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Identification of Undiagnosed Inflammatory Arthritis in a Community Health-Fair Screen

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Abstract

Purpose—The primary goals of this study were: 1) to identify individuals with undiagnosed inflammatory arthritis (IA) and rheumatoid arthritis (RA) in a community health-fair screen, and 2) to establish in a health-fair setting the diagnostic accuracy of combinations of the Connective Tissue Disease Screening Questionnaire (CSQ) and autoantibody testing for IA.

Methods—Screening for IA/RA was performed at health-fair sites using a combination of CSQ, joint examination, rheumatoid factor (RF) and anti-cyclic citrullinated (anti-CCP) antibody testing. IA was defined as ≥1 swollen joint/s suggestive of synovitis on joint examination by a trained clinician.

Results—Six-hundred one subjects were screened; 51.0% participating because of joint symptoms (pain, stiffness, or swelling). Eighty-four subjects (14.0%) had ≥1 swollen joint/s designated as IA on joint examination. Of the 601 subjects screened, 9 (1.5%) had IA and met ≥4 of 7 American College of Rheumatology criteria for RA but had no prior diagnosis of RA, and 15 (2.5%) had IA and RF and/or anti-CCP positivity, suggesting early RA. The diagnostic accuracy of combinations of CSQ and autoantibody testing for the identification of IA yielded maximal sensitivity, specificity, positive and negative predictive values of 95.3%, 99.2%, 71.4%, and 97.7%, respectively.

Conclusions—Health-fair screening may be an effective approach for the identification of individuals with undiagnosed IA/RA. A combination of CSQ and autoantibody testing alone has clinically useful diagnostic accuracy for the detection of IA. Decisions regarding which methodology to use for future health-fair IA/RA screening will depend on goals of screening and funding.

Keywords

inflammatory arthritis; rheumatoid arthritis; health-fair screening; diagnostic accuracy

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Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that leads to significant morbidity and increased mortality, and it is presumed to affect ~1% of the population [1–3]. Given that studies have shown that identification and treatment of RA-related inflammatory arthritis (IA) soon after the onset of symptoms leads to improved outcomes, methods to identify individuals in the community with early RA-related synovitis may lead to earlier treatment, with subsequent reduction in the morbidity and mortality associated with this disease [4,5].

Various strategies have been employed to identify cases of early IA/RA in the community including mailed or telephone questionnaires, or early arthritis clinics [6–11]. Screening for IA/RA using a staged approach has also been proposed, where subjects are initially screened with a self-completed questionnaire, with additional autoantibody testing and examination performed on subjects with initial findings suggestive of RA [12]. An alternative approach would be to provide screening for IA/RA in a community health-fair setting, where individuals with disease could be identified by arthritis-related questionnaires and autoantibody testing, with or without initial joint examination.

The primary goals of this current study were to 1) determine if subjects with IA (who if positive for RA-related autoantibodies may have RA) may be identified through a community health-fair screen using a combination of questionnaire, joint examination and RA-related autoantibody testing, and 2) to use data from this screen to determine the diagnostic accuracy of screening questionnaires and autoantibody testing for the identification of individuals with IA based on joint examination findings. This latter goal represents an initial evaluation of a methodology for wide-spread screening for IA/RA.

Methods

The Health-Fair

Health-fairs are becoming increasingly popular in the United States, and are a means for individuals to improve their health without visiting a health-care provider by providing education about conditions such as cancer or heart-disease, or by testing for common health disorders. Health-fairs are typically held at sites accessible to individuals including local schools, churches, or businesses, are usually operated by non-profit organizations and staffed by volunteers. The health-fair utilized for this arthritis screening study was managed by a nonprofit organization called ‘9Health Fair’ (so named due to its association with a local television station broadcast on channel 9) and has occurred annually since 1980 providing free screening for disorders including hypertension, osteoporosis, and glaucoma, as well as optional blood testing for a fee for disorders including hyperlipidemia, thyroid disease, and prostate cancer. While the health-fair’s primary goal is to improve the health of participants, it has also been used for health research, including an investigation in 1995 into the prevalence of thyroid disease [13]. Five health-fair sites in the Denver, Colorado U.S.A. metropolitan area were selected for this April 2008 arthritis screen based on proximity to the screening personnel and adequate physical space for screening.

Promotion and Education

Prior to the health-fair, education about IA/RA and information about the availability of health-fair arthritis screening was delivered through television interviews and news broadcasts, as well as through posting on the health-fair website. Additionally, at the time of screening, signs were posted at participating sites with the wording: *Free screening for rheumatoid arthritis (RA): Includes questionnaire, physical examination and blood testing.*

Participate if you: 1) have symptoms of arthritis (joint pain, stiffness, or swelling), 2) have a family history of RA, or 3) are just interested in finding out more about your health.

Inclusion/Exclusion Criteria

Subjects were eligible to participate in arthritis screening at no cost if they were willing to undergo questionnaire evaluation, joint examination and blood draw. Exclusions were age <18 years old and/or a prior diagnosis of RA, determined by staff at each screening site. There were no exclusions based on language; however, all participants spoke English. Due to cost issues, screening was capped at ~600 subjects.

Questionnaires

Participants in the arthritis screen completed a demographic questionnaire including contact information, age, race, sex, family history of RA, and reported why they were participating in the arthritis screen. Participants then completed the Connective Tissue Disease Questionnaire (CSQ), which is a self-completed 30-item questionnaire designed to screen for RA and other connective tissue diseases [14,15]. In prior studies the CSQ has shown 70–80% sensitivity and 85–95% specificity for the diagnosis of RA compared to ACR criteria met based on chart review or examination [14–17]. CSQ responses allow for determination of subjects (by self-report) as meeting one or more of the following six ACR RA criteria: 1) morning stiffness >1 hour, 2) arthritis of hand joints, 3) three or more joint areas involved (joints assessed include hands, wrists, elbows, and knees), 4) symmetric arthritis, 5) the presence of nodules, and 6) rheumatoid factor positivity (if known to the subject). For this health-fair screen, CSQ positive responses for RA ranged from 0 to 5 based on the self-reported ACR RA criteria met, as the presence of radiographic changes is not assessed by CSQ and CSQ responses regarding prior RF testing were excluded from this analysis to determine the performance of the CSQ assuming that subjects had no prior evaluation for IA/RA.

Joint examination

After questionnaires were completed, all subjects underwent joint examination by one of seven rheumatologists (see acknowledgment section: KD, CS, SBC, CR, JR, AG, SM) or a nurse/nurse practitioner (EH, LR) trained in rheumatologic joint examination. The joint examiners were not aware of subjects' CSQ responses at the time of the joint examination. To increase the specificity for IA/RA, the joints evaluated for tenderness and swelling were limited to bilateral proximal interphalangeals (PIPs), metacarpal-phalageals (MCPs), wrists, elbows, and metatarsal-phalagneals (MTPs) [9,15]. The shoulders, hips, knees, ankles, and the presence of nodules were not assessed by examination.

Autoantibody testing

Participants were tested for RF, anti-CCP, and C-reactive protein (CRP). All testing was performed at the Quest Diagnostics Regional Laboratory in Denver, Colorado. RF testing was performed using the Roche RFII nephelometry system and was considered positive if a level was ≥14 international units per milliliter (IU/mL). Anti-CCP2 was tested using the INOVA QuantaLite™ CCP2 IgG kit (San Diego, CA), and values ≥20 units per milliliter (U/mL) were considered positive. For anti-CCP, only values between 20 and 59 were reported as discrete integers; levels above or below this range were reported as <20 and ≥60, respectively. CRP was measured by nephelometry using the Roche CRP latex kit, and a level of ≥0.8 milligrams per deciliter (mg/dL) was considered positive.

Outcomes

The primary outcome for this screen was the presence of ≥1 swollen joint/s on examination suggestive of synovitis, designated as IA. This classification maximizes sensitivity for early IA/RA which may present with a limited number of swollen joints, and is similar to the IA classification utilized by the Leiden early arthritis cohort [18–20]. Additionally, in post-health-fair analysis, subjects with IA were evaluated for the number of ACR RA classification criteria that they met including: morning stiffness > 1 hour, hand arthritis, three or more joint areas, symmetry of arthritis, and autoantibody positivity. Morning stiffness was evaluated by the CSQ, and the arthritis criteria were determined on physical examination of the PIPs, MCPs, wrists, and elbows. The autoantibody criteria was determined by the RF and anti-CCP testing done at the time of the examination, with positivity for either RF or anti-CCP qualifying for the ACR RA antibody criteria, as it has been proposed that testing with RF and anti-CCP improves sensitivity (with equal specificity) for classification of RA over RF testing alone [21]. As nodules and radiographic findings were not evaluated, subjects could meet ≤5 criteria.

Follow-up

Participants received a letter 6–8 weeks after the health-fair detailing their results and providing recommendations for follow-up. Individuals with IA and/or autoantibody positivity were additionally contacted by phone and given recommendations for health-care follow-up tailored to their results (including recommendations for evaluation for causes of elevated RF other than RA). Also, information regarding subjects' evaluation for joint symptoms prior to the health-fair screen was obtained during this phone follow-up. Participants without IA but who were positive for anti-CCP, or who were RF positive and had a first-degree relative with RA were invited to participate in a research project designed to prospectively follow individuals with RA-related autoantibodies but no clinically-apparent IA/RA.

Statistical Analysis

Comparison of variables between autoantibody positive and negative groups was performed using t-test or chi-squared testing. The sensitivity, specificity, and positive and negative predictive values (PPV, NPV) of combinations of CSQ and autoantibody testing for the 'gold standard' of IA (determined on joint examination as ≥1 swollen joint/s) were calculated using 2×2 tables, with 95% confidence limits. Analyses were performed using SPSS version 16.0.1

Ethical considerations

This project was approved by ethical review committees at the 9Health Fair and the Institutional Review Board at the University of Colorado Denver.

Results

In the spring of 2008 approximately 91,000 people visited the health-fair at 155 sites in Colorado, Nebraska, and Wyoming. At the five Denver, Colorado health-fair sites offering arthritis screening, a total of 3,748 individuals overall underwent health screening. Of these, 609 participants were screened for IA, although only 601 had CSQ, examination, and autoantibody testing due to inability to obtain blood from 8 subjects. The percentage of total subjects at these 5 sites who participated in the arthritis screen was 16.2% (range by site: 12.4%–26.2%). Data is presented in Table 1 regarding the age, sex, and race distribution of the 601 subjects in comparison to the participants in the wider health-fair (N~91,000). The

majority of subjects (51.0%) participated in the arthritis screen because of joint symptoms (Table 1).

Subjects with IA

Of the 601 RA screening participants, 84 (14.0%) had ≥1 swollen joint on examination, designated as IA (Table 2). No subject had clearly identifiable MTP synovitis. In a post-health-fair evaluation, the five rheumatologists (see acknowledgment section: KD, CS, SBC, JR, and SM) who examined 90% of the 601 health-fair participants and who identified 80/84 subjects with IA each performed two sequential joint examinations of the bilateral wrists, elbows, MCPs, and PIPs of patients with three arthritic conditions: RA, psoriatic arthritis, and OA. The observers were blinded to their prior examination findings as well as the findings of other observers. The mean intra-observer agreement for joint swelling was 94% (range 88–99%) with a mean kappa of 0.88 (range 0.75–0.97). The inter-observer agreement was 78%, with a kappa of 0.55.

Subjects meeting ≥4 ACR RA criteria

Of the 84 subjects with IA, 11 met ≥4 ACR RA criteria. However, on phone-call follow-up, one of these eleven subjects reported a diagnosis of systemic lupus erythematosus (SLE) prior to the health-fair, and another reported a prior diagnosis of RA. After excluding these 2 individuals, 9 subjects fulfilled ACR criteria for RA and had no prior diagnosis to explain their IA (Table 3).

Subjects with IA and RF and/or anti-CCP positivity

Seventy-three subjects had IA and did not meet ≥4 ACR criteria for RA, and 15 of these were positive for RF and/or anti-CCP (Table 3). Of these 15, 10 were positive for only RF, and 5 were positive for RF and anti-CCP.

Subjects with RF and/or anti-CCP positivity and no IA

Forty-one subjects were positive for RF and/or anti-CCP and had no findings of IA: 27 were RF positive only, 11 anti-CCP positive only, and 3 were positive for both RF and anti-CCP (Table 3).

Diagnostic accuracy of the CSQ and RA-related autoantibody testing in identifying subjects with IA

The ranges of sensitivities, specificities and positive and negative predictive values of various combinations of parallel or serial CSQ and autoantibody testing for the identification of IA are reported in Table 4. The diagnostic accuracy of serial testing was determined assuming CSQ was administered first, followed by autoantibody testing if the CSQ was positive. A CSQ with ≥1 positive response/s or autoantibody positivity (RF and/or anti-CCP) resulted in the highest sensitivity (95.3%) for detection of IA (corresponding specificity of 32.4%). A maximal specificity of 99.2% for IA (corresponding sensitivity 11.8%) was achieved by considering as positive a CSQ with ≥4 positive responses *and* RF or anti-CCP positivity. The highest PPVs (46.0–71.1%) for identification of IA were found using a combination of CSQ positive responses (≥1, ≥2, etc) *and* concomitant autoantibody positivity. CRP testing alone yielded the lowest sensitivity/specificity, PPV/NPV for identification of IA.

Cost analysis

The cost to screen these 601 individuals including the CSQ ($1.50 per subject), laboratory testing ($20 for RF/anti-CCP; $5 for CRP), and paperwork processing was ~$42 per person screened. However, it required ~72 volunteer person-hours per 100 subjects to complete the

screening process, including follow-up contact. If these person-hours were reimbursed at an average of $50 per hour (including clinicians, phlebotomists, etc), the total cost to screen these 601 individuals to identify those that met ≥4 ACR RA criteria (N=9), or those who had ≥1 swollen joint/s and RF or anti-CCP positivity (N=15), was ~$2,000 per person. If one assumes that participants who had IA on joint examination but were RF/anti-CCP negative (N=58) or who had autoantibody positivity without IA (N=41) also warranted additional clinical evaluation, this screen cost ~$400 per 'person of interest' identified.

Discussion

This study has utilized a community health-fair to screen for IA/RA, identifying individuals with IA, likely RA, as well as RA-related autoantibody positive individuals without evidence of IA. These latter individuals may be in the pre-clinical phase of RA, and of these, the anti-CCP positive subjects and the proportion of RF positive subjects that have a first-degree relative with RA have been invited to participate in an ongoing longitudinal prospective study at the University of Colorado, with 5 subjects having enrolled as of December 2008.

Based on the diagnostic accuracy of combinations of CSQ and autoantibody testing presented here, in a health-fair setting a combination of CSQ and autoantibody testing may be a reasonable method to identify individuals that are likely to have IA/RA, especially in settings where initial joint examination is not feasible. However, it is important to consider the impact of the prevalence of IA in the screened population on the diagnostic accuracy of these screening tests. While the PPV/NPVs of CSQ and autoantibody testing established in this health-fair screen were high, they are substantially less in populations with 1% or even 5% estimated prevalence of IA (Table 4). There are several factors that may have influenced the prevalence of IA and/or autoantibody positivity in participants in this screen. Pre-health-fair education utilizing televised, internet and on-site poster promotions likely strongly influenced the type of subjects that participated in the screen, and the subsequent high prevalence of autoantibody positivity, specifically anti-CCP positivity (3.8%) found in this screen. Of interest, prior to the health fair, 182 healthy blood donors from the Denver area have been tested for anti-CCP and none were positive, significantly different that the prevalence of anti-CCP positivity of 3.8% in this screen ($p<0.01$). Also, clinicians performing joint examinations for this screen may have over-reported IA either individually or as a group. There was not time during the health-fair to perform repeat examinations by different examiners on each subject, and it was not feasible to compare examination findings between this group of clinicians and others. However, based on criteria for interpreting intra- and inter-observer variability presented by Landis et al, the results from intra- and inter-observer testing of the clinicians who examined the majority of screened individuals suggest substantial intra-observer reproducibility, and fair-to-moderate inter-observer reproducibility [22]. Additionally, the percentage of health-fair subjects determined to have IA on examination was similar between examiners. Overall, these results suggest that an individual examiner was not over-identifying IA.

There are also several factors that may have influenced the diagnostic accuracy of CSQ and autoantibody testing for IA. Firstly, as discussed above, there may have been over-reporting of swollen joints, leading to decreased sensitivity of CSQ and autoantibody testing for IA. Secondly, for determination of IA at the time of the screen, only PIPs, MCPs, wrists, and elbows were evaluated. As the CSQ also ascertains symptoms in the knees, subjects may have reported joint symptoms on the CSQ or had autoantibody positivity with swollen joints that were not identified because the symptomatic joints were not examined. To address this in part, we analyzed the CSQ eliminating knee responses, and changes in the sensitivity/specificity of the CSQ were minimal (<2%), suggesting that the knee did not significantly

influence the sensitivity/specificity of the CSQ for IA. However, subjects still may have had joint abnormalities that were missed on physical examination. Thirdly, individuals with positive CSQ responses may have had non-inflammatory joint disease such as OA driving their symptoms; alternatively, subjects that had IA may have had other inflammatory diseases that were not assessed by RF/anti-CCP testing. We chose to perform only RA-related autoantibody testing in this screen due to the likely higher prevalence of RA compared to other forms of autoimmune inflammatory arthritis, the diagnostic accuracy of RF and anti-CCP testing for RA, and data which suggests that early identification of RA leads to improved outcomes. As such, we may have missed other inflammatory disorders due to limited blood testing. However, the CSQ can classify subjects as having other connective tissue diseases which may lead to inflammatory arthritis including SLE or Sjogren's. Of the 58 subjects with IA who were negative for RF and anti-CCP, 34 had CSQ responses suggesting SLE and/or Sjogren's, which may explain the finding of IA in these individuals. Future health-fair screening for IA may benefit from additional questionnaire or laboratory measures to ascertain other causes for IA (including crystalline or sero-negative arthropathies). Lastly, the CSQ may not be optimally sensitive or specific because of subject-related factors including perception of symptoms, or culture or language-related issues [16]. In this screen 10 subjects with IA were identified that had zero positive CSQ responses, suggesting they were unaware of their symptoms, had asymptomatic joint swelling, or that they were unable to complete the CSQ accurately. Additionally, while all participants in this screen spoke some English, for a subset, English was their second language, which may have influenced CSQ responses. Future health-fair screens will need to assess the impact of language on the performance of screening instruments.

Regarding the cost of screening, in analyses using diagnostic accuracy of testing obtained during this screen (Table 4), if simultaneous CSQ and autoantibody testing were initially performed in absence of joint examination, and those with ≥2 positive CSQ responses *or* autoantibody positivity were referred for post-health-fair evaluation, then 73/84 subjects with IA would have been identified at a cost of ~$177 per subject with IA (CSQ and autoantibody testing costs only). This approach would miss only 11/84 individuals with IA, but would result in ~230 individuals referred for clinical evaluation that did not have IA in the joints evaluated in this health-fair screen. A caveat is that these calculations do not include the costs for a post-health-fair clinical evaluation (which based on Medicare reimbursement would be ~$200 for initial clinical rheumatologic evaluation and more if additional laboratory testing is needed) or person-hours required to perform the initial screen. Alternatively, using a serial screening approach (testing autoantibodies only in those with a positive CSQ response, and finally performing clinical evaluation in those with CSQ and autoantibody positivity), with a high-risk CSQ level set at ≥2 positive responses, it would cost ~$902 to perform initial CSQ testing for 601 individuals, and ~$5,380 to perform autoantibody testing in the 269 individuals with ≥2 positive CSQ responses (CSQ and autoantibody testing costs only). This approach would identify 19 subjects who had IA on examination, at a cost of ~$330 per individual with IA identified, and less than 20 subjects would have clinical evaluation without having IA; however, 65 people with IA would have been missed. Additionally, a serial screening approach would require additional administrative costs to identify, refer, and evaluate those identified in the initial screen. If initial screening was performed only with the CSQ and joint examination, with autoantibody testing done only in those subjects with IA on examination, or high-risk CSQ responses (≥2 positive responses), then all 84/601 individuals with IA would have been identified at a screening cost of ~$40 per individual with IA (~$902 for CSQ administration, and ~$2,500 for examiner screening [25 subjects screened per hour; assuming $100 per hour reimbursement for trained examiner]). Interestingly, this latter approach may be less costly than initially screening all health-fair participants with CSQ and autoantibody testing; however, it assumes that a clinician is available for such screening. Consideration of these

calculations and the varying sensitivity/specificity of different combinations of CSQ and autoantibody testing for identification of IA is of importance as methodologies are evaluated to screen larger numbers of individuals in the community for IA/RA, although ultimate decisions regarding which approach to use for screening will likely be based on costs, the ability to supply trained examiners at health-fair sites, and the ability to obtain follow-up for patients with suspected IA.

The rheumatology community now largely believes that early identification and treatment of IA and especially RA results in improved outcomes including decreased disability, improved work attendance, and possibly improved mortality [5,23,24]. However it is difficult to determine if community health-fair screening is ultimately cost-effective. Health-fair screening for IA/RA may lead to the identification of individuals whose IA will remain benign and who may not necessarily benefit from treatment (length-time bias). Additionally, finding individuals with IA/RA through health-fair screening may not lead to early intervention because subjects may lack access to follow-up care. For this screen, approximately 85% of subjects fulfilling ACR criteria for RA or with IA and RF and/or anti-CCP positivity reported on phone-call follow-up having health insurance and access to primary care. However, ~50% of these insured individuals also reported significant non-reimbursable payments for clinical evaluation or laboratory testing, and these expenses were the driving force behind their participation in the free RA screening. In future RA screens, the capability of individuals to get follow-up care needs to be considered, although we do not think that participants' lack of insurance should preclude screening for potentially modifiable disease such as RA. A follow-up study is planned one year after this screen to ascertain the impact of this screening on health-care utilization.

Conclusion

Health-fair screening may be an effective approach for identifying individuals with undiagnosed IA/RA, or those in the pre-clinical phase of disease. A combination of CSQ and RF/anti-CCP testing demonstrates fair performance for the identification of IA/RA, and these instruments may be useful for large-scale population screening where initial joint examination is not available. Education of the target population about IA/RA prior to screening is likely a key factor to ensure high prevalence rates of disease and optimization of the diagnostic accuracy of testing. Final decisions regarding which combination of tests to use for health-fair IA/RA screening will depend on the goal of screening and costs.

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Table 1

Descriptive Characteristics of Participants in a Health-fair Screen for Inflammatory Arthritis (IA) and Rheumatoid Arthritis (RA)

IA/RA screening participants (N=601)	Total health-fair participants (N=~91,000)	P-values
Sex		
Female 74%	Female 59%	P=0.02
Age		
Mean 59 years-old	Mean 53 years-old	P=0.45
Race		
White 88.5%	White 94.6%	P=0.50
Hispanic 5.7%	Hispanic 3.8%	P=0.50
Black 2.1%	Black 0.3%	P<0.01*
Asian 1.5%	Asian 0.8%	P=0.10
Other 2.1%	Other 0.5%	P<0.01*
Reason screened (data on 480 IA/RA Screen subjects)	N/A	N/A
Check-up, no symptoms 28%		
Relative with RA, no symptoms 21%		
Symptoms (pain, stiffness, swelling; +/− relative with RA) 51%		

* Other race includes mixed races as well as those not included in the categories of White, Hispanic, Black, and Asian. The significant increases in Black and Other races participating in this health-fair likely reflect the demographics of Denver compared with that of the other sites of the health-fair in more rural regions of Colorado, Nebraska, and Wyoming.

Abbreviations: IA=inflammatory arthritis; RA=rheumatoid arthritis; N/A=not applicable

Table 2

Examination, Antibody, and C-reactive Protein Results in 601 Subjects Participating in the Health-fair Rheumatoid Arthritis (RA) Screen

Findings	N (%)
CSQ Positive Responses*	
0	**198 (32.9)**
≥1	**403 (67.1)**
≥2	**269 (44.8)**
≥3	**165 (27.5)**
≥4	**61 (10.1)**
Examination Findings (N=601)	
≥1 swollen joint (designated as inflammatory arthritis[IA])**	**84 (14.0%)**
Number of participants with a specific joint region swollen	
Proximal inter-phalangeal (PIP) swollen	**23 (3.8%)**
- only PIP swollen	**6 (1.0%)**
Metacarpal-phalangeal (MCP) swollen	**65 (10.8%)**
Wrist swollen	**15 (2.5%)**
Elbow swollen	**1 (0.2%)**
MTP swollen	**0 (0%)**
≥2 swollen joints	**60 (10.3%)**
≥3 swollen joints	**36 (6.0%)**
Autoantibody Positivity (N=601)	
Any autoantibody positive (RF and/or anti-CCP)	**67 (11.1%)**
RF (with or without anti-CCP)	**55 (9.2%)**
RF-only (no anti-CCP)	**44 (7.3%)**
Anti-CCP (with or without RF)	**23 (3.8%)**
Anti-CCP-only (no RF)	**12 (2.0%)**
RF and anti-CCP	**11 (1.8%)**
CRP Positivity (>0.8 mg/dL)	**66 (11.0%)**
RF, anti-CCP, and CRP Positivity	**5 (0.8%)**
Meeting ≥4 ACR RA Criteria (and no prior diagnosis to explain arthritis)***	**9 (1.5%)**
≥1 swollen joint and RF or anti-CCP positivity, not meeting ≥4 ACR RA Criteria	**15 (2.5%)**
RF and/or anti-CCP positivity and no IA	**41 (6.8%)**
Anti-CCP positivity and no IA	**14 (2.3%)**

*CSQ=Connective Tissue Disease Screening Questionnaire. This is a subject-completed questionnaire which can assess self-reported fulfillment of the following ACR RA criteria: >6 weeks of arthritis symptoms; morning stiffness ≥1 hour, hand arthritis (fingers, wrists), 3 or more joint areas (hands, wrists, elbows, and knees), and symmetric arthritis; nodules. Radiographic findings are not assessed, and for this study, self-reported results of RF testing are not included. Each positive response was determined to be self-reported fulfillment of 1 ACR criteria for RA.

** Inflammatory arthritis (IA) was established if subjects had ≥1 swollen joint considered to be synovitis on examination of the PIPs, MCPs, wrists, or elbows by a rheumatologist or nurse trained in joint examination.

*** Fulfillment of the American College of Rheumatology (ACR) 1987 Revised RA criteria was determined using CSQ responses for morning stiffness >1 hour, examination findings based on joint swelling of the PIPs, MCPs, wrists, and elbows at the time of the RA screen, and RF and/or anti-CCP antibody positivity at RA screen. Nodules and radiographic findings were not assessed.

Abbreviations/units: IA=inflammatory arthritis; RA=rheumatoid arthritis; RF=rheumatoid factor, international units per milliliter (IU/mL), >14 IU/mL positive; anti-CCP=anti-cyclic citrullinated peptide antibody, units per mL, >5 units positive; CRP=C-reactive protein, milligrams per deciliter (mg/dL), ≥0.8 mg/dL positive; ACR=American College of Rheumatology.

Table 3

Comparisons between autoantibody positive and negative individuals who participated in the health-fair IA/RA screen

Findings	RF and anti-CCP negative N=534*	RF only N=44	Anti-CCP only N=12	RF and CCP N=11
Inflammatory arthritis (IA) present**	58 (10.9%)	17 (38.6%)(p<0.01)	1 (8.3%)(p>0.5)	8 (72.7%)(p<0.01)
# meeting ≥4 ACR criteria for RA ***	0 (0.0%)	6 (1.4%)	1 (8.3%)	2 (18.2%)
# with IA, not meeting ≥4 ACR RA criteria**	58 (10.9%)	10 (22.7%)	0 (0%)	5 (45.5%)
# with no IA**	480 (89.9%)	27 (61.4%)	11 (91.7%)	3 (27.3%)
CRP ≥ 0.8 mg/dL	54 (10.1%)	5 (11.4%)(p>0.5)	2 (16.7%)(p=0.35)	5 (45.5%)(p<0.01)
Levels of biomarkers, median (range)				
CRP	0.2 (0.0–13.1)	0.2 (0.1–2.6)	0.2 (0.1–2.7)	0.5 (0.1–2.0)
RF	6.0 (2–14)	25 (15–294)	7.5 (4–11)	70 (21–600)
Anti-CCP	≤19	≤19	29.5 (20–≥60)	≥60 (33—≥60)
Reason for Screening				
Check-up Only	28.7%	25.0% (p>0.5)	8.3% (p>0.5)	0% (p=0.04)
Relative with RA	28.3%	29.5% (p>0.5)	25.0% (p>0.5)	9.1% (p=0.31)
Symptoms	48.1%	63.4% (p=0.06)	66.7% (p=0.25)	91.9% (p<0.01)
Race				
White	89.7%	77.3% (p=0.02)	91.7% (p=1.0)	81.8% (p=0.33)
Black	2.2%	0% (p>0.5)	0% (p>0.5)	0% (p>0.5)
Hispanic	5.1%	11.4% (p=0.09)	8.3% (p=0.48)	9.1% (p=0.45)
Asian	1.1%	6.8% (p=0.03)	0% (p>0.5)	0% (p>0.5)
Sex, % Female	73.8%	72.7% (p>0.5)	91.7% (p>0.5)	45.5% (p>0.5)
Mean age (std)	59.1 (13.4)	61.0 (12.9)(p=0.38)	58.9 (11.9)(p>0.5)	54.5 (7.4)(p=0.24)

* All statistical comparisons are made using the RF and anti-CCP negative group as reference group.

** Inflammatory arthritis designated if ≥swollen joint/s present on physical examination; joints counted as swollen included proximal inter-phalageal (PIP) joints of the fingers, metacarpal-phalangeal joints (MCPs), wrists, and elbows.

*** American College of Rheumatology (ACR) Revised 1987 Criteria for RA (Arnett FC et al, 1988). For this analysis, only 5 of the 7 criteria were assessed as follows: 1) morning stiffness ≥1 hour; 2) hand arthritis, 3) three or more joint areas, and 4) symmetric arthritis determined by joint examination at time of screening; 5) RF and/or anti-CCP positivity by testing at the time of the screen. Subjects with fulfillment of ACR criteria were those with no diagnosis of RA prior to the health-fair.

Abbreviations/units: IA=inflammatory arthritis; RA=rheumatoid arthritis; RF=rheumatoid factor, international units per milliliter (IU/mL); anti-CCP=anti-cyclic citrullinated peptide antibody, units per milliliter (U/mL), only values between 20–59 were reported as discrete integers, levels below/above this range are reported as <20 or ≥60, respectively; CRP=C-reactive protein, milligrams per deciliter (mg/dL); std=standard deviation.

Table 4

Sensitivity, specificity, positive and negative predictive values (PPV/NPV) of Connective Tissue Disease Screening Questionnaire (CSQ) responses and autoantibody testing for the identification of individuals with inflammatory arthritis (IA)(N=84) on examination during health-fair screening [*]

CSQ and/or Autoantibody Testing	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	PPV, NPV (% and 95% confidence intervals) of testing in this screen where prevalence of IA was ~14% (95% confidence interval) [*]	PPV, NPV (Estimated Prevalence of IA 1%)	PPV, NPV (Estimated Prevalence of IA 5%)
CSQ only, ≥1 Positive Responses[**]	91.8 (83.2–96.3)	34.7 (30.6–39.0)	18.8 (15.2–22.9), 96.2 (92.1–98.3)	1.4, 99.8	6.9, 98.8
Parallel testing: CSQ or autoantibodies positive[***]	95.3 (87.7–98.5)	32.4 (28.4–36.6)	18.8 (15.3–22.9), 97.7 (93.7–99.2)	1.4, 99.9	6.9, 99.2
Serial testing: CSQ positive, then autoantibodies positive[***]	27.1 (18.3–38.0)	94.8 (92.4–96.5)	46.0 (32.1–60.5), 88.7 (85.7–91.2)	5.0, 99.2	21.5, 96.1
CSQ only, ≥2 Positive Responses[**]	78.8 (68.3–86.6)	61.4 (57.1–65.6)	25.2 (20.2–30.9), 94.6 (91.5–96.7)	2.0, 99.7	9.7, 98.2
Parallel testing: CSQ or autoantibodies positive[***]	87.1 (77.6–93.1)	56.4 (52.0–60.7)	24.5 (20.0–30.1), 96.4 93.4–98.1)	2.0, 99.8	9.5, 98.8
Serial testing: CSQ positive, then autoantibodies positive[***]	22.4 (14.3–32.9)	97.1 (95.1–98.3)	55.9 (38.1–72.4), 88.4 (85.4–90.8)	7.2, 99.2	28.9, 96.0
CSQ ≥3 Positive Responses[**]	57.6 (46.5–68.1)	74.8 (70.8–78.5)	27.4 (21.1–34.6), 91.5 (88.3–93.9)	2.3, 99.4	10.7, 97.1
Parallel testing: CSQ or autoantibodies positive[***]	72.9 (62.0–81.7)	68.4 (64.2–72.4)	27.6 (21.9–34.0), 93.9 (90.8–96.0)	2.3, 99.6	10.8, 98.0
Serial testing: CSQ positive, then autoantibodies positive[***]	15.3 (8.7–25.1)	98.4 (96.8–99.3)	61.9 (38.7–81.0), 87.6 (84.6–90.1)	8.8, 99.1	33.5, 96.0
CSQ ≥4 Positive Responses[**]	21.2 (13.4–31.7)	90.3 (87.3–92.7)	26.5 (16.8–38.8), 87.4 (84.2–90.1)	2.2, 99.1	10.7, 95.6
Parallel testing: CSQ or autoantibodies positive[***]	40.0 (29.7–51.2)	83.1 (79.6–86.2)	28.1 (20.5–37.1), 89.4 (86.2–91.9)	2.3, 99.3	11.7, 96.3
Serial testing: CSQ positive, then autoantibodies positive[***]	11.8 (6.1–21.0)	99.2 (97.9–99.8)	71.4 (42.0–90.4), 87.2 (84.2–89.8)	13.0, 99.1	43.7, 95.5
RF positive	29.4 (20.2–40.4)	94.2 (91.7–96.0)	45.4 (32.7–59.3), 89.0 (86.0–91.4)	4.8, 99.2	21.1, 96.2
Anti-CCP positive	10.6 (5.3–19.6)	97.3 (94.2–97.5)	39.1 (20.5–61.2), 86.9 (83.8–89.4)	3.8, 99.1	17.7, 95.4
RF or anti-CCP positive	30.6 (21.3–41.7)	92.1 (89.3–94.2)	38.8 (27.4–51.5), 89.0 (85.9–91.4)	3.8, 99.2	16.9, 96.2

CSQ and/or Autoantibody Testing	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	PPV, NPV (% and 95% confidence intervals) of testing in this screen where prevalence of IA was ~14% (95% confidence interval) *	PPV, NPV (Estimated Prevalence of IA 1%)	PPV, NPV (Estimated Prevalence of IA 5%)
RF and anti-CCP positive	9.4 (4.4–18.2)	99.4 (98.2–99.8)	72.7 (39.3–92.7), 86.9 (84.0–89.5)	13.7, 99.1	45.2, 95.4
CRP positive (≥0.8 mg/dL)	12.9 (6.9–22.4)	89.3 (86.2–91.3)	16.7 (9.0–28.3), 86.1 (82.9–88.9)	1.2, 99.0	6.0, 95.1

* For this study, the presence of ≥1 swollen joint suggestive of synovitis as determined by a rheumatologist or nurse trained in joint examination is classified as inflammatory arthritis (IA).

** CSQ=Connective Tissue Disease Screening Questionnaire. This is a subject-completed questionnaire which can assess self-reported fulfillment of the following ACR RA criteria (Arnett FC et al, 1988): >6 weeks of arthritis symptoms; morning stiffness ≥1 hour, hand arthritis (fingers, wrists), 3 or more joint areas (hands, wrists, elbows, and knees), and symmetric arthritis; nodules. Radiographic findings are not assessed, and for this study, self-reported results of RF testing are not included. Each positive response was determined to be self-reported fulfillment of 1 ACR criteria for RA.

*** Parallel testing: CSQ and autoantibodies are performed simultaneously; Serial testing: data is analyzed assuming that CSQ is performed first, and autoantibody testing is then performed only in those with 'high-risk' CSQ responses (which vary by cut-off evaluated: ≥1, ≥2, etc)

Abbreviations/units: PPV=positive predictive value; NPV=negative predictive value; CSQ=Connective Tissue Disease Screening Questionnaire; Anti-CCP=anti-cyclic citrullinated peptide antibodies, units per milliliter (U/mL), positive value >5 U/mL; RF=rheumatoid factor, international units per mL (IU/mL0, positive value >14 IU/mL; CRP= C-reactive protein, mg/deciliter (mg/dL), positive value ≥0.8 mg/dL; RA=rheumatoid arthritis; IA=inflammatory arthritis