Complexities in Assessment of Rheumatoid Arthritis: Absence of a Single Gold Standard Measure

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The clinical approach to rheumatic diseases differs considerably from the approach to typical chronic diseases in several important respects (**Box 1**). Further recognition of these differences may be informative in efforts to advance quantitative scientific patient assessment and management in rheumatic diseases, leading to improved patient outcomes.

ABSENCE OF A GOLD STANDARD IN RHEUMATIC DISEASES

Quantitative assessment and monitoring of typical chronic diseases, such as hypertension, diabetes, and osteoporosis, is characterized by a gold standard measure, such as blood pressure, hemoglobin A_{1c}, and bone density, to provide the primary information for diagnosis, assessment, prognosis, and monitoring for clinical decisions. Tight control according to this gold standard measure has been documented to result in better patient outcomes, including improved survival, largely, in many diseases. A patient history and physical examination are limited and often irrelevant

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Box 1
Differences of rheumatic diseases from typical chronic diseases

1. Absence of a single gold standard measure, such as blood pressure, creatinine, and so forth.
2. Laboratory tests are neither as sensitive nor specific as gold standard measures, and normal in >30% of patients, including rheumatoid factor, anti–cyclic citrullinated peptide antibodies, erythrocyte sedimentation rate, and C-reactive protein in rheumatoid arthritis, and anti-DNA, anti-Smith, and antiribonucleoprotein antibodies in systemic lupus erythematosus.
3. Diagnosis, management, classification criteria, and indices for management incorporate four types of information from a patient history, physical examination, laboratory tests, and imaging studies, rather than a single primary measure.
4. Information from a patient history is considerably more prominent in management decisions in rheumatic diseases than in typical chronic diseases, for which patient history and symptoms often are irrelevant, and can be captured as standardized, quantitative, scientific data using a validated patient self-report questionnaire.
5. Definitive diagnosis is based on physician's judgment rather than an objective marker.

to management decisions, which are based largely, if not entirely, on the gold standard measure.

Rheumatologists have attempted to implement a similar approach to patients with inflammatory rheumatic diseases for more than half a century. The discovery in the 1940s of rheumatoid factor[1,2] in rheumatoid arthritis (RA), and antinuclear antibodies (ANA)[3] in systemic lupus erythematosus (SLE), led to hopes that laboratory tests could be used effectively for diagnosis and management of all individual patients with RA, SLE, and other rheumatic diseases. Indeed, laboratory tests are included in assessment of virtually every patient suspected of having an inflammatory rheumatic disease by both primary care physicians and rheumatologists. As of 2009, however, no laboratory test or any other quantitative measure can serve as a gold standard for all individual patients with any rheumatic disease.

SENSITIVITY AND SPECIFICITY OF LABORATORY TESTS IN INFLAMMATORY RHEUMATIC DISEASES

Laboratory tests are abnormal in most patients who have RA or SLE, and are helpful in many patients. More than one third of patients with RA have at presentation, however, a normal erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and anti–cyclic citrullinated peptide antibodies (**Table 1**).[4–7] More than one third of patients with SLE have normal levels of anti-DNA antibodies, and ANA subset tests anti-Smith (anti-Sm) and antiribonucleoprotein (anti-RNP) (**Table 2**, **Fig. 1**).[8–10]

In addition to these false-negative results, ANA subsets indicate relatively little specificity for particular rheumatic diagnoses. For example, among a group of 150 patients with anti-Sm or anti-RNP antibodies, 64% of patients with anti-Sm and 51% of those with anti-RNP had a diagnosis of SLE (see **Table 2**). The percentages of patients with various other rheumatic and nonrheumatic diagnoses ranged from 1% to 12%, with little specificity (see **Table 2**).[8]

Information concerning autoantibodies and other biomarkers is invaluable in laboratory research to further characterize the pathogenesis, course, and outcomes of diseases, and to develop new therapies. Anti–tumor necrosis factor and other biologic