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Review Article

Evidence from a Multidimensional Health Assessment Questionnaire (MDHAQ) of the Value of a Biopsychosocial Model to Complement a Traditional Biomedical Model in Care of Patients with Rheumatoid Arthritis

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Patient self-report questionnaires such as a multidimensional health assessment questionnaire (MDHAQ) have advanced knowledge concerning prognosis, care, course and outcomes of rheumatoid arthritis (RA). The MDHAQ may overcome some limitations of a "biomedical model," the dominant paradigm of contemporary medical services, including limitations of laboratory tests, radiographs, joint counts, and clinical trials, to predict and depict the long-term course and outcomes of RA. A complementary "biopsychosocial model" captures components of a patient medical history on patient questionnaires as quantitative, standard, "scientific" scores for physical function, pain, fatigue, and other problems, rather than as "subjective" narrative descriptions. A rationale for a biopsychosocial model in RA includes the importance of a patient history in diagnosis and management compared to biomarkers in many chronic diseases such as hypertension and diabetes. Some important observations which support a biopsychosocial model in RA based on patient questionnaires include that MDHAQ physical function scores are far more significant than radiographs or laboratory tests to predict severe RA outcomes such as work disability and premature death; patient self-report measures are more efficient than tender joint counts and laboratory tests to distinguish active from control treatments in RA clinical trials involving biological agents; and MDHAQ scores are more likely than laboratory tests to be abnormal at presentation and to document incomplete responses to methotrexate at initiation of biological agents. Patient questionnaires can save time for doctors and patients, and improve doctor-patient communication. A standardized database of MDHAQ scores consecutive patients over long periods might be considered by all rheumatologists in routine clinical care. **(J Rheum Dis 2016;23:212-233)**

Key Words. Rheumatoid arthritis (RA), Multidimensional health assessment questionnaire (MDHAQ), Routine assessment of patient index data 3 (RAPID3), Biomedical model, biopsychosocial model

INTRODUCTION

Contemporary medical care of most diseases is dominated by a "biomedical model" paradigm (Table 1) [1]. In this model, the causes, diagnosis, prognosis, treatment, and outcomes of diseases are determined largely (some might say exclusively) by physical or somatic variables (Table 1). Each disease is regarded as resulting primarily from an identifiable "cause." The typical example of this model is seen in infectious diseases, in which an organism identified through laboratory tests defines the cause, treatment and likely outcome of the disease. This paradigm extends to most other diseases with the notable exception of some psychiatric illnesses.

In a biomedical model, mind and body generally are seen as distinct in the causation and course of diseases [1], other than in psychiatric diseases. The patient history is regarded as "subjective" [2] narrative, non-quantitative

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Table 1. Comparison of a "biomedical model" and a "biopsychosocial model" of disease

Variable	Biomedical model	Biopsychosocial model
Cause	Each disease has a single "cause"	Disease etiology is multifactorial: external pathogens, toxins, and internal host milieu, genes, behavior, social support
Diagnosis	Identified primarily through laboratory tests, radiographs, scans; information from patients of value primarily (or only) to suggest appropriate tests	A patient medical history provides 50%～90% of the information needed to make many, perhaps most, diagnoses
Assessment of status and prognosis	Also established most accurately on the basis of information from high technology sources, rather than from a patient	Information provided by a patient often is the most valuable data to assess clinical status and establish a prognosis
Results of treatment	Involves only actions of health professionals, e.g., medications, surgery	Must involve patient, family, social structure
Role of health professionals and patients in general health and disease outcomes	Health and disease outcomes are determined primarily by decisions and actions of health professionals	Health and outcomes of chronic diseases are determined as much by actions of individual patient as by health professionals

descriptive information to guide the clinician in seeking "objective" data from physical examination, laboratory tests, imaging, biopsies, microbiology cultures, etc. A medical history usually is not regarded as a source of "objective", quantifiable data that may in itself have diagnostic and prognostic value. Furthermore, health and disease outcomes generally are thought to be determined primarily, if not exclusively, by health professionals and the medical care system, with relatively little contribution (or responsibility) on the part of the individual patient (Table 1).

The value of a biomedical model is reinforced in daily medical practice by many spectacular advances over the 20th century. However, this model has limitations in relation to explaining the causes, prognosis, and outcomes of many diseases, particularly chronic diseases such as rheumatoid arthritis (RA). This article outlines how some limitations of a biomedical model may be addressed in many chronic diseases according to principles of a complementary "biopsychosocial model" (Table 1).

In a biopsychosocial model, the etiology of a disease is multifactorial. Information concerning diagnosis, prognosis, treatment, and outcomes of diseases is based in large part on a patient history and physical examination. and "objective" high-technology tests often add relatively little to clinical decisions. Standardization and quantitation of certain components of the patient history may be achieved according to patient self-report questionnaire scores. In some instances, these scores inform prognosis, monitoring, and outcomes of specific diseases at higher levels of significance than laboratory tests and other high-technology data. In this setting, patient questionnaire scores may be viewed as "scientific" data, according to the criteria of being standardized and quantitative. Databases which include patient questionnaire scores have proven of considerable value to advance knowledge concerning the course and care of patients with RA and other rheumatic diseases.

This review article updates evidence concerning the value of a biopsychosocial model to complement a traditional biomedical model in care of patients with RA, with emphasis on "scientific" data from patient self-report questionnaires, particularly a multidimensional health assessment questionnaire (MDHAQ) [3-9]. The article is divided into three sections concerning: a) limitations of a biomedical model in RA; b) a biopsychosocial model in RA, incorporating patient history data recorded on an MDHAQ and other patient questionnaires as complementary to a biomedical model; c) patient questionnaire data which support a biopsychosocial model concerning prognosis, course and outcomes of RA.

MAIN SUBJECTS

Limitations of a biomedical model in RA: laboratory tests, imaging, joint counts, and clinical trials

The traditional approach to RA according to a biomedical model, has led to major improvements in patient status and outcomes [9,10]. However, limitations of a biomedical model are seen in RA. Some types of limitations

are summarized below, classified according to limitations of laboratory tests [9,11-13], radiographs and imaging [14-16], formal joint counts [14,16-18], and clinical trials (Table 2) [14,19-24].

1) Some limitations of laboratory tests in RA

Patients who are suspected of having RA usually are tested for rheumatoid factor, anti-cyclic citrullinated peptide antibodies (ACPA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Data from these laboratory tests have been crucial to establish the inflammatory basis of RA in groups of patients, and are invaluable to develop new treatments. However, test results may be of limited value to guide clinical decisions in both new patients and individual patients in whom a diagnosis has been established, as results generally do not change clinical decisions is most patients.

Rheumatoid factor and ACPA are found in most patients with RA, and are not commonly found in the general population. A meta-analysis of 50 studies of rheumatoid factor and 37 studies of ACPA indicates that 69% of RA patients have positive rheumatoid factor tests and 67% positive ACPA tests (Table 2) [25]. These findings indicate that about 30% of RA patients have negative tests for these serologic markers. Furthermore, although uncommon, a positive test for rheumatoid factor or ACPA [25] is found in about 5% of the normal population.

Of course, a test for rheumatoid factor or ACPA is not ordered in most people in the general population. However, about 1 in 6 individuals in the general population sees a

Table 2. Some limitations of a biomedical model approach to rheumatoid arthritis

1) Some limitations of laboratory tests in RA
   a. Rheumatoid factor positive in 69% − negative in 31% of patients
   b. ACPA positive in 67% − negative in 33% of patients
   c. ESR and CRP normal in >40% of patients at presentation
   d. 5% of normal people have positive test for rheumatoid factor or ACPA − more people who do not have RA are positive than RA patients
   e. Laboratory tests not available at clinical visit in most settings
   f. Patient questionnaire physical function scores more significant in prognosis of work disability and mortality
2) Some limitations of radiographs in RA
   a. Not as sensitive as ultrasound, MRI
   b. Treatment should occur when normal − prior to damage
   c. Quantitative scoring not feasible in routine clinical care
   d. Patient questionnaire physical function scores more significant in prognosis of work disability and mortality
3) Some limitations of joint counts in RA
   a. Poorly reproducible − need for same observer at each visit, excluding other health professionals
   b. Similar or lower relative efficiencies than global and patient measures to document differences between active and control treatments in clinical trials
   c. Not as sensitive to detect inflammatory activity as ultrasound
   d. Most visits to a rheumatologist include a careful joint examination, but do not include a formal joint count
4) Limitations of clinical trials in RA
   (1) Pragmatic limitations
   a. Relatively short time frame in chronic diseases − too short to identify important clinical benefits or possible loss of efficacy over time
   b. Inclusion and exclusion criteria restrict eligibility to fewer than 10% of patients
   c. Statistical significance may not be clinically significant and vice versa
   d. Important variables affecting outcomes such as socioeconomic status usually ignored in reporting of clinical trial results
   e. Inflexible dosage schedules and restriction of concomitant medications
   f. Surrogate markers and indices may be suboptimal to detect changes in clinical status
   (2) Intrinsic limitations
   g. Design can greatly influence results − availability of a control group does not eliminate bias
   h. Data are reported in groups − ignore possible substantial variation in individual patients
   i. Risk/benefit of a therapy interpreted differently by different patients − all may be "correct"
   j. Loss of a "placebo effect" in a clinical trial

RA: rheumatoid arthritis, ACPA: anti-cyclic citrullinated peptide antibodies, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MRI: magnetic resonance.

doctor because of musculoskeletal problems. Many clinicians order a rheumatoid factor or ACPA test to "screen" for RA, even when there is no clinical evidence of RA, despite evidence that medical history and physical examination data are far more prominent in diagnosis and management decisions in RA than laboratory tests or ancillary studies [26]. Since the prevalence of RA is 0.5%～1%, even if rheumatoid factor or ACPA is tested in only 15% of the population, at a 5% "false-positive" rate, a positive test for rheumatoid factor or ACPA is seen in as many people who do not have RA as in people who have this disease (70% of 1%=0.70%, 5% of 15%=0.75%). False positive tests may lead to misdiagnosis and inappropriate therapy.

ESR and CRP are elevated in many patients with RA, more commonly in earlier decades than at this time, as mean ESR levels have declined from 50 mm/h in RA cohorts at baseline 1954～1980, to 41 mm/h in 1981～1984, to 35 mm/h after 1985 [27]. A report in 1994, indicated a normal ESR was found in about 40% of patients [28]. A 1996 report indicated mean ESR levels of 30 or less (normal for females who are 70% of RA patients) in 4 European settings in Norway, the Netherlands, Northern Ireland, and France [29]. A 2007 report indicated that ESR and CRP were normal in about 40% of patients from the USA and Finland (Table 2) [30].

The diagnosis of RA, as noted, depends primarily on the history and physical examination, rather than on laboratory tests, imaging, or other high-technology data [26]. If a physician seeks to establish a diagnosis of RA with laboratory tests, a "false negative" result will be seen for rheumatoid factor or ACPA in 3 of 10 patients, and a normal ESR or CRP will be seen in 4 of 10 patients.

To summarize, although these tests have been invaluable in analysis of groups to improve knowledge concerning pathogenesis and to develop new therapies, significant limitations are seen in their application to individual RA patients. Most rheumatologists have seen RA patients with advanced, irreversible joint damage, who reported that their primary care physician had not referred them for specialist evaluation years earlier because "my test for RA was negative and my doctor said I didn't need to see a rheumatologist."

"False positive" tests may lead to "over diagnosis" and unnecessary treatment with poor benefit/risk ratio, whereas "false negative" tests may lead to "under diagnosis", delayed treatment and poor long term outcomes. A better understanding of the limitations of laboratory tests could advance treatment and outcomes of RA, as discussed in greater detail in earlier reports [9,11-13,31].

2) Some limitations of radiographs in RA

Radiographs and other imaging tests of painful joints are ordered routinely by primary care physicians and rheumatologists in new patients suspected of having RA. Furthermore, radiographs and other imaging tests are ordered in patients with an established diagnosis of RA, to assess joint damage prior to treatment, in patients who are candidates for total joint replacement, to monitor therapy to prevent damage. Radiographic damage is correlated at high levels with duration of disease, laboratory measures and joint deformity on physical examination [32].

However, limitations of radiographs also are apparent in clinical care (Table 2). Treatment should be initiated prior to evidence of radiographic damage. Radiographs are less sensitive to detect abnormalities than magnetic resonance imaging (MRI) and ultrasound (Table 2). Radiographs are less significant in the prognosis of severe outcomes of RA, including work disability [33-37], premature mortality [34,38,39], costs [40,41], and even joint replacement surgery [42], than measures of functional status on patient questionnaires [16,39,43] (see below).

The rheumatology community has continued to emphasize radiographic progression as a primary variable to assess responses to therapy in RA, despite limited significance to predict severe long-term clinical outcomes. This emphasis may be explained in part by the dominance of a biomedical model, as radiographic damage is predicted by laboratory tests [32]. In addition, changes in radiographic scores may be documented in clinical trials over one year, and even shorter intervals in large groups, while severe outcomes such as work disability and death develop only over 5～15 years in most individual patients. Nonetheless, the primary predictors of severe outcomes are physical function assessed on a patient questionnaire and comorrbidities [34,38,39]. The 2014 treat-to-target consensus recommendations for RA suggested the use of validated composite clinical indices to guide therapy, but do not specifically recommend serial radiographs [44].

3) Some limitations of joint counts in RA

A joint examination is required for a diagnosis of RA, and a count of tender and swollen joints is the most specific measure of clinical status. A formal joint count is in-

cluded as an "objective" measure in the most widely used RA indices, such as the disease activity score (DAS), its version with a 28 joint count, DAS28 [45,46], and the clinical disease activity index (CDAI) [47]. Remission criteria established by an American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) committee include a requirement for one or fewer swollen joints as well as one or fewer tender joints [48].

Joint counts are weighted more prominently than the other 5 of 7 RA Core Data Set measures in criteria for improvement established by the ACR. Improvement of 20%, 50%, or 70% is required in both the number of tender and swollen joints to meet improvement criteria of "ACR 20, ACR 50, or ACR 70." By contrast, these levels of improvement are required for only 3 of the other 5 RA core data set measures (physician global estimate, ESR or CRP, patient self-report of physical function, pain, and patient global estimate) [49]. A patient whose score for pain may improves from, say, 8 to 0, but whose tender joint changed from 6 to 5, would not be regarded as improved by ACR Criteria.

Nonetheless, several limitations of the joint count have been described (Table 2) [16,50]. Joint counts are poorly reproducible in formal studies [51,52]. For example, in one study, interclass correlation coefficients for tender and swollen joint counts (SJCs) were found to be lower than seen for patient self-report questionnaire scores and laboratory tests [52]. Poor reliability has led to a requirement in clinical trials and other clinical research studies in RA that a joint count must be performed by the same observer at each assessment, which is not characteristic of a robust clinical measure such as blood pressure or temperature. This requirement limits possible collaborative care between rheumatologists and family practitioners and/or other health professionals to incorporate quantitative data into clinical decisions for patient management.

In clinical trials, joint count measures are at least as likely to improve with placebo treatment as the other 5 RA Core Data Set measures [53,54] (Table 2). The relative efficiencies of tender joint counts (TJCs) to document differences between active and control treatments are lower than physician and patient global estimates and patient self-report scores for physical function and pain, although relative efficiencies of SJCs are more similar to those of these other RA Core Data Set measures [55]. Counts of tender and swollen joints generally improve over 5 years while joint damage and functional disability may progress [56]. Joint examinations and joint counts are not as sensitive to detect synovitis and other signs of inflammatory activity as ultrasound or MRI [16,57].

Most visits to a rheumatologist include a careful joint examination, but not a formal joint count, despite emphasis on this practice in the rheumatology literature and at meetings over half a century [58]. It is critical in clinical decisions to recognize whether a patient might have 1 versus 11 swollen joints or 2 versus 12 swollen joints. However, the difference between 1 versus 2 or 11 versus 12 swollen joints is of relatively little consequence.

Assessment of 1 versus 11 or 2 versus 12 swollen joints can be accomplished in fewer than 10 seconds, while assessment of 1 versus 2 or 11 versus 12 swollen joints requires at least 90 seconds [60]. A careful joint examination is always required at each visit of an RA patient to monitor clinical status. However, a formal joint count may not be essential, particularly when quantitative data concerning clinical status are available from an MDHAQ/RAPID3 (routine assessment of patient index data 3) along with a careful joint examination, which may be more feasible in routine clinical care.

4) Some limitations of clinical trials in RA

The randomized controlled clinical trial mimics a laboratory experiment according to a "biomedical model" as a "gold standard" to recognize possible differences between the efficacy of a therapy compared to another therapy or a placebo [61]. However, clinical trials have many limitations, as summarized in earlier reports by several observers, including the senior author (Table 2) [14,19-24]. These limitations may be classified as "pragmatic," which might be overcome by broader and more inclusive trial designs, or "intrinsic" to the clinical trial methodology, as seen with any method, which cannot be overcome even by the best design (Table 2).

One important pragmatic limitation of RA clinical trials is a relatively short time frame, which may prevent recognition of long-term clinical advantages of some agents over time, and/or conversely, loss of efficacy of other agents over time. For example, a randomized controlled clinical trial in RA over 48 weeks indicated no significant differences in efficacy of 3 regimens, methotrexate monotherapy, auranofin (oral gold) monotherapy, and a combination of methotrexate and auranofin [62]. Furthermore, a meta-analysis of 117 treatment groups in 66 clinical trials reported in 1990, indicated no significant differences between 4 disease-modifying anti-rheumatic drugs

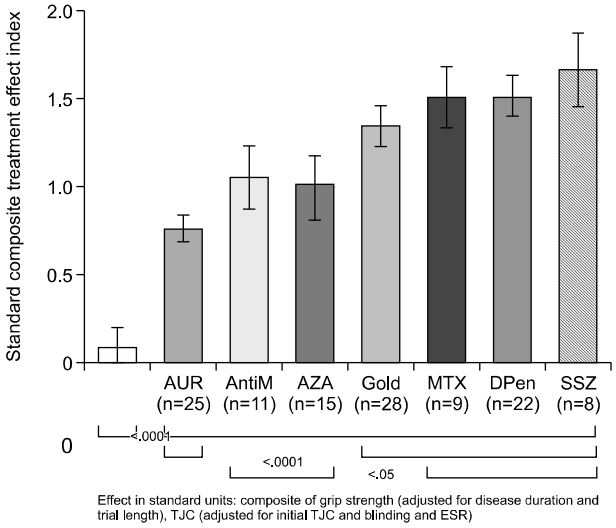


Figure 1. Standard composite treatment effect (in standard units). Meta-analysis of 66 clinical trials reported in 1990 concerning the efficacy of DMARDs in the treatment of RA [91]. This meta-analysis included 117 treatment groups: 11 for antimalarial drugs (e.g., hydroxychloroquine), 23 for auranofin, 29 for injectable gold, 7 for methotrexate, 19 for d-penicillamine, 6 for sulfasalazine, and 22 for placebo. All drugs have greater efficacy than placebo in the management of RA, determined according to a composite of grip strength (a measure of effectiveness of grip), TJC, and ESR, adjusted for disease duration, trial length, initial tender joint count, and blinding. In these analyses, no significant differences were seen between sulfasalazine, d-penicillamine, methotrexate, and injectable gold (From Felson et al. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum 1990;33:1449-61; with permission) [63]. DMARDs: disease-modifying anti-rheumatic drugs, RA: rheumatoid arthritis, TJC: tender joint count, AUR: auranofin, AntiM: antimalarial drug, AZA: azathioprine, MTX: methotrexate, DPen: d-penicillamine, SSZ: sulfasalazine, ESR: erythrocyte sedimentation rate.

(DMARDs), sulfasalazine, d-penicillamine, methotrexate, and injectable gold (Figure 1) [63].

The short-term clinical trial and meta-analysis results did not appear consistent with actual clinical experience, in which methotrexate appeared far more effective than other DMARDs. Therefore, analyses were performed on an early multi-center database of 7 rheumatology practices in which MDHAQ data were collected every 3 months over 10 years between 1985 and 1995 for duration of treatment courses of various DMARDs (onset of treatment was studied in 1990, and medical records were searched for earlier DMARD courses) [64]. Duration of treatment courses may be regarded as a surrogate composite measure of long-term effectiveness and safety of an agent.

Estimated duration of continuation of 1,083 courses of 6 DMARDs over 60 months in 477 RA patients at 2 years was approximately 80% for methotrexate, compared to 50% for hydroxychloroquine, penicillamine, parenteral gold, and azathioprine and only 20% for courses of oral gold (Figure 2A) [64]. After 5 years, approximately 60% of the methotrexate courses were continued, versus approximately 20% of the hydroxychloroquine, penicillamine, parenteral gold, and azathioprine courses, and virtually no course of oral gold (Figure 2A) [64]. However, when data were analyzed in a subset of patients only of 447 initial DMARD courses over only 1 year, conditions that mimic clinical trials (Figure 2B), continuation rates of courses of all 6 DMARDs were similar, including no difference between methotrexate versus parenteral versus oral gold (auranofin) [64].

The absence of statistically significant differences between DMARD courses over 1 year (Figure 2B), mimics results of clinical trials in Figure 1, but differs considerably from results seen in actual clinical care over 5 years (Figure 2A). Therefore, results of both the meta-analysis of clinical trials in Figure 1 and the observational multicenter study in Figure 2A are accurate and "correct," despite apparently discrepant findings. However, accurate data in the meta-analysis were not translated into long-term clinical care over 5 years, and the clinical trials results were not applicable to routine clinical care.

These analyses of differences in rates of DMARD continuation in routine care compared to clinical trials have been confirmed and extended to recognize that among RA patients treated after 1990, 79% of methotrexate courses were continued over 5 years [65]. Nonetheless, the medical literature continues to emphasize data from clinical trials almost exclusively as "evidence-based medicine" [61], while ignoring possibly contradictory observational data from routine clinical care. For example, a "systematic review" of DMARDs reported in 2008 concluded that there was "moderate evidence that sulfasalazine, leflunomide, and methotrexate were equivalent in efficacy, with no obvious major differences in adverse events and discontinuation rates among these three DMARDs" [66]. This report was based on data only from clinical trials, and ignored all reports from actual clinical care, including a 2007 report concerning an international database of 4,363 patients from 48 sites in 15 countries indicated that 83% had taken methotrexate, 43% sulfasalazine, and 21% leflunomide [67].

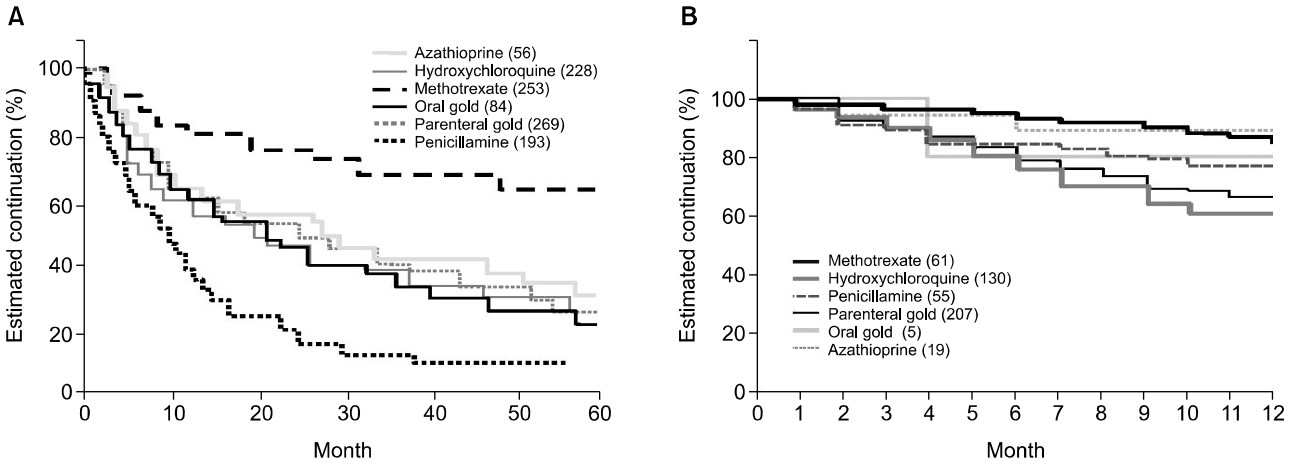


Figure 2. (A) Estimated continuation of all 1,083 courses of second line therapies in 532 patients with rheumatoid arthritis over 60 months. Differences between methotrexate and all other drugs, as well as between oral gold (auranofin) and all other drugs, are statistically significant ($p < 0.001$), while differences among other drugs are not significant. (B) Estimated continuation of 477 courses of the initial second line therapy used in the same 532 patients over 12 months. Differences between methotrexate versus oral gold (auranofin) are not statistically significant, and are considerably less apparent than in (A), in which estimated continuation was studied for all courses over 60 months (Pincus et al. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885-94) [64].

Differences between results of treatment with various medications in clinical trials and routine clinical care also reflect other pragmatic limitations of clinical trials (Table 2): Inclusion and exclusion criteria may restrict eligibility of patients with RA (or many other diagnoses) to fewer than 10% of all patients [68,69]. Surrogate markers such as SJCs or laboratory tests may not be optimally prognostic of long-term outcomes. Differences between a medication and a placebo that are statistically significant may indicate only marginal clinical significance. By contrast, clinically important differences may not be statistically significant due to insufficient numbers of patients for statistical power. Inflexible dosage schedules and restriction of concomitant medications do not represent the usual clinical pathways of patients in routine care. Important variables affecting outcomes other than whether a patient was randomized to a medication versus another medication or placebo, such as socioeconomic status [70] may be seen, but usually are ignored in reporting of the clinical trial. Finally, rare side effects cannot be identified in most trials, as discussed in greater detail elsewhere (Table 2) [71].

In addition to the pragmatic limitations discussed above, some limitations of clinical trials are intrinsic to the methodology, just as limitations exist to any scientific method (Table 2). The design of a trial may strongly influence results in favor or against a particular conclusion; a "control group" reduces, but does not eliminate, all sources of bias. For example, a simple clinical trial to compare a new medication versus placebo in a given condition is much more likely to be successful in patients who have no previous treatment for the condition than in patients who have "failed" two previous standard treatments. While the design cannot preordain results, it can greatly increase the probability that an intervention will or will not appear to be more efficacious than a placebo or control treatment (Table 2) [71].

Another intrinsic limitation of clinical trials is that data are reported in groups and generally ignore individual variation, while individual variation in responses to different therapies is characteristic of patients with RA and most diseases. Among patients randomized to 2 therapies, some individuals may have good responses to the therapy that is less-favored by the group, while other patients may have poor responses to the more-favored therapy. Furthermore, interpretation of adverse effects is not standardized, and depends on individual assessment of risks and benefits of any treatment, which may differ widely. Finally, the format of a clinical trial may affect a "placebo effect", in informing patients that they may receive one of two or more treatments, rather than the "best" treatment [71].

These observations suggest caution in interpretation of data from clinical trials to guide routine care

[14,19-24,71]. The Oxford Centre for evidence-based medicine noted in 2011 that: "While they are simple and easy to use, early hierarchies that placed randomized trials categorically above observational studies were criticized for being simplistic. In some cases, observational studies give us the 'best' evidence. For example, there is a growing recognition that observational studies–even case-series and anecdotes can sometimes provide definitive evidence" [72].

A complementary "biopsychosocial model" to overcome some limitations of a biomedical model

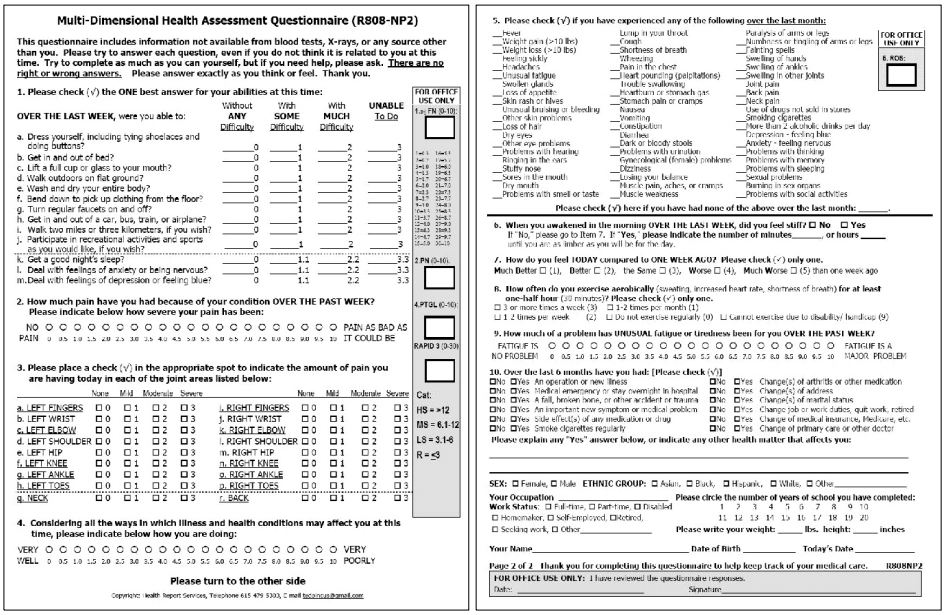
A "biopsychosocial model" provides a complementary view of health and disease to a biomedical model (Table 1) [1,5]. In a biopsychosocial model, disease etiology and severity are regarded as multifactorial, resulting from external pathogens, toxins, host genes, dysregulatory processes, psycho-socio-economic variables, behaviors, and social support, rather than a "reductionist" single "cause." Mind and body are not independent in development, course, and outcomes of disease, particularly chronic diseases. A biopsychosocial model proposes that health and disease outcomes are determined as much by actions of individual patients as by actions of health professionals.

Patient medical history data depicted as quantitative scores on standard patient questionnaires as the foundation for a "scientific," evidence-based biopsychosocial model

Even in traditional medical care conducted according to a biomedical model, a patient history is recognized as contributing substantially to diagnosis, management, prognosis, and assessment of outcomes [26,73-76]. In a biopsychosocial model, the importance of a patient medical history is recognized and regarded as having equal or greater importance compared to laboratory tests and other high technology data.

The experience of most physicians with patient questionnaires involves usage in clinical trials and other clinical research activities, or as "intake" questionnaires to capture medical history and demographic data at initial visits of new patients. Patient questionnaires for clinical trials and most clinical research may be long, and are not designed to have any impact on clinical care. Indeed, the study protocol directs that the questionnaire data be forwarded to a data center, without review at the clinical site. Intake questionnaires are not standardized, and most patients generally complete different versions of such questionnaires at different doctor's offices.

In recent years, it has become recognized that patient self-report questionnaires allow elements of a patient medical history to be collected as quantitative, standard "protocol-driven" information. Patient questionnaire scores may meet criteria for "scientific" data, analogous to laboratory tests, rather than as "subjective," non-quan-



Multi-Dimensional Health Assessment Questionnaire (R808-NP2)

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. Try to complete as much as you can yourself, but if you need help, please ask. There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

1. Please check (√) the ONE best answer for your abilities at this time:

OVER THE LAST WEEK, were you able to:	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
a. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
b. Get in and out of bed?	0	1	2	3
c. Lift a full cup or glass to your mouth?	0	1	2	3
d. Walk outdoors on flat ground?	0	1	2	3
e. Wash and dry your entire body?	0	1	2	3
f. Bend down to pick up clothing from the floor?	0	1	2	3
g. Turn regular faucets on and off?	0	1	2	3
h. Get in and out of a car, bus, train, or airplane?	0	1	2	3
i. Walk two miles or three kilometers, if you wish?	0	1	2	3
j. Participate in recreational activities and sports as you would like, if you wish?	0	1	2	3
k. Get a good night's sleep?	0	1.1	2.2	3.3
l. Deal with feelings of anxiety or being nervous?	0	1.1	2.2	3.3
m. Deal with feelings of depression or feeling blue?	0	1.1	2.2	3.3

FOR OFFICE USE ONLY
I.a. FN (0-10):
2.PN (0-60):
4.PTGL (0-10):
RAPID 3 (0-30):
Cat:
HS = >12
MS = 6.1-12
LS = 3.1-6
R = ≤3

2. How much pain have you had because of your condition OVER THE PAST WEEK? Please indicate below how severe your pain has been:

NO PAIN 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 PAIN AS BAD AS IT COULD BE

3. Please place a check (√) in the appropriate spot to indicate the amount of pain you are having today in each of the joint areas listed below:

	None	Mild	Moderate	Severe		None	Mild	Moderate	Severe
a. LEFT FINGERS	0	1	2	3	i. RIGHT FINGERS	0	1	2	3
b. LEFT WRIST	0	1	2	3	j. RIGHT WRIST	0	1	2	3
c. LEFT ELBOW	0	1	2	3	k. RIGHT ELBOW	0	1	2	3
d. LEFT SHOULDER	0	1	2	3	l. RIGHT SHOULDER	0	1	2	3
e. LEFT HIP	0	1	2	3	m. RIGHT HIP	0	1	2	3
f. LEFT KNEE	0	1	2	3	n. RIGHT KNEE	0	1	2	3
g. LEFT ANKLE	0	1	2	3	o. RIGHT ANKLE	0	1	2	3
h. LEFT TOES	0	1	2	3	p. RIGHT TOES	0	1	2	3
q. NECK	0	1	2	3	r. BACK	0	1	2	3

4. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

VERY WELL 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 VERY POORLY

Please turn to the other side

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5. Please check (√) if you have experienced any of the following over the last month:

Fever	Lump in your throat	Paralysis of arms or legs
Weight gain (>10 lbs)	Cough	Numbness or tingling of arms or legs
Weight loss (>10 lbs)	Shortness of breath	Fainting spells
Feeling sickly	Wheezing	Swelling of hands
Headaches	Pain in the chest	Swelling of ankles
Unusual fatigue	Heart pounding (palpitations)	Swelling in other joints
Swollen glands	Trouble swallowing	Joint pain
Loss of appetite	Heartburn or stomach gas	Back pain
Skin rash or hives	Stomach pain or cramps	Neck pain
Unusual bruising or bleeding	Nausea	Use of drugs not sold in stores
Other skin problems	Vomiting	Smoking cigarettes
Loss of hair	Constipation	More than 2 alcoholic drinks per day
Dry eyes	Diarrhea	Depression - feeling blue
Other eye problems	Dark or bloody stools	Anxiety - feeling nervous
Problems with hearing	Problems with urination	Problems with thinking
Ringing in the ears	Gynecological (female) problems	Problems with memory
Stuffy nose	Dizziness	Problems with sleeping
Sores in the mouth	Loosing your balance	Sexual problems
Dry mouth	Numbness, aches, or cramps	Rashes in sex organs
Problems with smell or taste	Muscle weakness	Problems with social activities

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8. KOS:

Please check (√) here if you have had none of the above over the last month: _____.

6. When you awakened in the morning OVER THE LAST WEEK, did you feel stiff? ☐ No ☐ Yes
If "No," please go to Item 7. If "Yes," please indicate the number of minutes_____, or hours ____

7. How do you feel TODAY compared to ONE WEEK AGO? Please check (√) only one.
Much Better ☐ (1), Better ☐ (2), the Same ☐ (3), Worse ☐ (4), Much Worse ☐ (5) than one week ago

8. How often do you exercise aerobically (swatting, increased heart rate, shortness of breath) for at least one-half hour (30 minutes)? Please check (√) only one.
☐ 3 or more times a week (3) ☐ 1-2 times per month (1)
☐ 1-2 times per week (2) ☐ Do not exercise regularly (0) ☐ Cannot exercise due to disability/ handicap (9)

9. How much of a problem has UNUSUAL fatigue or tiredness been for you OVER THE PAST WEEK?
FATIGUE IS NO PROBLEM 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 FATIGUE IS A MAJOR PROBLEM

10. Over the last 6 months have you had: [Please check (√)]

☐No ☐Yes	An operation or new illness	☐No ☐Yes	Change[s] of arthritis or other medication
☐No ☐Yes	Medical emergency or stay overnight in hospital	☐No ☐Yes	Change[s] of address
☐No ☐Yes	A fall, broken bone, or other accident or trauma	☐No ☐Yes	Change[s] of marital status
☐No ☐Yes	An important new symptom or medical problem	☐No ☐Yes	Change job or work duties, quit work, retired
☐No ☐Yes	Side effect(s) of any medication or drug	☐No ☐Yes	Change of medical insurance, Medicare, etc.
☐No ☐Yes	Smoke cigarettes regularly	☐No ☐Yes	Change of primary care or other doctor

Please explain any "Yes" answer below, or indicate any other health matter that affects you:

SEX: ☐ Female, ☐ Male ETHNIC GROUP: ☐ Asian, ☐ Black, ☐ Hispanic, ☐ White, ☐ Other_____

Your Occupation _____ Please circle the number of years of school you have completed:
Work Status: ☐ Full-time, ☐ Part-time, ☐ Disabled 1 2 3 4 5 6 7 8 9 10
☐ Homemaker, ☐ Self-employed, ☐Retired, 11 12 13 14 15 16 17 18 19 20
☐ Seeking work, ☐ Other_____ Please write your weight: _____ lbs. height: _____ inches

Your Name_____ Date of Birth _____ Today's Date _____

Page 2 of 2 Thank you for completing this questionnaire to help keep track of your medical care. R808NP2

FOR OFFICE USE ONLY: I have reviewed the questionnaire responses.
Date: _____ Signature_____

Figure 3. The multi-dimensional health assessment questionnaire (MDHAQ). (From Pincus et al. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol 2008;35:2136-47) [83].

titative, narrative descriptions. Tools for collecting patient history information as quantitative data include the health assessment questionnaire (HAQ) [77] and a multidimensional HAQ (MDHAQ) [78,79].

The MDHAQ compared to the HAQ

Both the HAQ [77] and MDHAQ (Figure 3) [78,79] are simple 1-page, 2-sided questionnaires which depict physical function, pain and patient global estimate as quantitative scores rather than as narrative descriptions. These scores are the 3 patient self-report measures among the 7 measures in the RA core data set [80]. Both questionnaires (Table 3) are completed by a patient in 5～10 minutes, and both have templates for quantitative scores.

The MDHAQ includes 10 activities, 8 verbatim from the HAQ (1 from each of the 8 HAQ categories), and 2 additional complex activities, added in the 1990s, as many patients had scores of "zero" on the HAQ, suggesting "normal" physical function, despite reporting ongoing limitations to perform more difficult physical activities [78]. The visual analog scales (VAS) for pain and patient global estimate on the MDHAQ are in a 21-circle format, rather than a 10-cm line as on the HAQ (Figure 3) [81], which facilitates scoring for patients, doctors and staff (Table 3).

RAPID3 is an index of only the 3 RA Core Data Set patient self-report measures of physical function, pain and patient global estimate [82,83]. RAPID3 is calculated easily on the MDHAQ, using a scoring template for physical function (FN) to convert the sum of ten 0～3 scores (range, 0～30) to a 0～10 physical function score through division by 3, and small boxes for recording the FN score, and VAS scores for pain (PN) and patient global estimate of status (PATGL) (each scored 0～10). The sum of these three variables is the composite RAPID3 score (0～30).

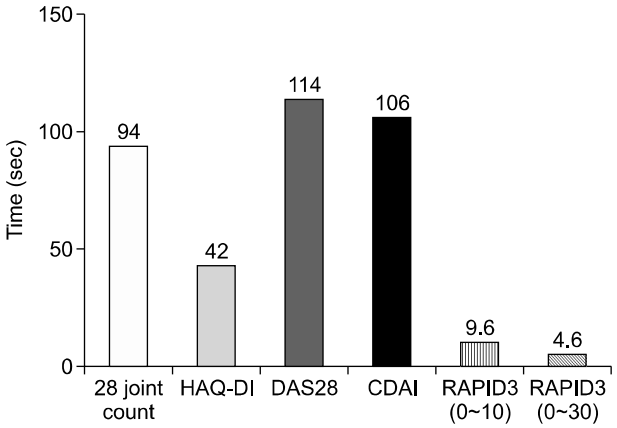

Figure 4. Time to score various rheumatoid arthritis indices in seconds, including 28 joint count, health assessment questionnaire-disability index (HAQ-DI), disease activity score 28 (DAS28), clinical disease activity index (CDAI), routine assessment of patient index data (RAPID3) scores 0～10, RAPID3 scored 0～30 (Pincus 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) [60].

Table 3. Comparison of HAQ and MDHAQ

Variable	HAQ	MDHAQ
First report	1980	1999
Patient completion	5～10 minutes	5～10 minutes
Number of activities of daily living	20	10
Pain VAS	10 cm line	21 circles
Patient global VAS	10 cm line	21 circles
Fatigue	No	21 circles
Psychological variables: sleep, anxiety, depression	No	3-HAQ format
Review of systems	No	60 symptoms
Medical history	No	Yes
Demographic data	No	Yes
Social history	No	Yes
Scoring templates	No	Yes
MD scan ("eyeball")	30 seconds	5 seconds
Time to score	41.8 seconds	4.5 seconds
Time to score index of 3 measures	Not available	9.5 seconds

HAQ: health assessment questionnaire, MDHAQ: multidimensional health assessment questionnaire, VAS: visual analog scales, MD scan: Time for physician to scan questionnaire.

RAPID3 on an MDHAQ requires about 5 seconds to score, compared to 42 seconds for the HAQ, and almost 2 minutes for a DAS28 or CDAI (Figure 4) [60].

Four categories of RAPID3 scores—for high, moderate, low disease severity, and remission in RA—are correlated significantly with similar categories using DAS28 and CDAI [60,83,84]. Thus RAPID3 can be useful in implementing a treat-to-target strategy in usual clinical care, analogous to DAS28 [46] or CDAI [47] while offering a number of pragmatic advantages over the other indices [8,85].

The MDHAQ includes 3 psychological items concerning sleep quality, anxiety and depression in the patient-friendly HAQ format (Table 3, Figure 3); the depression query is correlated significantly with the Beck Depression inventory [78], and provides a useful screening query. Also included is a rheumatoid arthritis disease activity index (RADAI) self-report joint count [52], which is correlated significantly with TJC (r=0.55) and SJC (r=0.42), in the same range as ESR with CRP (r=0.50) [60].

The MDHAQ includes a 60 symptom checklist (Table 3, Figure 3), introduced initially to serve as a review of systems, which provides a useful screen for non-inflammatory problems of distress, such as fibromyalgia or depression, in patients who check more than 16～20 of 60 symptoms. This finding may be particularly helpful in patients who may also meet formal criteria for RA, systemic lupus erythematosus (SLE) osteoarthritis (OA) or other rheumatic disease, and have secondary fibromyalgia [86,87], which may affect negatively responses to therapy.

The MDHAQ includes a 0～10 VAS for fatigue, regarded by many patients as a prominent problem affecting their RA status [88]. A query concerning the frequency of exercise also is included; limited exercise is as significant as smoking in the prognosis of 5-year mortality in normal older individuals [89].

The patient also records responses to 12 queries concerning recent medical history (Table 3, Figure 3)—surgeries, illnesses, hospitalization, new medications, adverse effects of medications, etc. At most visits, responses to these queries are all "No", which saves a physician at least 2 minutes. If a response is "Yes", that information should be known at the visit. Finally, demographic data, including date of birth, gender, ethnic group, marital status, occupation, and formal education level are queried, so a database can be developed directly from the questionnaire.

A 4-page MDHAQ is designed as a standard new patient intake questionnaire. The first 2 pages are the 2-page MDHAQ, summarized above, to provide quantitative scientific scores to help guide clinical decisions. The 3rd page contains a traditional "past history," including illnesses, hospitalizations, surgeries, allergies, family history, and medications, for entry into a medical database. The 4th page includes a review of medications, and consents for the patient to be monitored periodically (every 3, 6 or 12 months), even if they do not return to the same clinical setting, as well as for her/his data to be shared with colleagues of the patient's physician for medical research. Most settings have used a 2-page MDHAQ for both new and "return" patients, , without the contents of the 3rd and 4th pages, although these pages can be developed into a report for a medical record which has saved the senior author about 10～15 minutes for each new patient encounter. The 2 page MDHAQ is found on 2 sides of a single sheet of paper, similar to the original HAQ, from which it was derived.

Historically, a pencil and paper version of the MDHAQ has been completed by the patient in the waiting area after registration at the reception desk [90]. It was recognized that completion in the waiting area helps prepare the patient for the visit, improve doctor-patient communication, and save time for both doctor and patient [8]. An electronic MDHAQ version is now available. In some circumstances, it may be advantageous for the patient to complete an electronic version at home the day before the visit.

The MDHAQ allows a health professional to review information in 5～10 seconds that otherwise would require 10～15 minutes of conversation. Nonetheless, self-report of medical history information always requires interpretation by a knowledgeable health professional, as is the case with a laboratory test such as ESR or CRP, or ancillary study such as ultrasound or biopsy report.

Patient questionnaire data which support a biopsychosocial model concerning prognosis, course and outcomes of RA

Several differences from a strict biomedical approach are seen in use of patient questionnaires to provide quantitative evidence in support a biopsychosocial model:

1. Recognition of the importance of clinical variables, comparable to laboratory tests and imaging, in clinical decisions for the diagnosis and management of RA. As not-

ed above, a survey of 313 physicians, 154 rheumatologists and 159 non-rheumatologists indicated that a medical history and physical examination data are far more prominent in diagnosis and management decisions in RA than laboratory tests or ancillary studies, in contrast to 7 other prevalent chronic diseases dominated by vital signs (e.g., hypertension), laboratory tests (e.g., diabetes), or ancillary studies (e.g., ulcerative colitis) [26]. RA was the only one of the 8 chronic conditions in which a patient history and physical examination data accounted for more than 50% of the information required for diagnosis and management [26].

2. A need for uniform databases [91], such as the RA Core data set [92], which has advanced therapy and patient monitoring. Prior to the 1990s, clinical trials in RA were conducted according to a variety of measures, ranging from laboratory tests to grip strength, walking time, and various versions of a joint count. A core data set of 7 measures was a major advance to standardize clinical trials as well as clinical care in RA [80]. The 7 variables include 3 from a health professional - SJC, TJC, and physician estimate of global status (DOCGL); 3 from patient self-report - physical FN, PN, PATGL; and only a single laboratory test, ESR or CRP. The three most prominent indices used at this time are the DAS28 [45,46], CDAI [47], and RAPID3 [60].

3. The value of a consecutive patient database to provide complementary evidence concerning results of treatment and outcomes of chronic diseases to clinical trial data [93]. A primary reason for a need for clinical trials emerged from much clinical literature prior to about 1980, which included primarily selected patients, often with biased results. However, patients in clinical trials are highly selected—generally fewer than 20% of RA patients meet eligibility criteria, often far fewer [67,68,94]. A consecutive patient database can overcome limits of selection for clinical trials and in clinical care [93].

4. Recognition that "discovery science" [95] using long-term databases may in some instances be more informative than hypothesis-driven science. The term "discovery science" has been applied to recent molecular biology studies, e.g., large databases to analyze the human genome [96].

The "scientific" value of patient questionnaires to support a biopsychosocial model

Some examples of the "scientific" value of patient questionnaires to support a biopsychosocial model concerning prognosis, course and outcomes of RA, and to complement a biomedical model (Table 4) are summarized below:

Table 4. Value of patient questionnaire data to overcome limitations of biomedical model approach in prognosis and monitoring of RA

1. Physical function scores on MDHAQ and other questionnaires are far more significant than radiographs or laboratory tests in the prognosis of severe outcomes in RA, including work disability, costs, joint replacement surgery and premature death [33-35]
2. Formal education level, a surrogate for patient actions in disease, are as significant in the prognosis of mortality and more significant than age or duration of disease in RA status [101-105]
3. Individual patient self-report measures of physical function, pain, and patient global estimate of status, and RAPID3, are as efficient as joint counts, laboratory tests to distinguish active from control treatments in clinical trials [54,55,106]
4. Patient questionnaire scores, including RAPID3, are correlated significantly with DAS28 and CDAI in clinical trials [82,107-109] and clinical care [60,83]
5. MDHAQ scores are more reproducible than formal joint counts by physicians [16,51,52,110-113]
6. Patient questionnaire scores are more likely to be abnormal at baseline [8] and to document incomplete response to methotrexate and initiation of biological agent in RA than laboratory tests [114]
7. Remission criteria based on RAPID3 are similar to ACR/EULAR Boolean and SDAI remission criteria [115]
8. RAPID3 is effective to document change in clinical status in all rheumatic diseases [116]
9. Continuation of courses of DMARDs is more accurately described by observational data from clinical care than by data from clinical trials [64]
10. A survey of rheumatologists and non-rheumatologists, indicated that a medical history is far more prominent in diagnosis and management decisions in RA than laboratory tests or ancillary studies, in contrast to other chronic diseases [26]

RA: rheumatoid arthritis, MDHAQ: multidimensional health assessment questionnaire, RAPID3: routine assessment of patient index data 3, DAS: disease activity score, CDAI: clinical disease activity index, ACR: American College of Rheumatology, EULAR: European League Against Rheumatism, SDAI: simplified disease activity index, DMARDs: disease-modifying anti-rheumatic drugs.

1) Physical function scores on a patient self-report questionnaire are more significant than laboratory tests, radiographs, or other high-technology data to predict mortality, work disability and other severe outcomes of RA

Physical function scores on a patient self-report questionnaire are more significant than laboratory tests or radiographs to predict most severe long-term outcomes of RA, including premature mortality [34,97-99], as well as work disability [33-37], costs of care [40,41], and joint replacement surgery [42]. Physical function scores allowed comparison of mortality in patients with RA to patients with Hodgkin's Disease or coronary artery disease in an RA cohort studied between 1973 and 1982 (Figure 5). Patients in the most severe categories, i.e., good physical function in <80% of activities, Stage IV Hodgkin's Disease, or 3 vessel coronary artery disease experienced 5-year survivals in the range of 50%. By contrast, less severely-affected patients, i.e., good physical function in >80% of activities, Stage I/II Hodgkin's Disease, and right coronary artery disease, experienced 80%~90% 5-year survival (Figure 5). As noted above, physical function and lack of exercise are more significant than smoking in the prognosis of 5-year mortality or survival in normal older individuals [89].

The significance of physical function scores to predict premature mortality in RA has been confirmed over the years, including a review of all 53 cohorts which included prognostic variables for RA mortality (Figure 6) [39]. Physical function scores are significant in all but one study, similar to comorbidities as the most robust prognostic variables for mortality in RA. An intermediate level of significance is seen for extra-articular disease, rheumatoid factor, and ESR, while joint counts and radiographs were least significant among the 53 reports (Figure 6). The only major RA outcome predicted at higher levels of significance than physical function by laboratory tests, including rheumatoid factor, elevated ESR, elevated CRP,

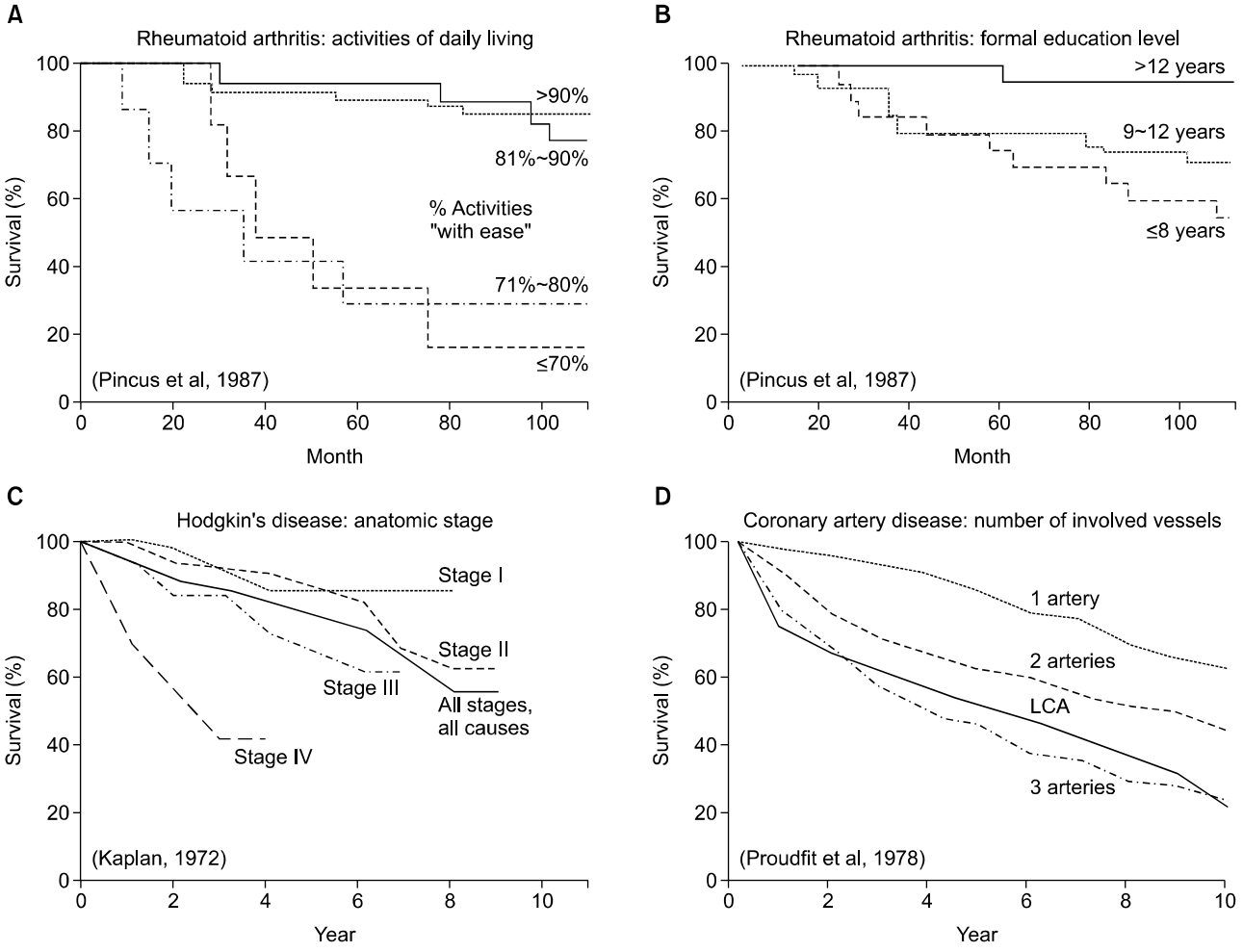

Figure 5. Nine to ten year survival according to quantitative markers in three chronic diseases, rheumatoid arthritis, Hodgkin's disease, coronary artery disease. Adapted from Figure 1 in the article of Pincus and Callahan (J Rheumatol 1986;13:841-5) [102].

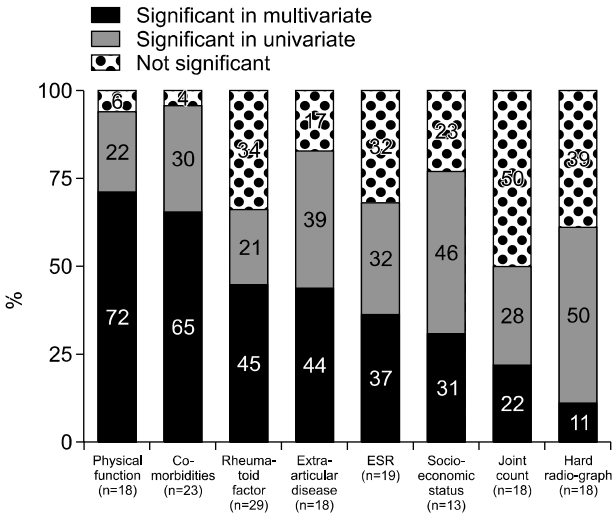

Figure 6. Significance of 8 variables as predictors of mortality, in a review of 84 reports concerning mortality in rheumatoid arthritis, 53 cohorts presented predictors of mortality. For each variable, n = the number of reports that included the variable, and bars indicate the percentage of those reports in which the variable was a significant predictor of mortality in multivariate analyses (black), in univariate analyses (dotted), or not significant (white). ESR: erythrocyte sedimentation rate. Adapted from Figure 2 in the article of Sokka et al. (Clin Exp Rheumatol 2008;26(5 Suppl 51):S35-61) [100].

the shared epitope of the major histocompatibility locus, is radiographic progression [32]. However, physical function scores on a patient questionnaire are far more significant than laboratory tests (or radiographic progression) in prognosis of other severe RA outcomes, including mortality [100].

2) Formal education level, a marker for socioeconomic status and patient's actions in health and disease, is significant in the incidence, prevalence, morbidity and mortality of RA

Formal education was identified as a significant predictor of mortality in RA initially in the same cohort in which physical function was most significant in prognosis of mortality (Figure 5B) [101,102]. Survival over nine years was about 95% in patients with more than 12 years of education, compared to about 80% in patients with 9～12 years of formal education, and 65% in patients with fewer than eight years of education (Figure 5B).

In this cohort studied between 1973 and 1982, declines in functional status were seen in almost all patients, and were substantially greater in patients with fewer than eight years of education than for patients with 9～12 years of education, which were in turn greater than those seen in patients with more than 12 years of formal education [101]. Overall, almost half of the patients with fewer than eight years of education died over the study period, while fewer than 10% had the best outcome of less than a 20% functional loss, in contrast to patients with more than 12 years of education, among whom half had less than 20% functional loss, and very few died. The association of poor outcome with low education level was explained only in small part by older age, non-Caucasian race, longer duration of disease, or any biomedical marker [101].

Associations between formal education levels and clinical status were seen in patients with RA according to all measures studied in a 1988 report [103]. Mean ESR was 48 for individuals with eight years or less of formal education, compared to 35 for high school graduates, and 29.3 for individuals with some college education, although college graduates had a higher level of 42. The TJC (on a 0～28 scale) was 16.3, 15, 9 and 10, in the four education categories, respectively; physical function scores (on a 0～3 scale) were 1.26, 1.04, 0.86 and 0.73; and pain scores (on a 0～10 scale) were 5.75, 5.85, 4.89 and 4.26. Patients with fewer than 11 years of education had at least a two-fold higher likelihood of having poor clinical status than those with 12 or more years of education for all measures studied [103].

Differences according to level of formal education were seen in scores for functional status and pain in patients with five different rheumatic diseases, RA, SLE, fibromyalgia, OA, and systemic sclerosis [104]. Differences in both physical function and pain scores according to education level were greater than according to age or duration of disease [104]. Similar observations of higher significance of formal education level than age, duration of disease, and sex in patient status have been reported recently from Korea [105].

Nonetheless, almost every clinical report includes the patients' mean age and duration of disease, but fewer than 20% include a measure of patient socioeconomic status—more than 30 years after reports indicating its importance. The MDHAQ facilitates collection of a patient's level of formal education as an important demographic variable, with no extra work on the part of a health professional or surrogate.

3) Patient self-report measures are as efficient as joint counts and laboratory tests to distinguish active from control treatments in clinical trials

Individual patient self-report measures of physical function, pain, and patient global estimate of status are as efficient as joint counts and laboratory tests to distinguish active from control treatments in clinical trials involving adalimumab [106], abatacept [82,84], certolizumab [107], and infliximab (Figure 7) [55]. Physician and patient global estimates tend to have the highest relative efficiencies, followed by SJC, physical function and pain on a patient questionnaire, while ESR or CRP and TJC are generally the least efficient among the seven core Data Set measures [55].

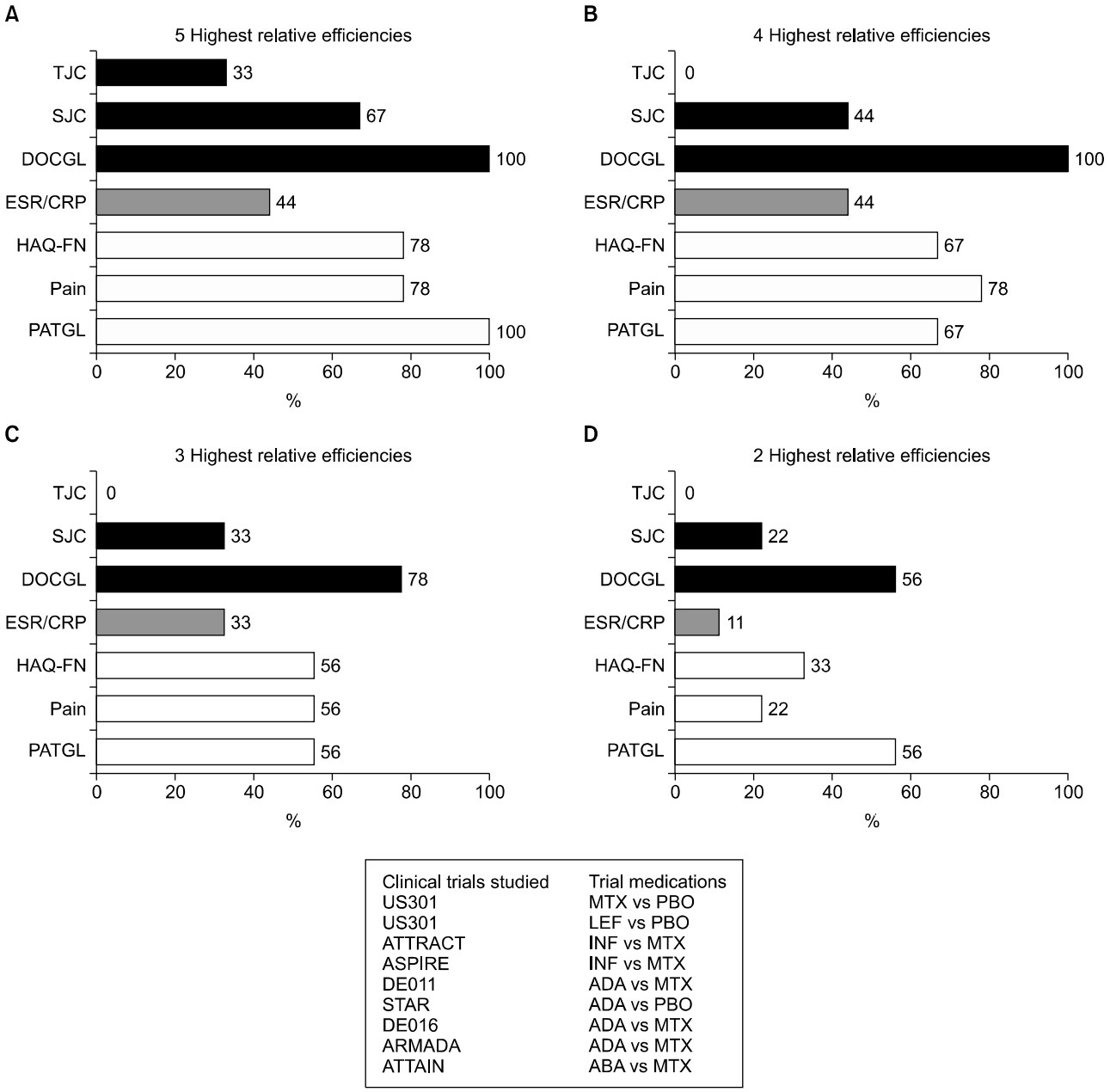

Figure 7. Relative efficiencies of 7 rheumatoid arthritis Core Data Set measures to distinguish active from control treatments in 9 clinical trials, involving methotrexate, leflunomide, placebo, infliximab, adalimumab, and abatacept according to arithmetic and percentage changes. TJC: tender joint count, SJC: swollen joint count, DOCGL: physician global assessment , ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, HAQ-FN: health assessment questionnaire- function, PATGL: patient global estimate of status, MTX: methotrexate, PBO: placebo, LEF: leflunomide, INF: infliximab, ADA: adalimumab, ABA: abatacept. Adapted from Figure 3 in the article of Pincus et al. (Clin Exp Rheumatol 2014;32 Suppl 85(5):S-47-54) [55].

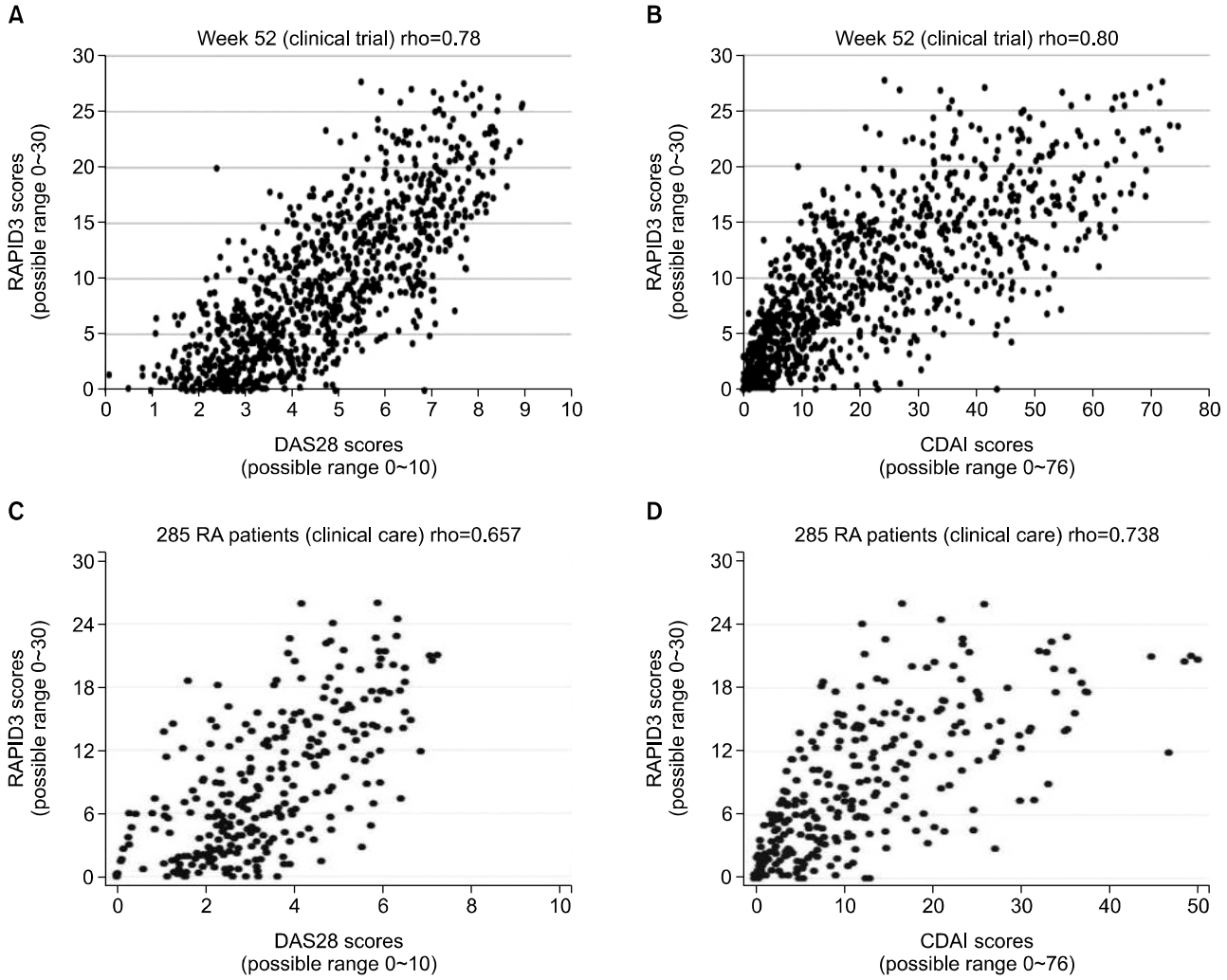

Figure 8. Spearman correlations of routine assessment of patient index data 3 (RAPID3) scores with (A, C) the disease activity score 28 (DAS28) and (B, D) clinical disease activity index (CDAI) in (A, B) the rheumatoid arthritis prevention of structural damage 1 (RAPID1) clinical trial of certolizumab pegol in 982 patients at 52 weeks and (C, D) in 285 patients with RA seen in usual clinical care. Adapted from (A, B) Figure 1 in the article of Pincus et al. (Arthritis Care Res (Hoboken) 2011;63:1142-9) [107] and (C, D) Figure 3 in the article of Pincus et al. (Bull NYU Hosp Jt Dis 2009;67:211-25) [90].

4) RAPID3 is correlated significantly with DAS28 and CDAI

RAPID3 is correlated significantly with DAS28 and CDAI in clinical trials [82,107-109] and clinical care (Figure 8) [60,90], including categories for high, moderate, low disease severity and remission [60,83,84,107]. RAPID3 gives similar results to DAS28 and CDAI to distinguish active from control treatments in clinical trials of leflunomide [108], methotrexate [108], adalimumab [109], abatacept [82] and certolizumab [107].

5) Patient questionnaire scores are more reproducible than formal joint counts

Patient questionnaire scores are more reproducible than formal joint counts [51,52,110-113] by physicians (Table 5). This phenomenon may be explained, in part, because a single observer (in this case the patient) is likely more consistent than 2 observers (a joint count has input from both doctor and patient) [113].

6) Patient questionnaire scores are more likely to be abnormal at baseline and to document incomplete response to methotrexate and initiation of biological agent in RA than laboratory tests

In clinical care, RAPID3 is more likely to be abnormal in new RA patients than laboratory tests [8]. Furthermore, RAPID3 and its components are more likely than ESR to document incomplete responses to methotrexate and ini-

tiation of a biological agent in RA (Table 6) [114]. ESR fell similarly by 33%～36% in 30 patients with "incomplete responses" to methotrexate, defined as initiation of subsequent biological therapy, and 63 patients with "adequate response," with no biological therapy over 5 years.

Table 5. Correlations and test-retest reliability of rheumatoid arthritis measures and indices at two time points

Measure/Index	Spearman rho	Interclass correlation coefficient
TJC28	0.76	0.83
SJC28	0.74	0.78
Physician global	0.69	0.79
Patient global	0.80	0.78
Function	0.98	0.96
Pain	0.83	0.88
ESR	0.84	0.95
CRP	0.71	0.97
DAS28	0.85	0.85
SDAI	0.87	0.88
CDAI	0.89	0.89
RAPID3	0.88	0.90
RADAI	0.89	0.92

TJC: tender joint count, SJC: swollen joint count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS: disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index, RAPID3: routine assessment of patient index data 3, RADAI: rheumatoid arthritis disease activity index.
From the article of Uhlig et al. Test-retest reliability of disease activity core set measures and indices in rheumatoid arthritis. Ann Rheum Dis 2009;68:972-5 [52].

By contrast, MDHAQ scores fell by 56%～79% over 2.6 years in adequate responders, but increased by 0%～31% in incomplete responders. Median RAPID3 fell from 10.6 to 3.6 (low severity=3.1～6, remission≤3) in adequate responders, and rose from 14.9 to 16.2 (high severity＞12) in incomplete responders. Therefore, RAPID3, but not ESR, recognized incomplete versus adequate methotrexate responses in usual clinical care, supporting a biopsychosocial model and somewhat contrary to a biomedical model.

7) RAPID3 criteria for remission in RA are similar to Boolean criteria and the simplified disease activity index

RAPID3 also provides criteria for remission in RA in the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort of patients who received usual care in France [115]. The prevalence of remission according to RAPID3 ≤3+ SJ≤1 (RAPID3 ≤3 and ≤1 swollen joint) was similar to ACR/EULAR Boolean criteria, simplified disease activity index (SDAI) , and CDAI, while the prevalence of remission according to RAPID3 and DAS28 was similar, but higher than for the more stringent indices (DAS), and 2 which do not require a formal joint count: using univariate and multivariate logistic regressions. Predictors of the 6 remission criteria, including 2 without a formal joint count, were younger age and better status according to Core Data Set clinical measures, but not the absence of rheumatoid factor, ACPA, abnormal CRP, or radiographic erosions [48]. Therefore, clinical measures according to a biopsychosocial model were more prognostic of remission than classical measures according to a

Table 6. Median levels of all patients for ESR, 3 (0～10) MDHAQ scores for physical function, pain and patient global estimate and composite RAPID3 scores at initiation of methotrexate 1996～2001 and mean of 2.6 years later in: A. 30 incomplete responders initiating biologic agent, B. 63 "control" adequate responders continuing methotrexate

Variable	A. 30 incomplete responders		B. 63 adequate responders ("controls")	
	MTX start	Biologic start	MTX start	Follow-up 6 2.6 years later (no biologic)
ESR (mm/hr)	28	18	24	16
MDHAQ-function (0～10)	3.2	3.3	2.3	1.0
Pain (0～10)	5.2	6.8	4.1	1.4
Patient global (0～10)	5.5	5.5	4.2	0.9
RAPID3 (0～30)	14.9	16.2	10.6	3.6

ESR: erythrocyte sedimentation rate, MDHAQ: multidimensional health assessment questionnaire, RAPID3: routine assessment of patient index data 3, MTX: methotrexate.
From the article of Pincus. RAPID3, an index of only 3 patient self-report core data set measures, but not ESR, recognizes incomplete responses to methotrexate in usual care of patients with rheumatoid arthritis. Bull Hosp Jt Dis 2013;71:117-20 [114].

Table 7. Rheumatic diseases in which routine assessment of patient index data 3 (RAPID3) has been reported to be informative about patient status and/or change in status

Rheumatic disease	Reference
Systemic lupus erythematosus	Askanase et al., 2011 [117] Castrejon et al., 2013 [116]
Osteoarthritis	Castrejon et al., 2013 [116]
Ankylosing spondylitis	Castrejon et al., 2013 [116] Danve et al., 2015 [118] Cinar et al., 2015 [119] Michelsen et al., 2015 [120] Park et al., 2015 [121]
Psoriatic arthritis	Castrejon et al., 2013 [116]
Gout	Castrejon et al., 2013 [116]
Vasculitis	Annapureddy et al., 2015 [122]
Fibromyalgia	Callahan et al., 1989 [104] DeWalt et al., 2004 [86] Pincus et al., 2009 [123]
Other	Castrejon et al., 2013 [116] Pincus et al., 2009 [123]

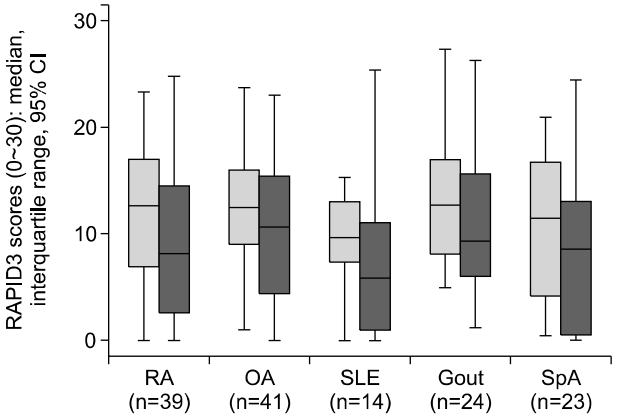

Figure 9. Improvement in routine assessment of patient index data 3 (RAPID3) scores over 2 months in patients with 5 rheumatic diseases, rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus (SLE), spondyloarthritis (SpA), gout. CI: confidence interval. Adapted from Figure 1 in the article of Castrejón et al. (J Clin Rheumatol 2013;19:169-74) [116].

biomedical model.

8) RAPID3 is informative to recognize change of patient status over time in many rheumatic diseases

MDHAQ/RAPID3 is informative to recognize change of patient status over time in many rheumatic diseases beyond RA (Table 7) [116]. In one study, RAPID3 scores were improved over 2 months by 27.5% in patients with RA, 16.8% in OA, 26.8% in SLE, 17.7% in spondyloarthropathies, and 26.4% in gout (Figure 9) [116]. RPID3 has been found useful in RA [116,117], OA [116], ankylosing spondylitis [116,118-121], psoriatic arthritis [116], gout [116], vasculitis [122] and others [116, 123]. These data again support the concept that patient self-report scores can be as "scientific" as laboratory tests.

CONCLUSION

Conclusion and possible future developments

This review describes some limitations of biomedical model data derived from 4 sources, laboratory tests, radiographs, joint counts, and clinical trials, and presents 8 lines of evidence illustrating the value of a biopsychosocial model informed by patient self-report questionnaires in RA:

1. Physical function scores on a patient self-report questionnaire are more significant than laboratory tests, radiographs, or other high-technology data to predict mortality, work disability and other severe outcomes of RA

2. Formal education level, a marker for socioeconomic status and patient's actions in health and disease, is significant in the incidence, prevalence, morbidity and mortality of RA

3. Patient self-report measures are as efficient as joint counts and laboratory tests to distinguish active from control treatments in clinical

4. RAPID3 is correlated significantly with DAS28 and CDAI

5. Patient questionnaire scores are more reproducible than formal joint counts

6. Patient questionnaire scores are more likely to be abnormal at baseline and to document incomplete response to methotrexate and initiation of biological agents in RA than laboratory tests

7. RAPID3 criteria for remission in RA are similar to Boolean criteria and the SDAI

8. RAPID3 is informative to recognize change of patient status over time in many rheumatic diseases

At present, patient reported data including HAQ and MDHAQ generally are collected on paper in most settings and then entered into different databases, either as discrete data elements or as scanned forms. Each database is constructed differently, with different names for variables, different coding, and general absence of standardization beyond the content of the questionnaire. However, optimal implementation of a "scientific" ap-

proach would suggest a need for standard database structure in addition to data content. The capacity to pool data for collaborative studies is limited, frequently time- consuming, and sometimes impossible (when scanning is the means of entry into the database), despite the fact that most of the information recorded is identical.

The next generation of medical information technology might incorporate standard formats of variable names, coding, and scoring of electronic entry and management of patient questionnaire data. Such measures could improve the capacity to compare, pool and study the data markedly. The introduction of a set of international standards for transfer of clinical and administrative data between software applications termed "health level 7" (HL7) is now mandated, and programs such as Substitutable Medical Applications and Reusable Technologies (SMART) on Fast Healthcare Interoperability Resources (FHIR) can allow exchange of electronic data with any electronic medical record (EMR). A standard Intake questionnaire for new patients could overcome manual or dictation entry of patient medical history information into an EMR, by a physician or assistant, saving time and improving accuracy. Standardization into a single format could take fuller advantage of the possibilities of information technology to advance medical care, and facilitate "scientific" recording of data from both biomedical model and biopsychosocial model paradigms.

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CONFLICT OF INTEREST

Dr. Pincus is president of Health Report Services, Inc., which holds a copyright and trademark for MDHAQ/ RAPID3, and receives royalties and license fees, all of which support further development of quantitative questionnaire measurement for patients and doctors in clinical rheumatology care.

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