Assessing the Value of Rheumatoid Factor Assays in a DoD Medical Facility

Jeffrey A. Feinstein, MD, Maj., USAF, MC, Synya Balanon, MD, Capt., USAF, MC, Ramon Arroyo, MD, Col., USAF, MC, and Daren Scroggie, MD

For better or for worse, this assay tends to be used as a screening tool for rheumatoid arthritis in primary care patients with nonspecific musculoskeletal pain. Is this use warranted?

Rheumatoid arthritis (RA) is one of the most common rheumatic conditions, affecting over two million Americans, two thirds of whom are under the age of 65.[1] In addition to its social significance, RA imposes a substantial economic impact on the United States, amounting to roughly $15,000 per patient per year or a total of $32 billion in 1998.[2,3] The anatomic damage that leads to deformity and disability begins early in the disease course making prompt diagnosis and initiation of treatment critical.

The revised criteria for the classification of RA developed by the American College of Rheumatology (ACR) in 1987 include the presence of rheumatoid factor (RF) as one of seven characteristics, four or more of which define RA and four of which must have been present for at least six weeks.[4] (The presence of RF is not one of these requisite four.) The ACR criteria are intended to permit standardization across research studies. These criteria, however, often are used to guide diagnosis by clinicians. Although respected rheumatology textbooks report that the RF assay lacks appropriate sensitivity and specificity to be used as a diagnostic tool, it tends to be used as such clinically.[5,6,7]

The purpose of the current study was to determine the sensitivity, specificity, and predictive value (negative and positive) of the RF assay in the diagnosis of RA within a diverse clinical setting comprised of primary and specialty care patients. To our knowledge, this is the first study to evaluate the ability of the RF assay to predict RA and distinguish it from other conditions, prospectively, in patients without known rheumatic illness who present with musculoskeletal ailments.

FLAWS IN PREVIOUS RF STUDIES

Several different assays for RF exist, the most common of which include latex fixation, laser nephelometry, and enzyme-linked immunosorbent assay (ELISA). The sensitivity, specificity, and predictive value of RF vary widely in medical literature, depending upon the method of analysis used and the patient population under investigation. Researchers have reviewed multiple sources of variation and bias in studies of diagnostic accuracy—including differences in patient populations (such as demographic features, disease severity, disease prevalence, and selection criteria), test protocols, reference standards, and in-

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Maj. Feinstein is a board-certified rheumatologist, **Capt. Balanon** is a board-certified internist, **Col. Arroyo** is the program director for the San Antonio Uniformed Services Health Care Consortium Rheumatology Fellowship, and **Dr. Scroggie** is a board-certified rheumatologist, all in the department of rheumatology, Wilford Hall Medical Center (WHMC), Lackland Air Force Base, TX. At the time of this study, Maj. Feinstein was a senior rheumatology fellow at WHMC.

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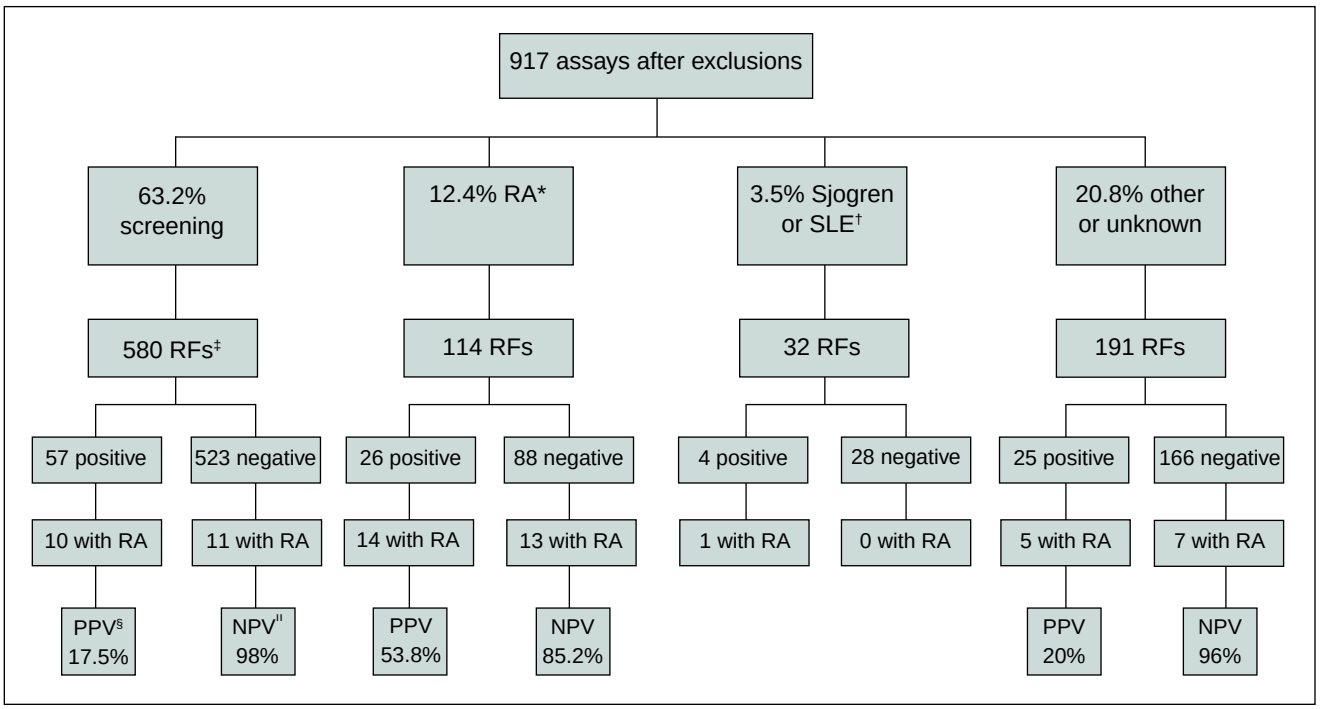

Figure 1. Reasons given by providers for ordering RFs and subsequent RA outcomes. *RA = rheumatoid arthritis. †SLE = systemic lupus erythematosus. ‡RFs = rheumatoid factor assays. §PPV = positive predictive value. ‖NPV = negative predictive value.

terpretation of results—that can explain differences in reported test performance of the RF assay.[8]

Six studies have evaluated the effects of increased disease prevalence, which tends to increase a test's sensitivity and has mixed effects on its specificity.[8] With regard to selection criteria, case-control studies have been shown to overestimate accuracy, whereas consecutive patient enrollment and retrospective study design do not appear to affect the diagnostic odds ratio.[9]

Most studies evaluating the RF assay as an RA screening tool use as the diagnostic reference standard the 1987 ACR classification criteria for RA. Aside from the fact that these criteria are only 91% sensitive and 89% specific,[4] the inclusion of the index test results within the reference standard creates both an incorporation bias and an inappropriate reference standard.

Related medical literature consists of studies that are either population-based or conducted in rheumatic disease subspecialty clinics. In both cases, a selection bias is at work. In the clinic-based studies, investigators measure the ability of the RF assay to distinguish between RA and other conditions in patients with known RA or other rheumatic conditions and normal controls. Clearly, the prevalence of RA in such a study population is much higher than that in the general population. Alternatively, population-based studies investigate the screening accuracy of the RF assay in an asymptomatic group of people in whom the prevalence of RA would be low.

In clinical practice, on the other hand, the pretest probability that undiagnosed musculoskeletal conditions have an RA etiology may be higher than it is in the general population but lower than it is in a rheumatic disease specialty clinic population. The screening accuracy of the RF assay determined by the aforementioned studies, therefore, is not entirely applicable to the primary care setting.

STUDY DESIGN

The local institutional review board approved this study as an exempt human protocol requiring a Health Insurance Portability and Accountability Act waiver. From September 1, 2000 through August 31, 2001, all clinicians practicing at the Wilford Hall Medical Center, Lackland Air Force Base, TX were required to

provide a rationale for each RF assay order. At the time of order entry, the clinician was prompted to select the reason for requesting an RF assay from a drop-down list. The possible selections were: (1) screening, (2) RA, (3) systemic lupus erythematosus (SLE), (4) Sjogren syndrome, (5) other, and (6) unknown. Screening, here, was understood to mean screening for RA in patients with nonspecific musculoskeletal pain, and choosing a specific condition was understood to mean testing to support a diagnosis suspected on the basis of history and physical examination. An electronic lab request and results retrieval database, then automatically recorded the following for each RF test: (1) the ordering provider, (2) the specific clinic from which the order originated, (3) the test result, (4) the reason for obtaining the assay, and (5) the date the test was performed.

A semiquantitative, commercially available, immunoglobulin (Ig) M ELISA RF assay (Sigma Diagnostics, Sigma-Aldrich Corporation, St. Louis, MO, procedure number EIA507) was used as the index test. According to data presented in the package insert, 3.7% of 150 normal controls were RF positive by this assay.[10] In a comparative study with 232 samples (182 normal donor samples, 25 samples previously found to be IgM RF positive, and 25 samples from patients with RA), the sensitivity and specificity of this assay for RA was 98.5% and 97.6%, respectively.[10]

In our study, measurements of less than 6 IU/mL were considered to be negative, and measurements of 6 IU/mL or above were considered to be positive for IgM RF, in conformance with World Health Organization standards.

Table 1. Clinical context and use of the rheumatoid factor assays ordered during the study period

Type of practice	Use	No. of assays (%)
Primary care	To screen for RA* in patients with nonspecific musculoskeletal pain	563 (59%)
Other	Unknown	154 (16%)
Rheumatology	As a prognostic tool and diagnostic aid	74 (8%)
Nonrheumatology	To test for RA in suspected cases	43 (4.5%)
Clinicians other than primary care providers	To screen for RA in patients with nonspecific musculo-skeletal pain	39 (4%)
Neurology	To evaluate peripheral neuropathy	33 (3%)
Clinicians treating patients with known or suspected Sjogren syndrome or SLE†	To evaluate patients' condition	32 (3%)
Ophthalmology	To evaluate uveitis	10 (1%)
Infectious disease	To evaluate endocarditis	5 (0.5%)
Total		**953 (100%)**

*RA = rheumatoid arthritis. †SLE = systemic lupus erythematosus.

There were no indeterminate test results. All consecutive patients for whom an RF assay had been ordered during the study period were included as subjects if they were 18 or older and had no preexisting RA.

Blinded to the results of the RF assays, ordering indications, referring providers, and referring clinics, we reviewed each patient's medical record, medications, radiographs (to determine more precisely the reason the RF assay was ordered), and ultimate diagnosis. We initiated record review one full year after completion of the last RF assay to allow sufficient time for the primary provider to have diagnosed the patient's condition accurately. (Although RF may be present in a patient's circulation for years prior to the onset of rheumatic disease, the purpose of this study was to determine the RF assay's clinical utility as a diagnostic tool—not its ability to predict the future development of a rheumatic disease.) Total duration of follow-up was two to three years. Data were collected by a senior rheumatology fellow, a board-certified internist, and a board-certified rheumatologist; the senior rheumatology fellow and the board-certified rheumatologist also

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Table 2. The diagnostic value of the rheumatoid factor assay based on reason given for ordering the assay

Reason for order	Sensitivity (95% CI*)	Specificity	PPV†	NPV‡
Screen for RA§ in patients with nonspecific musculoskeletal pain	0.476 (0.190, 0.700)	0.92 (0.90, 0.94)	0.18 (0.08, 0.27)‖	0.98 (0.97, 0.99)
Suspected RA	0.519 (0.330, 0.710)	0.87 (0.80, 0.93)	0.54 (0.35, 0.73)‖	0.86 (0.67, 1.00)
Other or unknown	0.360 (0.080, 0.640)	0.91 (0.86, 0.96)	0.20 (0.09, 0.41)	0.95 (0.92, 0.98)
All reasons given	0.525 (0.240, 0.810)	0.90 (0.85, 0.94)	0.27 (0.11, 0.43)	0.96 (0.93, 0.99)

*CI = confidence interval. †PPV = positive predictive value. ‡NPV = negative predictive value. §RA = rheumatoid arthritis. ‖Statistically significant values ($P < .001$).

determined the patients' ultimate diagnoses.

For the purpose of this study, the reference standard for determining the presence or absence of RA was defined as either satisfaction of the 1987 ACR criteria for RA or clinical diagnosis of RA by a board-certified rheumatologist and initiation of a disease modifying antirheumatic drug. After patients' diagnoses were entered into the database, we were unblinded to the test results, ordering rationale, referring provider, and clinic.

A VARIETY OF USES

During the study period, 953 RF assays were performed on 941 military health care beneficiaries. We excluded 36 RF assays from the analysis—24 performed on patients under age 18 and 12 that were duplicate tests. Of the remaining 917 assays, the reasons most often given for ordering the test were: screening (63.2%), other or unknown (20.8%), RA (12.4%), Sjogren syndrome (2%), and SLE (1.5%) (Figure 1). A total of 112 tests were positive for RF. Although the prevalence and incidence of RA in the military health care beneficiary population from which this study cohort was derived has not been studied formally, 61 patients had RA yielding a prevalence of 6.7%. No adverse events were attributable to performance of the index test (IgM RF ELISA) or the reference standard.

Our record review revealed that the assays were ordered by clinicians in various types of services and were used in a variety of clinical contexts (Table 1). The tests were used by primary care providers to screen for RA in patients with nonspecific musculoskeletal pain (n = 563); by rheumatologists as a prognostic tool and diagnostic aid (n = 74); by nonrheumatologists to test for RA in suspected cases (n = 43); by clinicians other than primary care providers to screen for RA in patients with nonspecific musculoskeletal pain (n = 39); by neurologists to evaluate peripheral neuropathy (n = 33); by clinicians treating patients with known or suspected Sjogren syndrome or SLE to evaluate their condition (n = 32); by ophthalmologists to evaluate uveitis (n = 10); by infectious disease specialists to evaluate endocarditis (n = 5); and by other types of providers for unknown reasons (n = 154).

Of the 33 patients with peripheral neuropathy who had the RF assay, three were RF positive and none had RA. Of the 10 patients with uveitis who were tested, three were RF positive and one had RA.

VALUE OF THE TEST

The sensitivity of a positive IgM ELISA RF assay for predicting RA was only 47.6% when used to screen for RA in patients with nonspecific musculoskeletal pain but increased to 51.9% when used to support a diagnosis of RA in suspected cases (Table 2). The specificity, positive predictive value, and negative predictive value also varied with the reason given for ordering the test. The 95% confidence intervals were wide for sensitivity and positive predictive value due to the low prevalence of RA in the study population. The only statistically significant difference was

that between the positive predictive values of the RF assay when used to screen for RA in patients with nonspecific musculoskeletal pain, 18% ± 9% (SD), versus when used to test patients with suspected RA, 54% ± 19% ($P < .001$, by chi-square analysis).

Of the 563 RF assays ordered by primary care providers other than internal medicine specialists (59%), 208 were for patients who had osteoarthritis (OA) and 17 were for patients who had RA. In this subgroup of assays, the value of RF in distinguishing RA from OA is dubious (Figure 2). RF has better sensitivity and specificity for RA than for OA among these assays, but since OA is substantially more prevalent than RA in the patient group for whom they were ordered (3% versus 37%), the positive predictive value of RF is equal for OA and RA (21%). In this primary care setting, therefore, the RF assay cannot distinguish RA from OA.

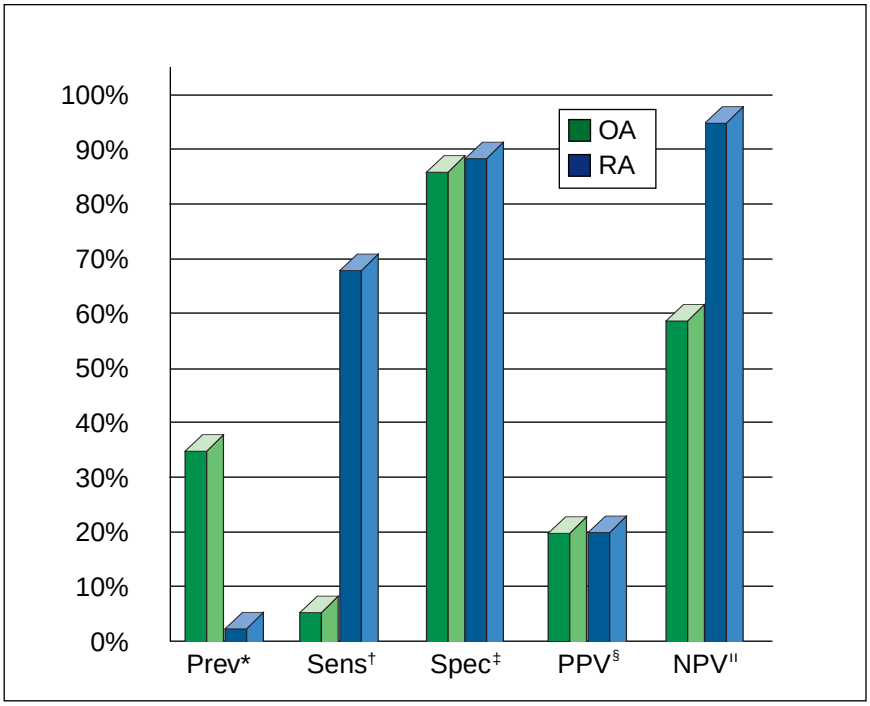

Figure 2. The diagnostic value of the rheumatoid factor (RF) assay for osteoarthritis (OA) and rheumatoid arthritis (RA) in a primary care clinic. In this setting, a positive RF has better sensitivity and specificity for RA than OA, but since the prevalence of OA is substantially higher than that of RA, the positive predictive value of the assay is equal for OA and RA. *Prev = prevalence. †Sens = sensitivity. ‡Spec = specificity. §PPV = positive predictive value. ||NPV = negative predictive value.

OPTIMIZING THE UTILITY OF RF ASSAYS

The primary objective of this study was to describe the clinical scenarios in which the RF assay is commonly used and to determine the test performance characteristics of the RF assay in this clinical setting. The patient selection criteria were chosen to reduce distortion based on participant variation (when the patient population under study does not reflect the patient population in which the test is clinically employed), disease prevalence variation, and context bias.

As the 1987 ACR classification criteria for RA are imperfect when measured against clinical diagnosis by experienced rheumatologists, use of these criteria as a reference standard can lead to inappropriate reference standard bias.[4,8] To minimize such bias, we defined the presence of RA as satisfaction of the ACR criteria or the clinical diagnosis of RA by a board-certified rheumatologist and initiation of a disease modifying antirheumatic drug (the reference standard against which the ACR criteria were measured). This broader case definition for RA reduces the incorporation bias inherent in the ACR criteria by virtue of the fact that the index test result is used to establish the final diagnosis. Furthermore, since retrospective study design does not alter the diagnostic odds ratio, it is an appropriate method for determining the diagnostic accuracy of the RF assay. [9]

Patients often present with arthralgia and myalgia. Only a skilled clinician conducting a thorough history and physical examination can distinguish arthritis from extraarticular pain and inflammatory from mechanical arthritis. The RF assay can be used as an adjunct to historical and physical data to provide further support for, or against, an inflammatory condition such as RA. In the evaluation of arthritis, however, laboratory tests such as the RF assay and radiographic imaging do not replace the patient history and physical examination.

The RF assay is nonspecific and is associated with several conditions (Table 3). Patients with active

Table 3. Possible rheumatologic and nonrheumatologic causes of a positive rheumatoid factor assay

Possible rheumatologic causes	Possible nonrheumatologic causes
• Rheumatoid arthritis	• Tuberculosis
• Sjogren syndrome	• Hepatitis
• Palindromic rheumatism	• Malignancy
• Systemic lupus erythematosus	• Thyroid disease
• Collagen vascular disease	• Endocarditis
• Dermatomyositis	• No pathologic cause
• Mixed connective tissue disease	
• Cranial arteritis	
• Polymyalgia rheumatica	
• Polyarthritis	
• Juvenile rheumatoid arthritis	
• Systemic sclerosis	
• Osteoarthritis	

hepatitis C infection, Sjogren syndrome, or OA have RF positivity rates of 75%, 63%, and 4%, respectively.[11,12] In the United States, almost 21 million people have OA, six million have Sjogren syndrome, nearly four million have hepatitis C virus infection, and just over two million have RA.[1,13,14] Given these numbers, it's not surprising that a positive RF assay used as a blind screening tool or diagnostic test apart from clinical suspicion is more likely to be associated with Sjogren syndrome or hepatitis C infection than with RA (Figure 3).[1,11–14]

At our institution, during the study period, the RF assay was most often used in a primary care setting to screen for RA in patients with nonspecific musculoskeletal pain. Although more than 80% of patients with RA and only 4% of patients with OA are RF positive, a positive RF assay was unable to distinguish between RA and OA in this clinical setting in which it was used most frequently.[11] This finding is a direct result of the substantially higher prevalence of OA compared to RA in this setting.

Less frequently, the RF assay is used to rule out RA in patients with unexplained neuropathy or inflammatory eye disease. It is unlikely that RA would present clinically with neuropathy in the absence of visible articular manifestations. It does not appear, therefore, that the use of RF in screening patients with neuropathy is warranted. Rather, history and physical examination are adequate to rule out RA as a predisposing condition for peripheral neuropathy. Alternatively, our data suggest that RF may be a plausible screening tool in the evaluation of unexplained iritis, though our sample size is too small to draw a definitive conclusion.

In an effort to compensate for the shortcomings of the RF assay, additional serologic assays have been developed to be used in conjunction with the RF assay and aide in the diagnosis of RA. Anti-cyclic citrullinated peptide (anti-CCP) antibodies, anti-keratin antibodies (AKA), and anti-perinuclear factor antibodies (APF) are promising serologies for the detection of RA. These tests, however, are not better predictors of disease severity than the RF assay.[15]

In a study of 179 patients with RA and 50 controls, the sensitivity was highest for IgM RF (75%) followed by anti-CCP antibodies (68%) and AKA (46%).[15] The specificity, on the other hand, was highest for anti-CCP antibodies (96%), followed by AKA (94%) and IgM RF (74%).[15] The sensitivity and specificity of APF ranges from 49% to 87% and 73% to 99%, respectively.[16–19]

While anti-CCP antibodies, AKA, and APF tests all are more specific than the RF assay, they lack sufficient sensitivity to be used as a tool to screen for RA in patients with nonspecific musculoskeletal pain. The most appropriate clinical use for these tests will take advantage of their relative specificity. They may, therefore, be useful in RF negative chronic inflammatory arthritis. In this context, a positive test would strongly suggest the diagnosis of RA. Finally, the added specificity of these tests may help distinguish RA from other inflammatory rheumatic conditions when the RF assay is positive.

The present study provides insight into how the RF assay is used by clinicians as well as the value of the assay in predicting RA in the clinical settings in which it is most commonly used. Based upon these

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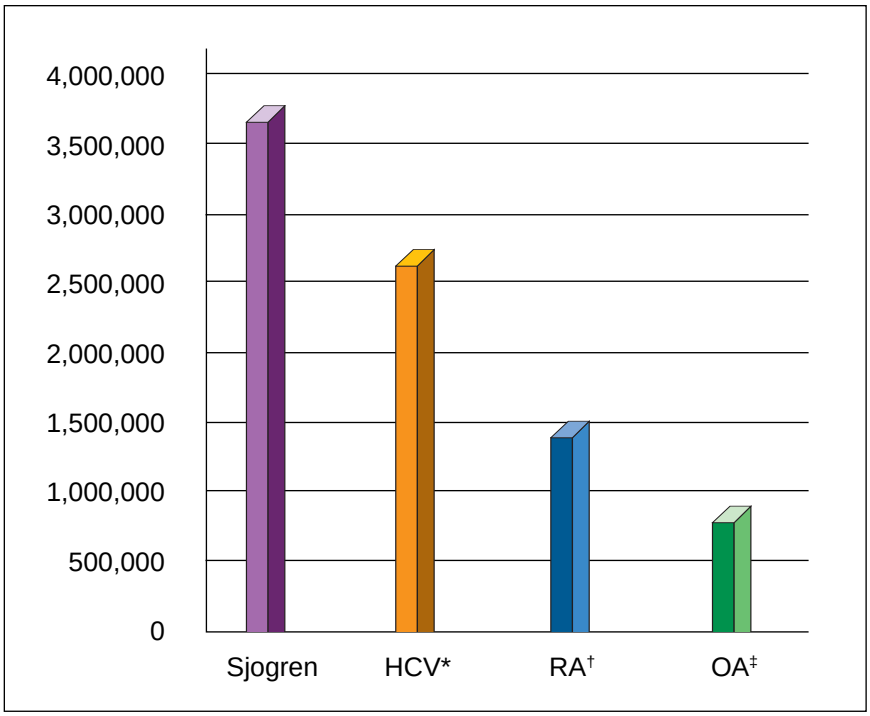

Figure 3. U.S. residents with positive rheumatoid factor assays, by diagnosis.[1,11–14] *HCV = hepatitis C virus. †RA = rheumatoid arthritis. ‡OA = osteoarthritis.

data, we believe that the RF assay has no role as a screening tool for RA in patients with nonspecific musculoskeletal pain. Rather, it should be ordered only when the patient's history and physical examination reveal evidence of a chronic inflammatory arthritis. Used as such, the RF assay may help clinicians categorize patients into more homogenous subgroups with similar clinical courses and prognoses.

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