Commentary

Predicting Rheumatoid Arthritis in At-risk Individuals

Laurette van Boheemen [1]; and Dirkjan van Schaardenburg [1,2]

[1]*Amsterdam Rheumatology and Immunology Center, Amsterdam, the Netherlands; and*
[2]*Amsterdam Rheumatology and Immunology Center, Amsterdam University Medical Center, Amsterdam, the Netherlands*

ABSTRACT

The typical evolution of rheumatoid arthritis (RA) is that a person with genetic risk factors develops autoantibodies and subclinical inflammation under relevant environmental influences, culminating in symptoms and finally clinically detectable arthritis. Because several of these characteristics can be present before the outbreak of clinical arthritis, it is possible to study the at-risk phase (the presence of ≥1 risk factors for RA in an individual) with the aim of quantifying the risk for that individual. As a person progresses through the different phases of disease development, different markers can be used for prediction. In the early asymptomatic phase, genetics, environmental factors, and autoantibodies are relevant, whereas in later phases additional markers, such as symptoms and imaging, come into play, conveying the risk of not only RA but sometimes even of imminent RA. Prediction is of limited use when not coupled with the possibility to intervene and lower the risk of RA. There is a clear need for effective preventive strategies that take the phase of disease development into account. On the other hand, selecting the right persons for preventive treatment according to their stage of disease development requires the improvement of current prediction models and strategies. This commentary presents an overview of risk factors and their combination into prediction models for use in different stages of RA development. Although clear progress has been made and assuming a future with effective options to intervene, there are still several gaps in our knowledge that need to be filled before it is clear who should be tested and when. (*Clin Ther.* 2019;41:1286–1298) © 2019 Published by Elsevier Inc.

Keywords: rheumatoid arthritis, preclinical, arthralgia, risk factors, prediction, prevention.

CASE REPORT

A 45-year-old woman visits a rheumatologist because of intermittent pain and stiffness in the hands and wrists for the past 5 months. She has not noticed joint swelling. There is morning stiffness lasting >60 min. She smokes 12 cigarettes per day and drinks 5 glasses of wine per week. Physical examination reveals no signs of synovitis. The visual analog scale pain level is 65 mm. The rheumatologist tests her for rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA), and results are positive for both. The patient is very worried she will develop RA just like her mother. What can we tell this patient about her absolute risk of developing RA?

PRE-RA

Before a patient is diagnosed with RA, a preclinical phase is present, consisting of multiple possible stages as described in detail by Deane and Holers[1] in this issue. In patients with RA, one can look in retrospect at the preclinical period for clues to RA disease pathogenesis, thus enabling identification of RA risk factors. However, individuals with these risk factors cannot be regarded as having pre-RA because many of them will not develop RA and we cannot yet entirely accurately predict RA development in these individuals. These persons should be termed as being at-risk of RA.[2]

For prediction of RA in at-risk individuals, it is relevant to understand that with progression through the different stages of the at-risk phase different markers of prediction may arise. Genetic risk factors

Accepted for publication April 10, 2019
https://doi.org/10.1016/j.clinthera.2019.04.017
0149-2918/$ - see front matter

are constant and present from birth. During life, environmental risk factors accumulate with varying exposure duration. Then, at a certain point in life, there is a breach in self-tolerance after which autoantibodies can appear as a result of the immune response.[3] During progression toward RA, the antibody response evolves, including epitope spreading[4] and a switch to a more proinflammatory phenotype.[5] As the phase of clinically apparent arthritis approaches, inflammatory markers and imaging abnormalities can appear[6] in parallel to clinical signs and symptoms.[7]

Consequently, in different stages of the at-risk phase, different markers can be used to calculate RA risk. To help individual prediction, separate risk markers can be combined into prediction models. In the earliest stages of RA development, genetic markers and environmental risk factors can be used for prediction, whereas in later stages, autoantibodies, symptoms, and imaging results can be added. Closer to RA onset, more risk factors have accumulated, resulting in more markers to be used for prediction and more accurate prediction. On the basis of the success of early treatment of RA,[8,9] intervention in the preclinical phase could be beneficial. To select suitable individuals for primary prevention, prediction models are required that accurately predict individual RA risk. For simplicity, we consider 2 groups of at-risk persons in this commentary: asymptomatic and symptomatic individuals. Autoantibodies are discussed in the latter group; however, in both cases, autoantibodies can be present.

RISK PREDICTION IN ASYMPTOMATIC INDIVIDUALS

Genetics

From the start of life, genetic factors are important in RA susceptibility. The strongest associations have been seen with female sex, a family history of RA, and the shared epitope (SE) susceptibility locus, a set of alleles within the major histocompatibility complex. The female to male RA prevalence is 3:1,[10] and having a family history of RA increases the risk of RA by 2- to 4-fold, with strongest risks seen in first-degree relatives (FDRs).[11] In addition, prevalence of disease is increased within certain ethnic groups, such as North American natives, who exhibit prevalence rates of RA of 5%−7% compared with approximately 0.5%−1% of the overall population.[12] However, the strongest genetic risk factor is the SE, which is believed to contribute up to 40% of genetic risk for RA, although other studies suggest less contribution.[13] Besides the SE, multiple other genetic factors are associated with RA, and there are now >100 non−major histocompatibility complex single-gene loci known, with the *PTPN22* 1858T allele as the most important contributor.[14] In aggregate, they may explain approximately 5% of the genetic association with RA outside the SE.[15] However, all currently known genetic risk factors combined explain only 16% of overall RA risk. In addition, most of the evidence regarding genetic risk factors comes from genome-wide association studies, and, until now, they cannot be used for individual prediction because of their low effect size.[16,17]

Environmental Factors

Environmental risk factors accumulate during life. Many individual environmental factors and several comorbidities have been associated with RA, and during the past few years, striking gene−environment interaction have been discovered. Smoking is the strongest environmental risk factor, with a clear dose response effect. Exposure to smoking accounts for 20%−30% of environmental risk.[18] It is most strongly associated with ACPA-positive RA, especially in the setting of the SE.[19] Several studies have reevaluated evidence for other established and controversial risk factors and provide an overview.[13,20–22] Obesity is also clearly associated with increased RA risk.[23,24] Environmental risk factors with moderate evidence of an association with higher RA risk include lower educational level (possibly linked to lifestyle or certain occupations),[25] high birth weight (>4 kg),[20] early age at menopause,[26] and high sugar intake,[27] whereas fish[28] and ω3 fatty acid consumption,[13] and moderate alcohol intake[21] are associated with lower risk. Breastfeeding and parity likely have a protective effect.[29,30] More inconclusiveness exists for other risk factors, such as (industrial) exposure to silica dust, solvents, air pollution, and UV light,[13,20] hormonal factors such as age at menarche[22] and oral contraceptives,[31,32] dietary factors such as intake of vitamin D[33] and antioxidants,[34,35] and higher intake of sodium, coffee, and meat.[13,21] Despite inconclusiveness about several individual dietary risk

factors, overall diet is important for RA risk. Long-term healthy eating patterns, according to the 2010 Alternative Healthy Eating Index, are associated with reduced risk of seropositive RA,[36] and an inflammatory diet pattern increases RA risk.[37] In addition, environmental risk factors differ between seropositive and seronegative RA.

Comorbid Diseases

Some comorbidities are known risk factors for RA development, such as obesity and diabetes mellitus. Obesity and diabetes mellitus contribute to RA prediction; however, effect sizes are low.[38,39] In recent years, disease of oral tissue, lung, and gut have been a main focus for possible novel predictive markers because of the hypothesis that mucosal surfaces (and potentially microbes) play a role in the pathogenesis of RA. For example, there is increasing evidence for periodontitis as a risk factor for RA.[40] Observational studies have linked inflammation in the oral cavity and specifically periodontitis to RA development,[41] and studies have identified candidate organisms in RA pathogenesis, such as *Porphyromonas gingivalis*. However, our group did not find that antibodies against *P gingivalis* are prognostic for RA development.[42] The contribution of other comorbidities to RA prediction is currently unknown.

Prediction Models

Given the many genes involved in the pathogenesis of RA, genetic risk scores have been developed to help individual prediction by totaling multiple validated genetic risk loci. These loci can then be combined with environmental risk factors into prediction models. An overview is given in Table I (based on the study by Karlson et al[20]). The model with the largest AUC combined multiple human leukocyte antigen (HLA) and non-HLA genetic loci with smoking status, producing an AUC of 0.86 (95% CI, 0.80−0.91).[47] The model classified 38% of patients with ACPA-positive RA vs. 3% of healthy controls as high risk and 70% of healthy controls versus 18% of patients with ACPA-positive RA as reduced risk. The ratio of the percentage of ACPA-positive cases to controls classified as high risk was 6.0.

These prediction models remain to be validated in different cohorts. Most genetic prediction models have been tested in a heterogeneous RA population versus healthy controls. Prediction might be improved if these models applied to more specific populations. Because the models mainly use genetic and environmental risk factors, FDRs of patients with RA are a good candidate population to screen. Sparks et al[48] indeed found better prediction of their model in a cohort of FDRs. A next step is to test whether adding new markers, such as lifestyle factors or periodontitis, to existing models increases predictive ability.

A drawback of case−control studies is that they use data collected previously and thus cannot effectively zoom in on certain details in the at-risk phase such as can be provided by, for example, symptoms or imaging as is possible in prospective cohorts (see below). However, the case−control studies add valuable information on which variables should be studied in prospective cohorts.

RISK PREDICTION IN PATIENTS WITH ARTHRALGIA

Autoantibodies

In clinical practice, RF and ACPA are often determined in patients with arthralgia suspected of having RA. Approximately two-thirds of patients with RA test positive for RF and/or ACPA at diagnosis, underlying their importance in this disease. In general, the prevalence of positive autoantibody tests increases closer to the time of onset of clinical arthritis.[3,49] However, autoantibodies have been found up to ≥15 years before diagnosis. During the preclinical phase, evolution of autoantibody responses can be seen, which can include level increases, isotype switching, affinity maturation, epitope spreading, and a changing glycosylation profile. IgG ACPA and, to a lesser extent, IgA ACPA increase significantly over time until RA onset. For RF, IgA isotypes appear first, followed by IgG-RF and IgM-RF.[50] Also toward RA diagnosis, epitope spreading increases,[4,51−53] and several months before onset of RA, the glycosylation profile of ACPAs change, giving ACPAs a more proinflammatory phenotype.[5] In contrast to antibody status, determining changes in autoantibody levels and characteristics is currently not a validated tool to predict risk of RA.[54]

Determining the presence of autoantibodies and initial autoantibody levels is feasible for predicting the risk of future RA.[55] The mere presence of RF alone or low-level ACPA is not associated with increased risk, but high-level ACPA or the

Table I. Prediction models for development of rheumatoid arthritis using genetic and environmental risk factors.

Study	Cohort; Variables	No. of Patients	Results
Karlson et al,[45] 2010	NHS (United States) and EIRA (Sweden); 14 SNPs, 8 HLA alleles, and clinical parameters: age, sex, smoking	NHS: 289 seropositive RA, 481 controls EIRA: 629 ACPA-positive RA, 623 controls	Genetic model NHS: OR = 2.9 (95% CI, 1.8−4.6) EIRA: OR = 3.4 (95% CI, 2.3−5.0) Genetic and clinical model: NHS: AUC = 0.66 EIRA: AUC = 0.75
Chibnik et al,[43] 2011	NHS (United States); 31 SNPs, 8 HLA alleles	542 RA, 551 controls	Seronegative RA: OR = 1.2 (95% CI, 0.8−2.1); AUC = 0.56 Seropositive RA: OR = 3.0 (95% CI, 1.9−4.7); AUC = 0.65 Erosive RA: OR, 3.2 (95% CI, 1.8−5.6). AUC = 0.64 Seropositive, erosive RA: OR = 7.6 (95% CI, 3.6−16.3); AUC = 0.71
Kurreeman et al,[15] 2011	EHR cohort (United States); genetic loci: 1 HLA allele, 29 SNPs	1552 ACPA-positive RA, 1504 controls	European ancestry: AUC = 0.71 (95% CI, 0.68−0.73) African ancestry: AUC = 0.63 (95% CI, 0.56−0.70) East Asian ancestry: AUC = 0.74 (95% CI, 0.59−0.89) Hispanic ancestry: AUC = 0.66 (95% CI, 0.56−0.76)
Karlson et al,[46] 2013	NHS (United States) and validation in EIRA (Sweden); 31 SNPs, 8 HLA alleles, and clinical parameters: age, smoking, alcohol, parity, occupational exposures, and HLA smoking interaction	NHS: 317 seropositive RA, 551 controls EIRA: 987 ACPA-positive RA, 958 controls	Epidemiologic, genetic, and gene environment interaction model NHS: AUC = 0.74 (95% CI, 0.72−0.79) EIRA women: AUC = 0.72 (95% CI, 0.71−0.76) EIRA men: AUC = 0.77 (95% CI, 0.75−0.83)
Scott et al,[42] 2013	WTCCC and UKRAGG (United Kingdom); genetic loci: 25 HLA alleles, 31 SNPs, and clinical parameter: smoking	WTCCC: 1516 RA, 1647 controls UKRAGG: 2623 RA, 1500 controls	HLA-SNP model UKRAGG: AUC = 0.76 (95% CI, 0.72−0.79) WTCCC: AUC = 0.80 (95% CI, 0.78−0.81)

(*continued on next page*)

Table I. (*Continued*)

Study	Cohort; Variables	No. of Patients	Results
			HLA-SNP smoking model UKRAGG: AUC = 0.86 (95% CI, 0.80−0.91) WTCC: AUC = 0.84 (95% CI, 0.81−0.87)
Lahiri et al,[38] 2014	EPIC NOAR (United Kingdom): alcohol use, smoking, occupation, BMI, diabetes mellitus, parity, breastfeeding	25,455 participants (184 developed IP, 138 developed RA)	Pack-years smoking in men and risk of IP: HR = 1.21 (95% CI 1.08−1.37) DM and risk of IP: HR = 2.54 (95% CI, 1.26−5.09) Alcohol units per day and risk of IP: HR = 0.36 (95% CI, 0.15−0.89) Obesity and risk of seronegative IP: HR = 2.75 (95% CI, 1.39−5.46) Parity ≥2 and risk of IP: HR = 2.81 (95% CI, 1.37 −5.76) Breastfeeding and risk of IP: HR = 0.66 (95% CI, 0.46 −0.94) IP risk score: AUC = 0.66
Yarwood et al,[82] 2015	Immunochip Consortium, validation in CORRONA; genetic loci, 45 SNPs, imputed amino acids at HLA-DRB1, HLA-DPB1 and HLA-B and clinical parameters: sex, smoking	Immunochip: 11,366 RA, 15,489 controls CORRONA: 2206 RA, 1863 controls	Genetic loci combined Immunochip: OR = 2.0 (95% CI, 1.9−2.1), AUC = 0.74 CORRONA: OR = 2.0 (95% CI, 1.9−2.1), AUC = 0.72 Addition of smoking: AUC = 0.80
Sparks et al,[48] 2015	NHS (United States), validation in EIRA (Sweden); genetic loci, 8 HLA alleles, 31 SNPs, and clinical parameters: family history, epidemiologic factors, smoking	NHS: 381 RA, 410 controls EIRA: 1752 RA, 1361 controls	Genetic loci combined NHS: AUC = 0.62 (95% CI, 0.58−0.67) EIRA: AUC = 0.58 (95% CI, 0.55−0.60) Genetic loci and clinical parameters NHS: AUC = 0.74 (95% CI, 0.7−0.78) EIRA: AUC = 0.69 (95% CI, 0.67−0.72)

ACPA = anticitrullinated protein antibodies, CORRONA = Consortium of Rheumatology Researchers of North America registry, DM = diabetes mellitus, EHR = electronic health record, EIRA = Epidemiologic Investigation of Rheumatoid Arthritis, HLA = human leukocyte antigen, HR = hazard ratio; IP = inflammatory polyarthritis, NHS = Nurses' Health Study, OR = odds ratio, RA = rheumatoid arthritis, SNP = single-nucleotide polymorphism, UKRAGG = RA Genetics Group Consortium UK, WTCCC = Wellcome Trust Case Control Consortium.

combination of ACPA and RF increase RA risk.[56,57] The positive predictive value (PPV) of ACPA positivity for RA development within 4 years in patients with arthralgia is 16%, whereas the PPV for RF and ACPA double positivity is 40%. In a cohort of FDRs, PPV is 58% and 64%, respectively, during 5 years.[58] Besides RF and ACPA, other RA-related autoantibodies have been detected, which can also be present in the preclinical stage, such as anticarbamylated protein antibodies, anti-IgG hinge antibodies, and anti−peptidyl arginine deiminase type 4.[59–61] In persons who test positive for ACPA and anticarbamylated protein antibodies, 58% develops RA.[62] Triple positivity for RF, ACPA, and anticarbamylated protein antibodies results in a higher specificity but lower sensitivity for RA risk compared with RF and ACPA positivity.[63] Autoantibodies other than RF and ACPA are not (yet) used in clinical practice; therefore, current prediction models, including autoantibodies, contain only RF and ACPA. Further exploration of other autoantibodies regarding timing of appearance and predictive utility is needed.

A problem with prediction based on autoantibody status is that autoantibodies are determined in a very small percentage of patients with RA before diagnosis. Depending on the local health care system and local guidelines for autoantibody testing, autoantibodies are mostly determined in a (small) subset of patients with arthralgia. In the Netherlands, where the primary health care system is well developed and RA is diagnosed early after the start of symptoms, only 6% of new patients are identified by autoantibody positivity before RA diagnosis.[20] Therefore, we should perhaps consider increasing autoantibody screening in primary care within a defined population. Because musculoskeletal symptoms are very prevalent in primary care,[64] autoantibody screening among all patients with arthralgia is not desirable. However, we could consider screening those with symptoms most associated with RA development, such as stiffness and arthralgia of the hand and feet. Another option is to consider screening a different population, such as FDRs, where RA-related antibodies can be associated with tender joints.[65] Needless to say, autoantibody status is futile in predicting seronegative RA.

B-Cell Clones

Recently, clonal changes in the B-cell receptor (BCR) repertoire in the blood of seropositive persons at risk for RA were studied as a novel predictive marker.[66] Dominant BCR clones were clones that were expanded beyond 0.5% of the total repertoire. If RF and/or ACPA-positive persons had $\geq$5 dominant BCR clones in the peripheral blood, the risk of RA increased by 6- to 9-fold. A first validation study found that at-risk individuals with RF and/or ACPA and $\geq$5 dominant BCR clones had an 83% risk (PPV) of developing arthritis within 36 months, whereas arthritis development did not occur in persons with <5 dominate clones. A second validation study of this model found an AUC of 0.96, making this a promising new marker for prediction in patients with seropositivity.[67]

Symptoms

In the clinically apparent at-risk stage, RA-related symptoms can be used for prediction. Both musculoskeletal symptoms and more general symptoms have been associated with RA, such as joint pain and swelling, in particular of the small joints of the hands, warmth, redness and burning sensations around the joints, early morning stiffness, muscle weakness and loss of motor control, fatigue, sleeping difficulties, and depressive symptoms.[68–70] The relevance of considering the type and location of symptoms for prediction is demonstrated by a study that found that autoantibody-positive patients with arthralgia of any type have an absolute risk of 20% of arthritis development, where the subgroup of those with symmetric arthralgia in small joints and morning stiffness have a 60% risk of arthritis.[56] However, musculoskeletal symptoms, including arthralgia, are common in primary and secondary care, and most of these patients are not suspected of having RA. Symptoms and signs that differentiate patients with arthralgia who will potentially progress to RA from other patients with arthralgia are well recognized by rheumatologists. A cohort study of patients with arthralgia suspected of developing RA according to their rheumatologist found that within 1 year 11% had progressed to RA versus 0.2% of patients with arthralgia not suspected of having RA.[71] In general, fewer persons develop RA in arthralgia cohorts compared with autoantibody-positive cohorts because

autoantibody status is a stronger risk factor compared with symptoms. However, the significant difference in RA development between the 2 groups indicates the discriminative ability of the rheumatologist based on patient symptom patterns. A drawback of this approach, however, is its subjectivity, which is a problem for research. Therefore, in 2017, a European League Against Rheumatism (EULAR) taskforce explicated the clinical expertise and composed a definition of arthralgia suggestive of progression to RA: clinically suspect arthralgia (CSA).[72] CSA consists of 7 clinical parameters; 5 are obtained by history taking (symptom duration < 1 year, symptoms of metacarpophalangeal joints, morning stiffness >60 min, and most severe symptoms in the early morning) and 2 by physical examination (difficulty with making a fist, positive squeeze test of metacarpophalangealjoints). Its main goal is to include homogenous groups of patients in clinical studies.

Symptom characteristics in the at-risk phase remain to be explored in large, prospective cohorts. Recently, data from qualitative studies in at-risk individuals have been used to develop the Symptoms in Persons at Risk for RA questionnaire, which aims to capture the prevalence and predictive utility of symptoms.[73] The first results indicate a high burden of symptoms in at-risk patients. In addition, different symptom patters can be distinguished. Joint pain rapidly increasing and then remaining constant was reported by 9%, joint pain gradually increasing over time by 16%, and a more intermittent pattern by 53% (23% and 30% for pain-free periods in between and always some pain present, respectively). It remains possible that an explosive onset of symptoms rapidly followed by synovitis may be underrepresented in such cohorts. Data on predictive ability are awaited.

Imaging

Articular and extraarticular symptoms in individuals at risk for RA have not fully been explained yet. One potential explanation is the presence of subclinical synovitis or tenosynovitis causing the symptoms. This explanation has been investigated with different imaging techniques. Whereas for some at-risk individuals (autoantibody positive or CSA), symptomatic joints had signs of synovitis on magnetic resonance imaging (MRI) and ultrasonography, other patients experience joint related symptoms in the absence of imaging synovitis.[74–76] Furthermore, imaging synovitis can be present in healthy individuals without joint symptoms.[77] Nevertheless, several studies indicated that multiple imaging techniques could have predictive capabilities. In patients with CSA, 31% of patients with MRI-detected subclinical synovitis developed arthritis within 1 year, whereas arthritis development was unusual in the absence of subclinical synovitis.[78] In addition, MRI-detected synovitis, bone marrow edema, and tenosynovitis were all associated with future RA development in patients with undifferentiated arthritis.[79] Ultrasonographic evidence of synovitis and a positive positron emission tomography result targeting macrophages were also associated with future arthritis development; however, most painful or tender joints in at-risk individuals had no evidence of synovitis.[7,55,80,81]

Prediction Models

Clinical symptoms associated with RA have been combined with antibody status, demographic factors, and imaging results into prediction models. An overview is given in Table II (based on the study by Karlson et al[20]). The model with the largest AUC uses a set of symptoms individually related to arthritis development combined with autoantibody status to predict arthritis development, producing an AUC of 0.82 (95% CI, 0.75–0.89).[68] In the lowest risk category, 12% of autoantibody-positive persons developed arthritis, whereas in the highest risk category, 81% developed arthritis (hazard ratio, 14.86; 95% CI, 8.4–28).

These clinical prediction models remain to be validated in different cohorts, and since the publication of the EULAR definition for CSA, clinical prediction models can be validated in homogenous groups of patients with CSA. Symptoms are an important part of clinical prediction models, and it may prove valuable to also incorporate information on symptom location and symptom pattern to improve prediction of RA. A next step is to test whether adding new markers to existing models increases predictive ability, for example, different types of autoantibodies or imaging results. Currently, only one prediction model incorporates imaging results,[55] and one

Table II. Prediction models for development of rheumatoid arthritis using serologic and clinical risk factors.

Study	Cohort; Variables	No. of Patients	Results
van de Stadt et al,[68] 2013	Patients with seropositive arthralgia: autoantibody status, family history, alcohol use, VAS pain, morning stiffness, joint swelling, and symptom duration; pattern and location were combined into a risk score	374 Patients with arthralgia (131 developed arthritis)	AUC = 0.82 (95% CI, 0.75−0.89) Intermediate- vs low-risk group: HR = 4.52 (95% CI, 2.42−8.77) High- vs. low-risk group: HR = 14.86 (95% CI, 8.4−28) PPV high risk: 81% (FU = 5 years)
de Hair et al,[37] 2013	Patients with seropositive arthralgia: smoking and BMI were analyzed separately and combined	55 Patients with arthralgia (15 developed arthritis)	Smoking ever vs never: HR = 9.6 (95% CI, 1.3−73) Obesity BMI ≥25 vs < 25: HR = 5.6 (95% CI, 1.3−25) PPV ever smoker and BMI >25: 60% (FU = 27 months)
Rakieh et al,[55] 2015	ACPA-positive arthralgia patients: high level RF and/or ACPA, small joint pain, morning stiffness and ultrasonographic PD signal were combined into a risk score	100 Patients with arthralgia (50 developed RA)	Harrell C = 0.67 (95% CI, 0.59−0.74) Progression to IA (PPV): Low risk: 0% Moderate risk: 31% High risk: 62% (FU = 5 years)
Tak et al,[66] 2017	Patients with seropositive arthralgia, validation in separate cohort of seropositive patients: ≥5 dominant B-cell clones as a single biomarker	21 Autoantibody-positive patients (11 developed arthritis), 10 controls Validation in 50 patients with autoantibody-positive arthralgia	Original cohort: Sensitivity: 78% Specificity: 92% PPV: 72% (FU = 3 years) NPV: 94% Validation cohort: RR = 6.3 (95% CI, 2.7−15) PPV: 83% (FU = 5 years)

ACPA = anticitrullinated protein antibody, BMI = body mass index, DM = diabetes mellitus, EIRA = Epidemiological Investigation of RA, EPIC NOAR = The European Prospective Investigation of Cancer, Norfolk, FU = follow up, HR = hazard ratio, IA = inflammatory arthritis, IP = inflammatory polyarthritis, NHS = Nurses' Health Study, NPV = negative predictive value, OR = odds ratio, PD = power Doppler, PPV = positive predictive value, RA = rheumatoid arthritis, RR = relative risk, VAS = visual analog scale.

study reports the effects of adding ultrasonographic results to a clinical prediction model.[44] Both studies indicate that adding ultrasonographic results resulted in a slight improvement of the model (Table III)

WHO DO WE TARGET FOR RA PREDICTION AND HOW SPECIFIC CAN WE GET?

Back to Our Case

When using the clinical prediction model with the highest AUC,[68] the patient is assigned to the high-

Table III. Research agenda.

Research agenda for RA prediction in at-risk individuals
• Validation of genetic and environmental prediction models in first-degree relative cohorts.
• Validation of clinical prediction models in clinically suspect arthralgia cohorts.
• Investigate the feasibility of autoantibody screening in primary care patients with clinically suspect arthralgia.
• Investigate the predictive value of rheumatoid arthritis associated autoantibodies other than rheumatoid factor and anticitrullinated protein antibody.
• Development of new models for prediction for antibody-negative individuals.
• Investigate the predictive utility of symptoms in the at-risk phase.
• Investigate whether changes in symptom patterns and symptom intensity can predict imminent rheumatoid arthritis.

risk group, resulting in an 81% risk of arthritis development within 4 years. However, what if the patient would have been screened at an earlier stage, for example, where the autoantibody response has not yet fully developed? If she would have had low positive RF and negative ACPA results, she would be assigned to the medium-risk group, resulting in a 44% risk of arthritis development within 4 years.

Who Do We Screen for Prediction and How Accurate Can We Get?

Identifying RA in an early phase is difficult, and because posttest chances strongly depend on the pretest risks, adequate person selection is important when predicting RA development. The closer a person approaches RA onset, the more accurate prediction gets, whereas earlier in the at-risk phase, prediction is more challenging. However, the chances might be better to reverse RA development in earlier development stages. For very early prediction, efforts to combine risk factors in population cohort studies have led to prediction models, including genetic and environmental risk factors, producing AUCs of 0.56–0.86.[16,39,43,45–48,82] However, on a population level, risk is mainly expressed as a relative risk and odds ratios are low. Quantifying progression to RA with genetic modeling alone is not fit for clinical use. To more closely resemble the phenotype of patients seen in usual rheumatology practice (eg, seropositive patients with arthralgia), clinical prediction models have been developed that include items such as autoantibody levels, smoking, obesity, and symptoms, producing AUCs of 0.67–0.82,[55,68] with hazard ratios of up to 14.9. Overall, the current clinical models are still not highly accurate. There is one outstanding exception, the BCR test for clonality, which provides accurate prediction for autoantibody positive at-risk individuals.

Steps to Improve Prediction Accuracy

Prediction of an individual's absolute risk for RA remains very challenging. The patient case example illustrates that autoantibodies are strong predictors for RA, and, currently, ACPA is the best predictor we have. Population screening on ACPA positivity, however, is costly, and the yield is very low. A Dutch population study found that only 1% of 40,136 participants had an ACPA level $\geq$6.2 U/mL.[83] FDRs might be a more suitable population for autoantibody screening before symptom occurrence. However, as described earlier by Karlson et al,[20] despite an increased risk of RA in FDRs, the yield of such screening is still low and autoantibody screening should perhaps be restricted to those with additional environmental risk factors, such as FDRs, who smoke. Overall, this finding indicates the importance of validating current prediction models in applicable target populations.

To improve prediction, primary care needs to be incorporated and current prediction models need to be tested in primary care patients, for example, patients who would usually be referred to the rheumatologist. A next step will be to see whether adding new predictive markers to existing models will further improve predictive ability. The BCR-clone model[62] performs very well in ACPA-positive patients, and addition of this model to the clinical prediction model from van de Stadt et al[68] resulted in a more sensitive prediction, especially in individuals in the low- and intermediate-risk groups.[66] It remains to be investigated whether the BCR-clone model can predict risk in seronegative individuals. Furthermore, RA-associated autoantibodies other than RF and ACPA could be added to existing models and symptoms, and imaging results associated with future

RA could be incorporated. A more sensitive model with a higher PPV would be desirable; however, prediction models must remain simple enough for routine use in clinical practice, perhaps even in primary care.

As a final note, for future research on RA prediction, it is important that definitions of environmental factors, symptoms, and imaging results are harmonized to maximize comparability. In addition, it will be critical to use homogenous classification and nomenclature for the various stages of RA development.[84]

Primary Prevention

Ultimately, we want to accurately predict RA development at the individual level to select persons for preventive intervention. Depending on the timing, the type of intervention will differ. In an early phase with few symptoms and biomarkers, the predicted risk will generally be low; however, it may be high enough to drive low-risk intervention directed at lifestyle changes, such as smoking cessation, dietary changes,[36] weight reduction, and dental care to prevent periodontitis. Personalized risk calculation could help motivate those at risk for developing RA to make health behavior improvements.[85]

With progression through the at-risk stages, prediction can become more accurate, and interventions with a higher risk of adverse effects and higher cost might be tolerated to halt RA development, such as the temporary use of medication. Apart from studies on such interventions, research on the attitudes of at-risk persons toward preventive treatment, both lifestyle and pharmaceutical, is also needed.

ACKNOWLEDGEMENT

The authors wish to acknowledge the support of the Dutch Arthritis Society.

REFERENCES

1. Deane K, Holers VM. The natural history of rheumatoid arthritis. *Clin Ther*. 2019;41(7):1256–1269.
2. Raza K, Gerlag DM. Preclinical inflammatory rheumatic diseases: an overview and relevant nomenclature. *Rheum Dis Clin North Am*. 2014;40:569–580.
3. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. 2004;50:380–386.
4. van de Stadt LA, de Koning MH, van de Stadt RJ, et al. Development of the anti-citrullinated protein antibody repertoire prior to the onset of rheumatoid arthritis. *Arthritis Rheum*. 2011;63:3226–3233.
5. Rombouts Y, Ewing E, van de Stadt LA, et al. Anti-citrullinated protein antibodies acquire a pro-inflammatory Fc glycosylation phenotype prior to the onset of rheumatoid arthritis. *Ann Rheum Dis*. 2015;74:234–241.
6. Nielen MM, van Schaardenburg D, Reesink HW, et al. Increased levels of C-reactive protein in serum from blood donors before the onset of rheumatoid arthritis. *Arthritis Rheum*. 2004;50:2423–2427.
7. Gent YY, Voskuyl AE, Kloet RW, et al. Macrophage positron emission tomography imaging as a biomarker for preclinical rheumatoid arthritis: findings of a prospective pilot study. *Arthritis Rheum*. 2012;64:62–66.
8. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet*. 1997;350:309–318.
9. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52:3381–3390.
10. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality. *Am J Epidemiol*. 1980;111:87–98.
11. Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. *Nat Rev Rheumatol*. 2016;12:335–343.
12. Ferucci ED, Templin DW, Lanier AP. Rheumatoid arthritis in American Indians and Alaska Natives: a review of the literature. *Semin Arthritis Rheum*. 2005;34:662–667.
13. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2017;31:3–18.
14. Stanford SM, Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. *Nat Rev Rheumatol*. 2014;10:602–611.
15. Messemaker TC, Huizinga TW, Kurreeman F. Immunogenetics of rheumatoid arthritis: understanding functional implications. *J Autoimmun*. 2015;64:74–81.
16. Kurreeman F, Liao K, Chibnik L, et al. Genetic basis of autoantibody positive and negative rheumatoid arthritis risk in a multi-ethnic cohort derived from electronic health records. *Am J Hum Genet*. 2011;88:57–69.

17. Sparks JA, Costenbader KH. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases. *Rheum Dis Clin North Am*. 2014;40:637—657.
18. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis*. 2010;69:70—81.
19. Kim K, Jiang X, Cui J, et al. Interactions between amino acid-defined major histocompatibility complex class II variants and smoking in seropositive rheumatoid arthritis. *Arthritis Rheumatol*. 2015;67: 2611—2623.
20. Karlson EW, van Schaardenburg D, van der Helm-van Mil AH. Strategies to predict rheumatoid arthritis development in at-risk populations. *Rheumatology (Oxford)*. 2016;55:6—15.
21. van Beers-Tas MH, Turk SA, van Schaardenburg D. How does established rheumatoid arthritis develop, and are there possibilities for prevention? *Best Pract Res Clin Rheumatol*. 2015;29:527—542.
22. Alpizar-Rodriguez D, Finckh A. Environmental factors and hormones in the development of rheumatoid arthritis. *Semin Immunopathol*. 2017;39:461—468.
23. Feng J, Chen Q, Yu F, et al. Body mass index and risk of rheumatoid arthritis: a meta-analysis of observational studies. *Medicine (Baltimore)*. 2016;95:e2859.
24. Qin B, Yang M, Fu H, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. *Arthritis Res Ther*. 2015;17: 86.
25. Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure? *Rheumatology (Oxford)*. 2012;51(3): 499—512.
26. Alpizar-Rodriguez D, Pluchino N, Canny G, Gabay C, Finckh A. The role of female hormonal factors in the development of rheumatoid arthritis. *Rheumatology (Oxford)*. 2017;56(8):1254—1263.
27. Hu Y, Costenbader KH, Gao X, et al. Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women. *Am J Clin Nutr*. 2014;100:959—967.
28. Di Giuseppe D, Crippa A, Orsini N, Wolk A. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther*. 2014;16:446.
29. Chen H, Wang J, Zhou W, Yin H, Wang M. Breastfeeding and risk of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol*. 2015;42:1563—1569.
30. Ren L, Guo P, Sun QM, et al. Number of parity and the risk of rheumatoid arthritis in women: a dose-response meta-analysis of observational studies. *J Obstet Gynaecol Res*. 2017;43:1428—1440.
31. Chen Q, Jin Z, Xiang C, Cai Q, Shi W, He J. Absence of protective effect of oral contraceptive use on the development of rheumatoid arthritis: a meta-analysis of observational studies. *Int J Rheum Dis*. 2014;17:725 —737.
32. Qi S, Xin R, Guo W, Liu Y. Meta-analysis of oral contraceptives and rheumatoid arthritis risk in women. *Ther Clin Risk Manag*. 2014;10:915 —923.
33. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. *Clin Rheumatol*. 2012;31:1733—1739.
34. Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell LA. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. *Am J Epidemiol*. 2003;157:345—354.
35. Costenbader KH, Kang JH, Karlson EW. Antioxidant intake and risks of rheumatoid arthritis and systemic lupus erythematosus in women. *Am J Epidemiol*. 2010;172: 205—216.
36. Hu Y, Sparks JA, Malspeis S, et al. Long-term dietary quality and risk of developing rheumatoid arthritis in women. *Ann Rheum Dis*. 2017;76: 1357—1364.
37. Sparks JA, Barbhaiya M, Tedeschi SK, et al. Inflammatory dietary pattern and risk of developing rheumatoid arthritis in women. *Clin Rheumatol*. 2019;38:243—250.
38. de Hair MJ, Landewe RB, van de Sande MG, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:1654—1658.
39. Lahiri M, Luben RN, Morgan C, et al. Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register–the EPIC-2-NOAR Study). *Ann Rheum Dis*. 2014;73:219—226.
40. Hashimoto M, Yamazaki T, Hamaguchi M, et al. Periodontitis and Porphyromonas gingivalis in preclinical stage of arthritis patients. *PLoS One*. 2015;10, e0122121.
41. Arkema EV, Karlson EW, Costenbader KH. A prospective study of periodontal disease and risk of rheumatoid arthritis. *J Rheumatol*. 2010;37:1800——.
42. de Smit M, van de Stadt LA, Janssen KM, et al. Antibodies against Porphyromonas gingivalis in seropositive arthralgia patients do not predict development of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:1277—1279.
43. Chibnik LB, Keenan BT, Cui J, et al. Genetic risk score predicting risk of rheumatoid arthritis phenotypes and age of symptom onset. *PLoS One*. 2011;6, e24380.
44. van Beers-Tas MH, Blanken AB, Nielen MJ, et al. The value of joint ultrasonography in predicting arthritis in seropositive arthralgia patients: a prospective cohort study.

Arthritis Res Ther. 2018 Dec 19;20(1):279.
45. Karlson EW, Chibnik LB, Kraft P, et al. Cumulative association of 22 genetic variants with seropositive rheumatoid arthritis risk. *Ann Rheum Dis*. 2010;69:1077—1085.
46. Karlson EW, Ding B, Keenan BT, et al. Association of environmental and genetic factors and gene-environment interactions with risk of developing rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013;65:1147—1156.
47. Scott IC, Seegobin SD, Steer S, et al. Predicting the risk of rheumatoid arthritis and its age of onset through modelling genetic risk variants with smoking. *Plos Genet*. 2013;9, e1003808.
48. Sparks JA, Chen CY, Jiang X, et al. Improved performance of epidemiologic and genetic risk models for rheumatoid arthritis serologic phenotypes using family history. *Ann Rheum Dis*. 2015;74:1522—1529.
49. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum*. 2003;48:2741—2749.
50. Kokkonen H, Mullazehi M, Berglin E, et al. Antibodies of IgG, IgA and IgM isotypes against cyclic citrullinated peptide precede the development of rheumatoid arthritis. *Arthritis Res Ther*. 2011;13:R13.
51. Arkema EV, Goldstein BL, Robinson W, et al. Anti-citrullinated peptide autoantibodies, human leukocyte antigen shared epitope and risk of future rheumatoid arthritis: a nested case-control study. *Arthritis Res Ther*. 2013;15:R159.
52. Brink M, Hansson M, Mathsson L, et al. Multiplex analyses of antibodies against citrullinated peptides in individuals prior to development of rheumatoid arthritis. *Arthritis Rheum*. 2013;65:899—910.
53. Sokolove J, Bromberg R, Deane KD, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. *PLoS One*. 2012;7, e35296.
54. WJJ Falkenburg, van Schaardenburg D. Evolution of autoantibody responses in individuals at risk of rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2017;31:42—52.
55. Rakieh C, Nam JL, Hunt L, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. *Ann Rheum Dis*. 2015;74:1659—1666.
56. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis*. 2010;69:490—494.
57. Gerlag DM, Safy M, Maijer KI, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. *Ann Rheum Dis*. 2019;78:179—185.
58. Ramos-Remus C, Castillo-Ortiz JD, Aguilar-Lozano L, et al. Autoantibodies in prediction of the development of rheumatoid arthritis among healthy relatives of patients with the disease. *Arthritis Rheumatol*. 2015;67:2837—2844.
59. Kolfenbach JR, Deane KD, Derber LA, et al. Autoimmunity to peptidyl arginine deiminase type 4 precedes clinical onset of rheumatoid arthritis. *Arthritis Rheum*. 2010;62:2633—2639.
60. Shi J, van de Stadt LA, Levarht EW, et al. Anti-carbamylated protein (anti-CarP) antibodies precede the onset of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:780—783.
61. van de Stadt LA, de Vrieze H, Derksen NI, et al. Antibodies to IgG4 hinge can be found in rheumatoid arthritis patients during all stages of disease and may exacerbate chronic antibody-mediated inflammation. *Arthritis Rheumatol*. 2014;66:1133—1140.
62. Shi J, van de Stadt LA, Levarht EW, et al. Anti-carbamylated protein antibodies are present in arthralgia patients and predict the development of rheumatoid arthritis. *Arthritis Rheum*. 2013;65:911—915.
63. Verheul MK, Bohringer S, van Delft MAM, et al. Triple positivity for anti-citrullinated protein autoantibodies, rheumatoid factor, and anti-carbamylated protein antibodies conferring high specificity for rheumatoid arthritis: implications for very early identification of at-risk individuals. *Arthritis Rheumatol*. 2018;70:1721—1731.
64. Wiitavaara B, Fahlstrom M, Djupsjobacka M. Prevalence, diagnostics and management of musculoskeletal disorders in primary health care in Sweden - an investigation of 2000 randomly selected patient records. *J Eval Clin Pract*. 2017;23:325—332.
65. Young KA, Deane KD, Derber LA, et al. Relatives without rheumatoid arthritis show reactivity to anti-citrullinated protein/peptide antibodies that are associated with arthritis-related traits: studies of the etiology of rheumatoid arthritis. *Arthritis Rheum*. 2013;65:1995—2004.
66. Tak PP, Doorenspleet ME, de Hair MJH, et al. Dominant B cell receptor clones in peripheral blood predict onset of arthritis in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis*. 2017;76:1924—1930.
67. Musters A, van Beers-Tas M, Doorenspleet M, et al. OP0204 Dominant B cell receptor clones in peripheral blood predict onset of arthritis in individuals at risk for rheumatoid arthritis: a validation cohort. *Ann Rheum Dis*. 2018;77:151.
68. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction

rule for the development of arthritis in seropositive arthralgia patients. *Ann Rheum Dis*. 2013;72:1920–1926.
69. Stack RJ, van Tuyl LH, Sloots M, et al. Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: a qualitative exploration of symptom development. *Rheumatology (Oxford)*. 2014;53:1646–1653.
70. van Nies JA, Alves C, Radix-Bloemen AL, et al. Reappraisal of the diagnostic and prognostic value of morning stiffness in arthralgia and early arthritis: results from the Groningen EARC, Leiden EARC, ESPOIR, Leiden EAC and REACH. *Arthritis Res Ther*. 2015;17:108.
71. van Steenbergen HW, van der Helm-van Mil AH. Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms. *Rheumatology (Oxford)*. 2016;55:1140–1141.
72. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. *Ann Rheum Dis*. 2017;76:491–496.
73. van Beers-Tas MH, Ter Wee MM, van Tuyl LH, et al. Initial validation and results of the symptoms in persons at risk of rheumatoid arthritis (SPARRA) questionnaire: a EULAR project. *RMD Open*. 2018;4, e000641.
74. Gent YY, Ter Wee MM, Ahmadi N, et al. Three-year clinical outcome following baseline magnetic resonance imaging in anti-citrullinated protein antibody-positive arthralgia patients: an exploratory study. *Arthritis Rheumatol*. 2014;66:2909–2910.
75. Krabben A, Stomp W, van der Heijde DM, et al. MRI of hand and foot joints of patients with anticitrullinated peptide antibody positive arthralgia without clinical arthritis. *Ann Rheum Dis*. 2013;72:1540–1544.
76. van Steenbergen HW, van Nies JA, Huizinga TW, Reijnierse M, van der Helm-van Mil AH. Subclinical inflammation on MRI of hand and foot of anticitrullinated peptide antibody-negative arthralgia patients at risk for rheumatoid arthritis. *Arthritis Res Ther*. 2014;16:R92.
77. Mangnus L, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AH. Magnetic resonance imaging-detected features of inflammation and erosions in symptom-free persons from the general population. *Arthritis Rheumatol*. 2016;68:2593–2602.
78. van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. *Ann Rheum Dis*. 2016;75:1824–1830.
79. Nieuwenhuis WP, van Steenbergen HW, Mangnus L, et al. Evaluation of the diagnostic accuracy of hand and foot MRI for early rheumatoid arthritis. *Rheumatology (Oxford)*. 2017;56:1367–1377.
80. Nam JL, Hensor EM, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. *Ann Rheum Dis*. 2016;75:2060–2067.
81. van de Stadt LA, Bos WH, Meursinge Reynders M, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther*. 2010;12:R98.
82. Yarwood A, Han B, Raychaudhuri S, et al. A weighted genetic risk score using all known susceptibility variants to estimate rheumatoid arthritis risk. *Ann Rheum Dis*. 2015;74:170–176.
83. van Zanten A, Arends S, Roozendaal C, et al. Presence of anticitrullinated protein antibodies in a large population-based cohort from The Netherlands. *Ann Rheum Dis*. 2017;76:1184–1190.
84. Gerlag DM, Raza K, van Baarsen LG, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. *Ann Rheum Dis*. 2012;71:638–641.
85. Sparks JA, Iversen MD, Yu Z, et al. Disclosure of personalized rheumatoid arthritis risk using genetics, biomarkers, and lifestyle factors to motivate health behavior improvements: a randomized controlled trial. *Arthritis Care Res (Hoboken)*. 2018;70:823–833.

Address correspondence to: Laurette van Boheemen, MD, Amsterdam Rheumatology and Immunology Center, PO Box 58271, 1040 HG Amsterdam, the Netherlands. E-mail: l.v.boheemen@reade.nl