An evidence-based approach to laboratory tests in usual care of patients with rheumatoid arthritis

T. Pincus[1], K.A. Gibson[2], R.H. Shmerling[3]

[1]*Rush University School of Medicine, Division of Rheumatology, Chicago, USA;*
[2]*University of New South Wales, Liverpool Hospital Department of Rheumatology, Sydney, Australia;*
[3]*Harvard Medical School, Beth Israel Deaconess Medical Center/Division of Rheumatology, Boston, USA.*

Theodore Pincus, MD
Kathryn A Gibson, MD, PhD
Robert H. Shmerling, MD

Please address correspondence to:
Theodore Pincus, MD,
Professor of Medicine,
Rush University School of Medicine,
Division of Rheumatology
1611 West Harrison Street,
Chicago IL 60612, USA.
E-mail: tedpincus@gmail.com

Received on October 10, 2014; accepted in revised form on October 11, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 85): S23-S28.

Key words: rheumatoid arthritis, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, erythrocyte sedimentation rate, C-reactive protein, laboratory tests

Competing interests: none declared.

ABSTRACT

Laboratory tests often are regarded as the most important information in clinical care by patients and doctors, and dominate clinical decisions in many chronic diseases such as diabetes and hyperlipidemia. Most patients with rheumatoid arthritis (RA) have a positive test for rheumatoid factor or anti-cyclic citrullinated peptide antibodies (ACPA), or an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, about a third of RA patients, have negative tests for rheumatoid factor or ACPA, and more than 40% have a normal ESR or CRP at presentation ("false-negative" results). Furthermore, many normal people have a positive test for rheumatoid factor or ACPA but do not have RA, even among those with extensive musculoskeletal pain ("false-positive" results). Abnormal laboratory tests are the most significant predictor of high levels of radiographic progression, and therefore regarded as indicators of "poor prognosis RA". By contrast, laboratory tests are far less predictive of severe long-term outcomes such as work disability and premature mortality than functional difficulties reported on a patient questionnaire. A patient questionnaire score is abnormal in 89% of RA patients at presentation, and therefore more useful than ESR or CRP to document subsequent clinical improvement or deterioration. In clinical practice, patient questionnaire scores and RAPID3, an index of physical function, pain, and patient global estimate of status, identify incomplete responses to methotrexate more effectively than ESR. Improved understanding of the limitations of laboratory tests in diagnosis and management of individual patients with RA (and all rheumatic diseases) could improve patient care and outcomes.

Laboratory tests often are regarded by most patients and doctors as the most important information collected in clinical care. The discovery in the 1940s of rheumatoid factor (1, 2) in most patients with rheumatoid arthritis (RA), and antinuclear antibodies (ANA) (3) in almost all patients with systemic lupus erythematosus (SLE), led to hopes that laboratory tests could provide *gold standard* biomarkers in rheumatic diseases, as seen in hypertension, diabetes, and many chronic diseases, to apply to diagnosis, prognosis, and monitoring of all individual patients.

Most patients with RA have a positive test for rheumatoid factor or anti-cyclic citrullinated peptide antibodies (ACPA) (4-7), or an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (8). Reduction in levels of rheumatoid factor, ESR or CRP often (but not always) accompanies clinical improvement in RA, suggesting control of pathophysiologic mechanisms. Changes in values of laboratory tests appear considerably more "scientific" than changes in other measures of RA status, such as tender joint counts or patient questionnaire scores for pain.

Laboratory measures have contributed invaluably to understanding of pathogenesis and to development of new treatments for RA. However, laboratory tests cannot be applied to diagnosis, prognosis and monitoring of each *individual* patient with RA, unlike serum glucose or haemoglobin A1c. This article reviews and updates information concerning advantages and limitations of laboratory tests in routine clinical care of RA and rheumatic diseases (9-13).

Positive laboratory tests in RA

The majority of patients with RA do have positive tests for rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA) (4-7), both of which are prominent in revised classification criteria for RA. A meta-analysis indicated a positive likelihood ratio of 12.5 for RA in 37 studies of ACPA (using the

former term anti-CCP antibodies) *versus* the general population, and a positive likelihood ratio of 4.9 for RA in 50 studies of rheumatoid factor (Table I) (7). Elevated levels of rheumatoid factor are associated with higher levels of radiographic progression (14), leading to a dictum that abnormal laboratory tests identify *poor prognosis* RA (15).

The majority of patients with RA also have an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (8) and an abnormal ESR or CRP often provides inclusion criteria for clinical trials (16). Reductions in ESR and CRP are seen in groups of patients in all successful clinical trials of RA therapies and contribute to improvement criteria which indicate efficacy of an active treatment compared to a control treatment. Furthermore, a normal ESR or CRP is required to meet RA remission criteria (17).

Table I. Meta-analysis of features of autoantibodies in 37 reports concerning anti-cyclic citrullinated peptide antibodies (anti-CCP or ACPA), and in 50 reports concerning rheumatoid factor (RF).

	Anti-cyclic citrullinated peptide antibodies (anti-CCP or ACPA)	Rheumatoid factor (RF)
Number of studies	37	50
Positive likelihood ratio	12.5	4.9
Sensitivity	67%	69%
Specificity	95%	85%
% of patients with negative test result	33%	31%

From: Nishimura K *et al.: Ann Intern Med* 2007; 146: 797-808 (7).

Table II. Percentage of patients who were positive for rheumatoid factor (RF) and mean erythrocyte sedimentation rate (ESR) levels in 4 locations in the European Research on Incapacitating Diseases and Social Support (EURIDISS) project reported in 1996.

Location	n.	% RF positive	Mean ESR (mm/Hr)
Oslo, Norway	237	73%	26 (20)
Nancy, France	135	62%	29 (26)
Groningen, Netherlands	283	81%	28 (24)
Belfast, N Ireland	51	71%	28 (27)

From: Smedstad LM, Moum T, Guillemin, Kvien TK, Finch MB, Suurmeijeru TP, van dan Heuvel WJ: *Br J Rheumatol* 1996; 35: 746-751.

Table III. Percentages of 1556 patients with rheumatoid arthritis (RA) seen in usual care in Wichita KS USA, reported in 1994, whose values for erythrocyte sedimentation rate (ESR) were ≥28 mm/Hr versus <28 mm/Hr.

	ESR ≥28 mm/h	ESR <28 mm/h
Females	63%	37%
Males	55%	45%

From: Wolfe F, Michaud K: *J Rheumatol* 1994; 21: 1227-1237. Wichita KS, USA.

A perspective on laboratory tests in RA

No rheumatology blood test is abnormal in 100% of *individual* patients with any rheumatic disease, and 100% within the normal range in all individuals who do not have that rheumatic disease, in contrast to serum glucose in diabetes, haemoglobin levels in anaemia, and other biomarkers in many other diseases. The meta-analysis noted above indicated that ACPA is found in 67% and rheumatoid factor in 69% of patients with RA (Table I) (7). Findings in a similar range are reported from most clinical sites, such as in 4 settings from the 1990s European Research on Incapacitating Diseases and Social Support (EURIDISS) project in Norway, France, the Netherlands, and Northern Ireland (Table II) (18). Therefore, about 1 in 3 patients, have negative tests for these serologic markers.

ESR or CRP are normal in about 40% of patients with RA, reported initially in 1994 by Wolfe and Michaud (19) (Table III). Mean ESR levels were 28–30 mm/Hr in data reported in 1996 from the 4 sites in the EURIDISS project (Table II) (18). A 2009 report from two sites, Nashville, TN, USA and Jyväskylä, Finland, indicated similar patterns, despite vastly different medical care systems. Mean ESR at presentation was 30 mm/Hr at both sites, and 45–47% of RA patients had ESR <28 mm/Hr (Table IV) (8).

Mean ESR levels reported in the rheumatology literature have declined over the second half of the 20th century, from 50 mm/Hr in RA cohorts at baseline in 1954-1980, to 41 mm/Hr in 1981-1984, to 35 mm/Hr after 1985 (Table V) (20). This observation may be explained in part by changes in the natural history of the disease, changes in treatment, both of these possibilities, and or other variables. Furthermore, while a decline in ESR or CRP is seen concomitantly with clinical improvement in many patients and in *groups* of patients in clinical trials and routine care, ESR and CRP may remain persistently elevated in other *individual* patients who experience clinical improvement (21).

"False negative" and "false positive" test results

The meta-analysis depicted in Table I indicates that a negative test, *i.e.* "false negative," or "seronegative" as used by the rheumatology community, result for rheumatoid factor or anti-CCP is found in more than 30% of people with a diagnosis of RA. Furthermore, "false positive" results are seen in people who have other inflammatory diseases, and some who may not have any inflammatory rheumatic disease at all. The meta-analysis presents a specificity of 95% for ACPA (anti-CCP), *i.e.* 5% of people in the non-RA population have a positive test for ACPA, and 85% for rheumatoid factor, *i.e.* 15% of people in the non-RA population have a positive test for rheumatoid factor (7).

The prevalence of RA is about 0.5% (22, 23), or about 10 in 2,000 people.

Table IV. Number (%) of rheumatoid arthritis patients at presentation with erythrocyte sedimentation rate (ESR) < or ≥28 mm/hr compared to C-reactive protein (CRP) < or ≥10 in:
a) 1744 patients in Jyväskylä, Finland, and
b) 170 patients in Nashville, TN, USA.
Note similar findings in both settings despite extensive differences in medical systems.

a. Jyväskylä, Finland

CRP	ESR		Total
	≥28 mm/hr	<28 mm/hr	
≥10 mg/L	775 (44%)	202 (12%)	977 (56%)
<10 mg/L	199 (11%)	568 (33%)	767 (44%)
Total	974 (56%)	770 (44%)	1,744 (100%)

b. Nashville, TN, USA

CRP	ESR		Total
	≥28 mm/hr	<28 mm/hr	
≥10 mg/L	48 (28%)	22 (13%)	70 (41%)
<10 mg/L	29 (17%)	71 (42%)	100 (59%)
Total	77 (45%)	93 (55%)	170 (100%)

From: Sokka T, Pincus T: *J Rheumatol* 2009; 36: 1387-1390.

Table V. Median and mean erythrocyte sedimentation rate (ESR) values in 23 studies of patients with rheumatoid arthritis (RA) initiated in 1954-1996, including 7 initiated in 1954-1980, 8 in 1981-1984, and 8 in 1985-1996.

1st yr of study	# of studies	Median mm/h	Mean mm/h
1954-1980	7	47	50
1981-1984	8	38	41
1985-1996	8	36	35

From: Abelson B, Sokka T, Pincus T: *J Rheumatol* 2009: 36, 1596.

If 70% have a positive rheumatoid factor test, about 0.35% or 7 in 2,000 people has RA and a positive rheumatoid factor test. However, if 15% of the normal population has a positive test, about 300 people in 2,000 in the general population have a positive test for rheumatoid factor (12).

Of course, tests for rheumatoid factor or ACPA are not ordered in all people, and the results of a test must be viewed in the context of the clinical circumstances in which the test was ordered (24). Nonetheless, the prevalence of musculoskeletal symptoms in the population ranges from 15–45% (22, 25) including fibromyagia in about 2% of the population (26, 27). If 2% of people have fibromyalgia and 15% of these people are positive for rheumatoid factor, 0.3% of people (2% of 15%) or 6 in 2,000 will have fibromyalgia and be seropositive, almost as many as with RA. If false-positive results among people with soft tissue rheumatism and osteoarthritis also are considered, it appears likely that at least as many people with musculoskeletal symptoms and rheumatoid factor have RA as do not have RA, based on population data.

The specific details of these analyses are less important than the evidence that a positive rheumatoid factor or ACPA test does not indicate a definitive diagnosis of RA and a negative test does not exclude this diagnosis. Furthermore, available data concerning the prevalence of positive laboratory tests in RA are derived from patients seen at rheumatology treatment centers. Patients are less likely to be referred by primary care physicians, if these tests are normal. Some patients who are seronegative report to a rheumatologist that a physician has told them "Your test for rheumatoid arthritis was negative" which delayed referral. Evidence that more than 30% of patients with RA have negative tests for rheumatoid factor or ACPA, and 40% have normal ESR or CRP, may be underestimates, and may contribute to delays in diagnosis and treatment.

The likelihood of abnormal quantitative data at baseline for ESR *versus* other measures

Clinical decisions in RA are recognised to be guided primarily by a patient history and physical examination (28), in contrast to other chronic diseases, in which clinical decisions are guided by biomarkers such as blood pressure, laboratory tests, or imaging studies. However, the only quantitative data in the medical records of many patients with RA in usual care are laboratory tests. This practice reduces the capacity to monitor, recognise and document clinical improvement or deterioration in patient status according to quantitative data.

Analyses of 287 RA patients seen in 3 clinical care centers indicated that at presentation ESR was abnormal in 57% and CRP in 58% (29) (Table VI). By contrast, scores on a patient questionnaire were abnormal for physical function in 70% and pain in 89% of patients (29). It is not possible to recognise and document clinical improvement according to a measure that is normal at baseline. Self-report scores also are as responsive to change over time as any of the RA Core Data Set measures (30, 31). Therefore, a strong case could be made that scores for physical function and pain, although only indirectly related to pathophysiologic mechanisms, are at least as valuable as ESR to monitor the clinical status of patients with RA.

Documenting incomplete responses to methotrexate

ESR also is less likely than patient self-report questionnaire scores to recognise an incomplete response to methotrexate in RA patients, as demonstrated in an analysis of patients in whom methotrexate was initiated between 1996 and 2001 and for whom 5-year follow-up was available (Table VII). All patients had available ESR and the 3 patient self-report measures from the RA Core Data set on a multidimensional assess-

Table VI. Percentage of 287 patients with rheumatoid arthritis who have abnormal measures at presentation.

Measure	% of patients with abnormal value at presentation
Erythrocyte sedimentation rate (ESR) >28 mm/Hr	57%
C-reactive protein (CRP) >10	58%
Rheumatoid factor positive	69%
ACPA positive	67%
Function score >2/10	70%
Pain score >2/10	89%

From: Sokka T *et al.: J Rheumatol* 2009; 36: 1387-90.
Nishimura K *et al.: Ann Intern Med* 2007; 146: 797-808.
Pincus T, Swearingen CJ: *Arthritis Rheum* 2009; 60 (Suppl.): S160.

Table VII. Median levels of RA measures of erythrocyte sedimentation rate (ESR), and 3 patient self-report measures on a multidimensional health assessment questionnaire (MDHAQ), for physical function, pain, patient estimate of global status, and routine assessment of patient index data (RAPID3), in all patients at initiation of methotrexate in 1996-2001 compared to median levels of 63 "adequate responders" 2.6 years after initiation of methotrexate and 30 "incomplete responders" at the time of initiation of a biological agent at a mean of 2.6 years after initiation of methotrexate.

	63 Adequate Responders ("Controls")		30 Incomplete Responders	
	At initiation of methotrexate	Follow-up at mean of 2.6 years later (no biologic agent)	At initiation of methotrexate	At initiation of biologic agent at mean of 2.6 years later
Erythrocyte sedimentation rate (0-150)	24	16	28	18
MDHAQ-Function (0-10)	2.3	1.0	3.2	3.3
Pain (0-10)	4.1	1.4	5.2	6.8
Patient Global estimate (0-10)	4.2	0.9	5.5	5.5
RAPID3 (0-30)	10.6	3.6	14.9	16.2

MDHAQ: multidimensional health assessment questionnaire; RAPID3: routine assessment of patient index data.
From: Pincus T, Swearingen CJ: *Bull Hosp Jt Dis* 2013; 71(2): 117-20.

ment questionnaire (MDHAQ) (32), physical function, pain, and patient global estimate of status, each scored 0–10, as well as RAPID3, an index of these 3 measures scored 0–30 (33). RAPID3 was not used clinically until 2006, so clinical decisions in these patients were not based on RAPID3.

"Incomplete response" to methotrexate was defined as initiation of subsequent biological therapy, and "adequate response" as no biological therapy over 5 years. The measures were analysed in all patients at the initial visit at which methotrexate was prescribed, as well as at a subsequent visit, either when biological therapy was prescribed – in 30 "incomplete responders," or 2.6 years after methotrexate initiation (the mean interval to biological therapy in "incomplete responders") in 63 "adequate responders" (Table VII).

Median ESR fell similarly by 33%–36% in both incomplete and adequate responders (Table VII). Median MDHAQ scores for physical function, pain, patient global estimates, and RAPID3 fell by 56–79% over 2.6 years in adequate responders, but increased by 0–31% in incomplete responders. Median RAPID3, an index of the 3 measures, fell from 10.6 to 3.6 (low severity=3.1–6, remission3) in adequate responders, and rose from 14.9 to 16.2 (high severity>12) in incomplete responders. The data also indicate higher RAPID3 scores at baseline initiation of methotrexate in those who were, subsequently, incomplete responders (14.9) than in those who were adequate responders (10.6). These data indicate that patient self-report measures on the MDHAQ and the composite RAPID3, but not ESR, recognise incomplete *versus* adequate methotrexate responses in usual clinical care.

Laboratory tests in prognosis of RA

Laboratory tests are of considerable value in the prognosis of many diseases. Rheumatoid factor and ACPA are the most significant predictors of radiographic progression in RA (other than a prior radiograph), consistent with description of seropositive patients as having "poor prognosis RA." Rheumatoid factor and ESR also are significant in the prognosis of premature mortality in some cohorts of patients with RA (34). However, severe long-term outcomes of work disability and premature mortality are predicted at considerably higher levels of significance by patient self-report MDHAQ physical function than by laboratory tests (or radiographs) (34, 35).

For example, a cohort of 210 RA patients monitored between 1985 and 1990 had baseline measurement of rheumatoid factor, ESR, radiographic score, and MDHAQ physical function (Fig. 1). Patients who would survive or die over the next 5 years were distinguished at considerably higher levels of significance by MDHAQ physical function score than by ESR, rheumatoid factor, or radiographic score (Fig. 1) (36).

These findings are not unique to this cohort. A summary of 53 reports in which a possible prognostic marker for RA mortality was available (Fig. 2) indicated that physical function and comorbidity were far more likely to be significant in univariate and multivariate analyses to predict premature mortality than a laboratory test (or joint count or radiograph) (Fig. 2) (34). One caveat is that the radiographs which are analysed as possible predictors of mortality are hand (and sometimes feet) radiographs, but the joints most predictive of mortality are large joints – hips, knees, and shoulders (37). If radiographic scores were available and scored for large joints, it is possible that radiographs might be more significant in the prognosis of RA than in reports based on hand (and foot) joints.

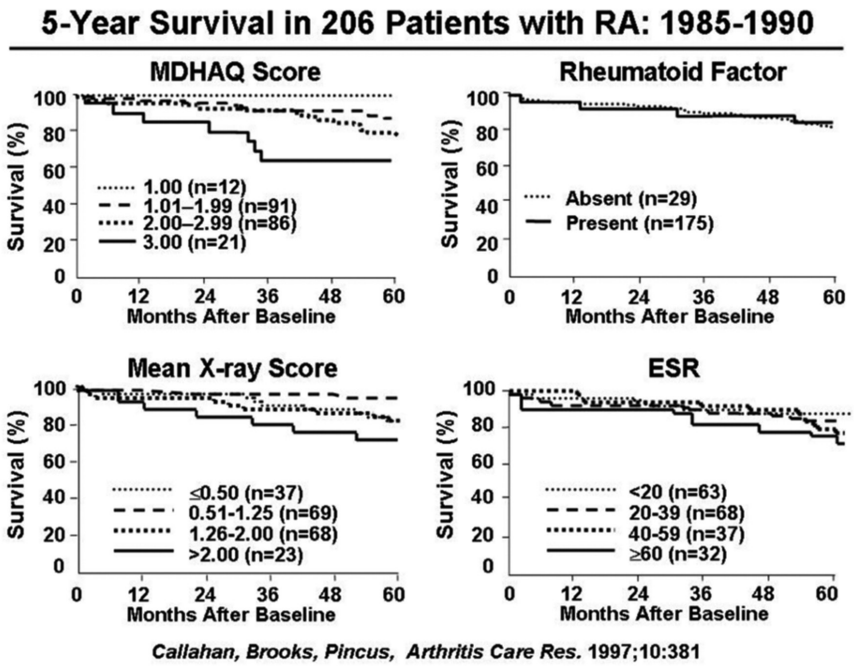

Fig. 1. Survival over 5 years in a cohort of 210 RA patients monitored between 1985 and 1990 according to 4 variables: MDHAQ scores for physical function, rheumatoid factor, radiographic score, and erythrocyte sedimentation rate (ESR). Note that MDHAQ function distinguished patients who would survive or die over the next 5 years at considerably higher levels than rheumatoid factor or ESR.
From: Callahan LF, Pincus T, Huston JW, 3rd, Brooks RH, Nance EP, Jr., Kaye JJ: *Arthritis Care Res* 1997; 10(6): 381-94. (36)

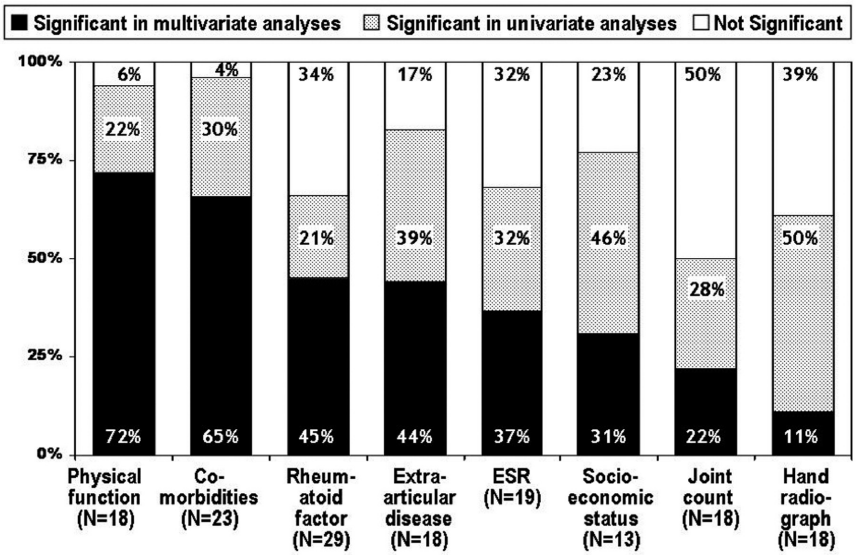

Fig. 2. Significance of 8 variables as predictors of mortality in RA in a review of 84 reports concerning 53 cohorts. For each variable, n = the number of reports that included the variable and bars indicate the percentage of those reports in which the variable was a significant predictor of mortality in multivariate analyses (black), in univariate analyses (dotted), and the percentage in which the variable was not significant (white). Physical function (and comorbidities) were significant predictors of mortality in all but one of 18 (and 23) studies, respectively. Rheumatoid factor was not significant in 10 of 29 studies (34%) and erythrocyte sedimentation rate (ESR) was not significant in 6 of 19 reports (32%).
[Adapted from: Sokka T, Abelson B, Pincus T: *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S35-61].

Pragmatic considerations

One final issue concerning laboratory tests is that they often are not available at the time at which a clinical decision is made. A clinician may arrange for a laboratory test in advance of a visit, or contact a patient at a later date, but these practices do not occur in most clinical settings at this time. Therefore, clinical decisions are made without laboratory data – often without any quantitative data at all.

Conclusions

Laboratory research is essential to provide new insights into pathogenesis and new treatments for rheumatic diseases. However, in usual clinical care, laboratory tests for RA often have limited sensitivity and specificity, high levels of false-positive and false-negative results, a lesser capacity than patient self-report questionnaire scores to provide a sensitive measure for documenting future improvement, recognise incomplete responses, and predict work disability and premature mortality. Laboratory tests are useful in many patients and essential in a few, but physicians and patients often attribute disproportionate importance to laboratory tests in rheumatic diseases. A more sophisticated understanding of rheumatology laboratory tests may help improve care and outcomes for patients with RA and all rheumatic diseases.

References:

1. WAALER E: On the occurrence of a factor in human serum activating the specific agglutintion of sheep blood corpuscles. 1939. *APMIS* 2007; 115: 422-38; discussion 439.
2. ROSE HM, RAGAN C *et al*.: Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc Soc Exp Biol Med* 1948; 68: 1-6.
3. HARGRAVES MM, RICHMOND H, MORTON R: Presentation of two bone marrow elements; the tart cell and the L.E. cell. *Proc Staff Meet Mayo Clin* 1948; 23: 25-8.
4. SCHELLEKENS GA, DE JONG BA, VAN DEN HOOGEN FH, VAN DE PUTTE LB, VAN VENROOIJ WJ: Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998; 101: 273-81.
5. VAN GAALEN FA, LINN-RASKER SP, VAN VENROOIJ WJ *et al*.: Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004; 50: 709-15.
6. RIEDEMANN JP, MUNOZ S, KAVANAUGH A: The use of second generation anti-CCP antibody (anti-CCP2) testing in rheumatoid arthritis--a systematic review. *Clin Exp Rheumatol* 2005; 23 (Suppl. 39): S69-76.
7. NISHIMURA K, SUGIYAMA D, KOGATA Y *et al*.: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis.

Ann Intern Med 2007; 146: 797-808.

8. SOKKA T, PINCUS T: Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. *J Rheumatol* 2009; 36: 1387-90.
9. LICHTENSTEIN MJ, PINCUS T: How useful are combinations of blood tests in "rheumatic panels" in diagnosis of rheumatic diseases? *J Gen Intern Med* 1988; 3: 435-42.
10. SHMERLING RH, DELBANCO TL: The rheumatoid factor: an analysis of clinical utility. *Am J Med* 1991; 91: 528-34.
11. SHMERLING RH, DELBANCO TL: How useful is the rheumatoid factor? An analysis of sensitivity, specificity, and predictive value. *Arch Intern Med* 1992; 152: 2417-20.
12. PINCUS T: A pragmatic approach to cost-effective use of laboratory tests and imaging procedures in patients with musculoskeletal symptoms. *Prim Care* 1993; 20: 795-814.
13. PINCUS T: Advantages and limitations of quantitative measures to assess rheumatoid arthritis: joint counts, radiographs, laboratory tests, and patient. *Bull NYU Hosp Jt Dis* 2006; 64: 32-9.
14. OLSEN NJ, CALLAHAN LF, BROOKS RH *et al*.: Associations of HLA-DR4 with rheumatoid factor and radiographic severity in rheumatoid arthritis. *Am J Med* 1988; 84: 257-64.
15. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
16. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
17. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63: 573-86.
18. SMEDSTAD LM, MOUM T, GUILLEMIN F *et al*.: Correlates of functional disability in early rheumatoid arthritis: a cross-sectional study of 706 patients in four European countries. *Br J Rheumatol* 1996; 35: 746-51.
19. WOLFE F, MICHAUD K: The clinical and research significance of the erythrocyte sedimentation rate. *J Rheumatol* 1994; 21: 1227-37.
20. ABELSON B, SOKKA T, PINCUS T: Declines in erythrocyte sedimentation rates in patients with rheumatoid arthritis over the second half of the 20th century. *J Rheumatol* 2009; 36: 1596-9.
21. WOLFE F, PINCUS T: The level of inflammation in rheumatoid arthritis is determined early and remains stable over the longterm course of the illness. *J Rheumatol* 2001; 28: 1817-24.
22. HELMICK CG, FELSON DT, LAWRENCE RC *et al*.: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008; 58: 15-25.
23. SILMAN AJ, PEARSON JE: Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res* 2002; 4 (Suppl. 3): S265-72.
24. WOLFE F, CATHEY MA, ROBERTS FK: The latex test revisited. Rheumatoid factor testing in 8,287 rheumatic disease patients. *Arthritis Rheum* 1991; 34: 951-60.
25. MAKELA M, HELIOVAARA M, SIEVERS K, KNEKT P, MAATELA J, AROMAA A: Musculoskeletal disorders as determinants of disability in Finns aged 30 years or more. *J Clin Epidemiol*. 1993; 46: 549-59.
26. CROFT P, RIGBY AS, BOSWELL R, SCHOLLUM J, SILMAN A: The prevalence of chronic widespread pain in the general population. *J Rheumatol* 1993; 20: 710-3.
27. WOLFE F, ROSS K, ANDERSON J, RUSSELL IJ, HEBERT L: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
28. CASTREJON I, MCCOLLUM L, TANRIOVER MD, PINCUS T: Importance of patient history and physical examination in rheumatoid arthritis compared to other chronic diseases: Results of a physician survey. *Arthritis Care Res* (Hoboken) 2012; 64: 1250-5.
29. PINCUS T, SWEARINGEN C: Erythrocyte sedimentation rate (ESR) is the least likely of Core Data Set measures to identify an "abnormal state" in new patients with RA to monitor therapeutic responses, according to 3 definitions of "abnormal state.". *Arthritis Rheum* 2009 60 (Suppl.): S117.
30. PINCUS TR, B., STRAND V, BERGMAN M: Relative efficiencies of the 7 rheumatoid arthritis (RA) Core Data Set measures to distinguish active from control treatments in 9 comparisons from clinical trials of 5 agents *Clin Exp Rheumatol* In Press 2014.
31. CASTREJON I, BERGMAN MJ, PINCUS T: MDHAQ/RAPID3 to recognize improvement over 2 months in usual care of patients with osteoarthritis, systemic lupus erythematosus, spondyloarthropathy, and gout, as well as rheumatoid arthritis. *J Clin Rheumatol* 2013; 19: 169-74.
32. PINCUS T, SOKKA T, KAUTIAINEN H: Further development of a physical function scale on a MDHAQ [corrected] for standard care of patients with rheumatic diseases. *J Rheumatol* 2005; 32: 1432-9.
33. PINCUS T, SWEARINGEN CJ, BERGMAN MJ *et al*.: RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds. *Arthritis Care Res* (Hoboken) 2010; 62: 181-9.
34. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S35-61.
35. YELIN E, MEENAN R, NEVITT M, EPSTEIN W: Work disability in rheumatoid arthritis: effects of disease, social, and work factors. *Ann Intern Med* 1980; 93: 551-6.
36. CALLAHAN LF, PINCUS T, HUSTON JW, 3RD, BROOKS RH, NANCE EP, JR., KAYE JJ: Measures of activity and damage in rheumatoid arthritis: depiction of changes and prediction of mortality over five years. *Arthritis Care Res* 1997; 10: 381-94.
37. PINCUS T, BROOKS RH, CALLAHAN LF: Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Intern Med* 1994; 120: 26-34.