (95% CI 0.7 to 0.9). PPV of ACPA/RF combined with IFN score for development of arthritis was 65%. |
### Table 2 Continued

| Author, Year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Measured factors | Main result |
|--------------|------------------|-----------|-------------------------------|---------------------------------------------------------------|-----------------|-------------|
| Tak et al, 2017 | Seropositive individuals (ACPA and/or RF) at risk for RA | 71 | 26 (37) | NP | Test cohort: no arthritis 69 (42–78), arthritis 15 (0–65) Validation cohort: at least 36 months | Dominant BCR clones (BCR signals representing ≥0.5% of the repertoire) in PB and synovial tissue | Presence of ≥5 dominant BCR clones in PB was associated with arthritis development (validation cohort: RR 6.3, 95% CI 2.7 to 15). PPV of ≥5 dominant BCR clones for development of arthritis: 72% in test cohort and 83% in validation cohort. |

Patients in refs 22 31 36 37 52 54 55, in refs 30 34, in refs 27 49 and in refs 38 50 51 56 are derived from the same cohort. Studies depicted in grey have provided absolute risks.

*One patient that developed gout during follow-up was excluded from analyses.
†Mean (SD).
‡Median (range).
§Patients in this study were selected based on high ACPA serum level (median 419 U/mL, IQR 131.0–1216.0).
ACPA, anticitrullinated protein antibodies; apo, apolipoprotein; AUC, area under curve; BCR, B cell receptor; CD, cluster of differentiation; CRP, C reactive protein; EPSTI, epithelial stromal interaction; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte macrophage colony-stimulating factor; HDLc, high density lipoprotein cholesterol; (hs)CRP, (high sensitivity) C reactive protein; IFN, interferon; IFI44L, interferon-induced protein 44 like; IFI6, interferon alpha-inducible protein 6; IFIT1, interferon induced protein with tetratricopeptide repeats 1; IL, interleukin; LDLc, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; MIG, monokine induced by gamma interferon; MIP, macrophage inflammatory protein; MXA, myxovirus resistance protein A; NK cells, natural killer cells; NP, not provided; OAS3, 2′–5′-oligoadenylate synthetase 3; PB, peripheral blood; PBMC, peripheral blood mononuclear cell; PCT, procalcitonin; PPV, positive predictive value; RA, rheumatoid arthritis; RANTES, regulated on activation, normal T cell expressed and secreted; RF, rheumatoid factor; RR, relative risk; RSAD2, radical S-adenosyl methionine domain containing 2; SPLA2, secretory phospholipase A2; TNF-α, tumour necrosis factor-α; Treg, regulatory T cell; US, ultrasound.
not select on the presence of autoantibodies. Studies that showed no predictive value of CRP were mostly conducted in autoantibody-positive arthralgia. This could imply that CRP has a predictive value in autoantibody-negative patients in particular; further studies are needed to clarify this.

Other serological markers have been assessed. In one study, differences were observed in the lipid profile of patients with and without progression to arthritis. After correction for ACPA, a lower apolipoprotein A1 level was associated with arthritis development. Another study evaluated 14-3-3-η and showed that the PPV of 14-3-3-η for arthritis development was 86%. However, when corrected for ACPA and RF, 14-3-3-η did not predict onset of arthritis. Other serological biomarkers showed trends towards higher levels in patients with progression to arthritis. None of these markers was evaluated in other studies.

In conclusion, most results on serological markers of inflammation have not been validated in independent studies. Only CRP has been studied in several cohorts of patients with seropositive arthralgia and was shown to be of limited value.

THE PREDICTIVE ACCURACY OF IMAGING MARKERS DETECTING SUBCLINICAL INFLAMMATION IN ARTHRALGIA

Different imaging modalities (US, MRI, positron emission tomography and scintigraphy) have been used to study the presence of local subclinical inflammation, while others did. The studies that did not observe an association either included patients with seropositive arthralgia, ACPA-positive persons with non-specific MSK symptoms or patients with new-onset inflammatory arthralgia; studies that did observe an association included patients with arthralgia based on clinical characteristics, and differences in results might be partly explained by differences in patient selection. Furthermore, US protocols, joint regions assessed and US features reported on differed across the studies. It is also important to note that none of the studies have used a healthy reference population to define thresholds at which US findings should be classified as abnormal. Since a previous study has shown that US lesions (greyscale synovial effusion or synovitis with or without power Doppler signal) are also present in the majority (88%) of healthy volunteers, it might be important to correct for normal, physiological findings when defining a positive US.

Finally, few studies have evaluated the predictive value of US abnormalities in relation to the presence of other predictors; therefore, the additive value of US abnormalities to regularly used biomarkers is unknown. Despite these shortcomings, the data obtained suggest that of the different US features, power Doppler signal might have the highest predictive value for the development of arthritis.

Studies on the predictive value of MRI have been performed. Studies within autoantibody-positive non-specified arthralgia did not observe associations between MRI features at the knee (bone marrow oedema (BME) or synovitis) and progression to clinical arthritis. A small MRI study evaluating synovitis and BME in small joints of 28 patients with ACPA-positive arthralgia was also negative. However, larger studies in 130 patients with CSA revealed that MRI-detected inflammation was associated with progression to arthritis, independent of ACPA, CRP and clinical factors. Interestingly, in multivariable analyses, the effect size of MRI-detected inflammation was almost equal to that of ACPA (HR 5.1 for MRI and 6.4 for ACPA). MRI-detected tenosynovitis had a higher accuracy than synovitis or BME. Altogether subclinical inflammation identified by MRI is a predictor for RA development, when measured in small hand and feet joints, but not in knee joints (which may not be the location where synovitis begins in RA). As with US, age-matched symptom-free controls to define thresholds at which MRI features should be viewed as abnormal are lacking in most MRI-based studies. This may have affected the results as it has been recently shown that the predictive accuracy and specificity of a positive MRI increased when this was taken into account.

In conclusion, imaging studies in arthralgia have been conducted in different patient populations, evaluating different joints and different inflammatory features. None of the studies were independently replicated and none compared MRI and US in the same patients with arthralgia. Further studies using similar protocols in homogeneous patient groups are warranted.

MARKERS CHARACTERISING IMMUNE CELL DYSFUNCTION

It has been suggested that immune system dysregulation is an early feature of RA frequently preceding the onset of arthritis. Several markers have been studied. The number of regulatory T cells (Tregs) in the peripheral blood appeared not to be indicative of RA development in patients with seropositive arthralgia. In contrast, others showed that reduced naïve T cells and Tregs and increased inflammation-related cells were predictive of progression to arthritis in ACPA-positive persons with non-specific MSK symptoms. Seropositive patients who developed arthritis had a significantly decreased number of peripheral CD8+ T cells and memory B cells compared with non-converters. B cell subtypes have been studied; patients with seropositive arthralgia with a low B cell score, measured as expression of CD19, CD20, CD79α and CD79β, had an increased risk of arthritis if there was also a high type I interferon signature. B cell receptor...
### Table 3: Ultrasonography in the preclinical phase of RA

| Author, year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Locations scanned | Ultrasound/measured factors | Controls used to define positive US | Main result |
|--------------|------------------|-----------|------------------------------|---------------------------------------------------------------------|-------------------|-----------------------------|-------------------------------------|-------------|
| van de Stadt et al, 2010<sup>43</sup> | ACPA+ and/or RF+ arthralgia (secondary care) | 43 | 65 (23) | 11 (9)* | Only painful joints and adjacent and contralateral joints | Y | Y | Y | N | N | At patient level US abnormalities were not associated with arthritis development. |
| Pratt et al, 2013<sup>44</sup> | Main study on arthritis, 46 patients with new-onset inflammatory arthralgia (secondary care) | 379† | 162 (42) | NP | MCP, PIP and MTP joints, bilaterally | Y | Y | N | Y | N | The presence of MSUS abnormalities was not associated with development of persistent inflammatory arthritis in patients presenting with arthralgia, in the absence of clinical synovitis. |
| Rakieh et al, 2015<sup>45</sup> | ACPA+ persons with aspecific musculoskeletal symptoms (primary and secondary care) | 100 | 50 (50) | 7.9 (0.1–52) | Wrist, MCP and PIP joints, bilaterally | N | Y | N | N | N | PD signal was not associated with arthritis development (HR 1.9, 95% CI 0.8 to 4.2, independent of tenderness of small joints, morning stiffness, RF and/or ACPA and SE). PPV of PD signal for development of arthritis: 67%. |
| Van der Ven et al, 2016<sup>46</sup> | Arthralgia in ≥2 joints in hands, feet or shoulders <1 year (secondary care) | 196‡ | 36 (23) | NP | Wrist, MCP, PIP and MTP joints, bilaterally | Y | Y | N | N | N | The presence of PD signal (OR 3.4, 95% CI 1.7 to 7.0) was associated with development of arthritis, independent of ACPA. |
| Nam et al, 2016<sup>47</sup> | ACPA+ persons with aspecific musculoskeletal symptoms (primary and secondary care) | 136 | 57 (42) | 8.6 (0.1–52) | Wrist, MCP, PIP and MTP joints, bilaterally | Y | Y | N | Y | N | Both GS and PD associated with arthritis development: GS=2 hour, 2.8 (0.4–20), PD=2 hours, 3.7 (2.0–6.9). PPV of GS>2 for development of arthritis was 48% and of PD=2 75%. |
| Zufferey et al, 2017<sup>48</sup> | RF and ACPA polyarthralgia of ≥6 weeks duration (secondary care) | 80 | 9 (11) | NP | Wrist, MCP, PIP, elbow and knee joints, bilaterally | Y | N | N | N | N | US synovitis at baseline was associated with progression to RA. OR was 7.5 (95% CI 1.2 to 43) for grade ≥2 in ≥2 joints, independent of gender and CRP. PPV of US significant synovitis for development of arthritis: 25%. |

*Mean (SD).
146379 had a swollen joint count ≥1 at baseline. Outcome was persistent inflammatory arthritis.
†Only 159 completed the 12 months’ follow-up. Studies depicted in grey have provided absolute risks.
ACPA, anticitrullinated protein antibodies; CRP, C reactive protein; GS, greyscale; MCP, metacarpophalangeal; MSUS, musculoskeletal ultrasound; MTP, metatarsophalangeal; N, no; NP, not provided; PD, power Doppler; PIP, proximal interphalangeal; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope; SONAR, Swiss sonography in arthritis and rheumatism; US=ultrasound; Y, Yes.
| Author, year | Study population | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | MRI strength | Contrast enhancement | Locations scanned | Measured factors | Controls used to define positive MRI | Main result |
|-------------|-----------------|-----------|------------------------------|-------------------------------------------------|------------------------------------------|--------------|----------------------|-------------------|----------------|----------------------------------|-------------|
| van de Sande et al, 2011 | ACPA+ and/or RF+ arthralgia (secondary care) | 13* | 4 (31) | 3 (1–6)§ | 37 (25–45)§ | 1.5T | Y | Knee joint | Maximal enhancement, rate of enhancement, synovial volume and enhancement shape curve distribution | N | No differences in MRI findings between patients with and without progression to arthritis. |
| de Hair et al, 2014 | ACPA+ and/or RF+ individuals at risk for RA (secondary care and public fans) | 55† | 15 (27) | 13 (6–27) | 27 (14–47) | 1.5T or 1T | Y | Arbitrary knee joint | Synovitis and hydrops in four compartments, BME, erosions and cartilage damage | N | None of the MRI parameters were associated with arthritis development. |
| Gent et al, 2014 | ACPA+ arthralgia (secondary care) | 28 | 12 (43) | NP | NP | 3 years follow-up | 1.5T | Y | Wrist, MCP and PIP joints of both hands | Synovitis and BME according to RAMRIS | N | No difference in MRI-detected synovitis and BME scores in patients with and without progression to arthritis. |
| van Steenbergen et al, 2014 | ACPA-clinically suspect arthralgia (secondary care) | 64 | 5 (8) | NP | 9 (5–11) | 1.5T | Y | Wrist, MCP and MTP joints, of most painful side | Synovitis and BME according to RAMRIS | N | Higher scores for MRI inflammation (sum of BME and synovitis scores), synovitis and BME in patients who developed clinically detectable arthritis. |
Table 4 Continued

| Author, year       | Study population                          | Cases (n) | Progression to arthritis (%) | Median duration from study entry to diagnosis of arthritis, months (IQR) | Median duration of follow-up, months (IQR) | MRI strength | Contrast enhancement | Locations scanned | Measured factors                          | Controls used to define positive MRI | Main result |
|--------------------|------------------------------------------|-----------|-------------------------------|------------------------------------------------------------------------|--------------------------------------------|--------------|----------------------|-------------------|-----------------------------------------|--------------------------------------|-------------|
| van Steenbergen et al, 2016 24 | Clinically suspect arthralgia (secondary care) | 150‡      | 30 (20−)                      | 1.7 (1−4)                                                                  | 17 (9−24)                                  | 1.5T         | Y                    | Wrist, MCP and MTP joints, of most painful side | Synovitis and BME according to RAMRIS Tenosynovitis in wrist and MCP joints | Y           | MRI-detected inflammation was associated with progression to arthritis, independent of age, symptom localisation, CRP and ACPA (HR 5.1, 95% CI 1.8 to 19). PPV of MRI-detected inflammation for arthritis development within 1 year; in all patients 31%; in ACPA+ patients 71%. |

*IgM-RF-positive and/or ACPA-positive individuals with arthralgia (n=12) or with a first-degree relative with RA with arthralgia (n=1).†IgM-RF-positive and/or ACPA-positive individuals with arthralgia (n=34) or with a first-degree relative with RA with or without arthralgia (n=16). Information on family history of RA was missing for five patients in whom no arthritis developed.

‡One patient who developed gout during follow-up was excluded from analyses. In six patients MRI was not performed. Patients in refs 25 35 37 are all recruited via referral from the Academic Medical Center, Amsterdam, and from the rheumatology outpatient clinic of Reade. Patient in refs 19 38 39 are all included in the Leiden Clinically Suspect Arthralgia Cohort. The study depicted in grey has provided absolute risks.

§Median (range).
ACPA, anticitrullinated protein antibodies; CRP, C reactive protein; BME, bone marrow oedema; MCP, metacarpophalangeal; MTP, metatarsophalangeal; N, No; NP, not provided; PIP, proximal interphalangeal; PPV, positive predictive value; RA, rheumatoid arthritis; RAMRIS, rheumatoid arthritis MRI scoring system; RF, rheumatoid factor; Y, Yes.
(BCR) clones, defined as BCR clones expanded beyond 0.5% of the total repertoire, have also been studied in the peripheral blood of 71 seropositive individuals at risk of RA and were associated with an enhanced risk of arthritis.52

Unfortunately, most of the abovementioned studies did not address whether the novel markers added to the predictive utility of regularly used biomarkers and validation was lacking. In addition, most of the studied markers are not high-throughput available in daily clinical practice.

CONCLUSION
The processes causing arthralgia to progress to clinically evident RA are insufficiently understood. Most studied predictors are not pathognomonic for this transition or for RA, and the predictive accuracy of most markers has not been validated in different studies. Only ACPA positivity has been observed to associate with RA development across multiple studies. In addition none of the predictors studied, including ACPA, was sufficiently predictive on its own, and the vast majority of studies did not combine different types of predictors. The few studies that did combine different markers (eg, imaging and ACPA) revealed that combinations were also insufficient for adequate risk stratification in many patients (as PPVs were <80%).24 Therefore more research is needed to obtain adequate risk stratification in patients with arthralgia.

Ideally, future studies should be performed in homogeneous patient groups, for example, patients fulfilling the EULAR definition of arthralgia at risk for RA. In this way, patients with comparable prior risks for RA will be selected, and validation of findings in different cohorts will be possible. Results of these future studies should provide data to support the development of robust algorithms to differentiate patients with arthralgia likely to progress to RA from those unlikely to do so. Importantly the variables within these algorithms and their weightings may well be better for algorithms designed for use in different contexts, for example, primary and secondary care.

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No additional data are available.

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Correction: Which patients presenting with arthralgia eventually develop rheumatoid arthritis?

Boeters DM, Raza K, vander Helm-van Mil AHM. Which patients presenting with arthralgia eventually develop rheumatoid arthritis? The current state of the art. *RMD Open* 2017;3:e000479.

The third author’s surname is misspelt. It should be ‘van der Helm-van Mil.’

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