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SPECIAL ARTICLE

Cutting Edge Diagnostics in Rheumatology: The Role of Patients, Clinicians, and Laboratory Scientists in Optimizing the Use of Autoimmune Serology

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Introduction

Autoimmune serology has become a potentially powerful tool for experienced clinicians. However, it currently is not being used optimally due to lack of widely used standardized assays, local working conditions, traditions, different technology, cost constraints by medical insurers, and ability on the part of clinicians to correctly interpret the results of certain assays. New serologic technologies and assays are developed by laboratory scientists and the commercial industry at a very fast pace and may eventually lead to better reproducibility in confirming a diagnosis and estimating prognosis, ultimately improving the quality of clinical care. To achieve this goal, the accuracy of such testing must be demonstrated in studies involving sufficiently large patient populations before a new assay can be accepted for clinical use. In the past, there have been very few studies with a prospective, unbiased, multicenter design. Thus, the clinical accuracy of certain laboratory diagnostic studies is still unknown.

To be useful in a clinical day-to-day diagnostics setting, the differential diagnostic potential and performance characteristics of a test must be known so that clinical misinterpretation, false diagnoses, and potentially harmful treatment can be avoided. The degree to which an assay will give false-positive or false-negative results is important. To aid in developing a followup and therapeutic strategy in a given patient, the prognostic significance of identifying a certain autoantibody in a patient with clinical findings of an autoimmune disease should be known. Presence of autoantibodies indicating a poor prognosis in the clinical setting of early signs of disease should lead to appropriate followup and monitoring of risk manifestations. Such findings should also evoke early awareness of the potential need for effective treatment, before irreversible organ damage takes place. Factual knowledge about these matters necessitates close collaboration between patients, experienced and motivated clinicians, and laboratory scientists, as well as cooperation with the diagnostics industry. Once a diagnostic assay has been developed, standardized postmarketing surveillance and quality assurance by manufacturers and laboratories alike should be mandatory (1).

Clinical diagnostics

Many years of increasing clinical experience have led to the development of clinical criteria to support a given diagnosis (Table 1) (2–9). Because systemic rheumatic diseases frequently involve multiple organ systems, there is rarely a single pathognomonic criterion. Usually, multiple criteria must be fulfilled to confirm a particular diagnosis. As more criteria can be identified in a particular patient or group of patients, the greater the likelihood that a diagnosis or tentative classification of the disease is correct. The more knowledgeable the clinician is with regard to the clinical and laboratory characteristics of diseases, the greater the chance that a diagnosis is correct. Each of the diseases listed in Table 1 have clinical subgroups with somewhat dissimilar manifestations and, hence, prognosis. Interestingly, each of those subgroups is associated

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Table 1. Classification and diagnostic criteria for inflammatory rheumatic diseases and prognostic subgroups of these syndromes

Disease	Reference
Juvenile rheumatoid arthritis	2,15
Adult rheumatoid arthritis	14,20,62,63
Systemic lupus erythematosus	12,60,64
Systemic sclerosis	6,11,65
Polymyositis/dermatomyositis	10,66,67
Sjögren's syndrome	68–70
Mixed connective tissue disease	3,4,71
Small-vessel necrotizing vasculitides	5,7,8,57,58,72
Antiphospholipid syndrome	9

with different autoantibody profiles and specificities (10–15).

Serodiagnostics

In the laboratory, the technical aspects of autoimmune serology require diagnostic and differential diagnostic expertise akin to that needed in the complicated area of clinical medicine. Autoantibodies occurring in only 1 particular disease, which can thus be regarded as a disease-specific marker, tend to be rare (16). Autoantibodies that were previously assumed to relate specifically to 1 disease are now found to be associated with a variety of autoimmune diseases (17). Data related to certain autoantibodies and their disease specificities may rely on old technology and on studies published several decades ago. Presence of multiple disease-related autoantibodies occurring in a single serum (antibody profile) may be more indicative that a certain diagnosis is correct than the presence of a single antibody (16,18–20). Other laboratory findings, such as a polyclonal increase in immunoglobulins or depressed complement levels, may provide clues that a patient is likely to have a systemic rheumatic disease and stimulate a request for autoimmune serology.

New technologies commonly focus on achieving high diagnostic (nosographic) sensitivity and less on reaching high diagnostic specificity. Diagnostic specificity generally decreases when a high sensitivity for a certain assay is achieved. When a new test is introduced, clinicians may overlook the loss of diagnostic specificity and focus only on how sensitive the assay may be in predicting a disease state. New assays frequently are released before the ability of the assay to accurately predict a specific diagnosis is fully known. Pretesting sera from local control patients with inflammatory rheumatic diseases usually measures the predictive ability of any given assay. However, prototype sera can only be obtained from patients that have given informed consent and are willing to donate their blood for this purpose. This testing needs to be attended by close collaboration with experienced clinicians who strive for an accurate diagnosis. They must be willing to monitor and record the clinical manifestations of each patient selected to donate prototype serum so the individual patient can be classified into a prognostic subgroup (Table 1) (10–13). This testing is necessary to demonstrate that the diagnostic specificity of new assays does not suffer because of attempts to increase sensitivity.

A significant association of a certain autoantibody with a characteristic diagnostic subgroup or manifestation is likely to be a biologic "fingerprint" reflecting pathophysiologically important mechanisms or, perhaps, an etiopathogenetic event operating in a diseased tissue. Frequently, the close correlation between a certain disease manifestation and the associated autoantibody is closer than the correlation with a genetic marker (e.g., HLA type) or a particular histopathology pattern. It is extremely important that this close association not be blurred by arbitrarily increasing assay sensitivity to attain a 100% negative predictive value. For example, the association of anti–double-stranded DNA (anti-dsDNA) antibodies in systemic lupus erythematosus (SLE) patients and the risk of lupus nephritis has been documented in several publications (12,16,21). Although there continues to be some controversy about this association (22,23), the sensitivity versus specificity issue still exists. Assays giving positive results due to low-level and low-affinity anti-dsDNA antibodies fail to reveal this important clinical association (24). Such highly sensitive assays will also find low-affinity anti-dsDNA antibodies in other chronic inflammatory rheumatic diseases, illustrating their lack of specificity for SLE and lupus nephritis.

Sensitive assays may, however, become clinically useful if the cutoff value differentiating sera of SLE patients from sera of inflammatory disease controls is reset at an appropriate value to attain a 90–95% specificity for the diagnosis of SLE. When the cutoff value is reset, the frequency of anti-dsDNA antibodies in an SLE cohort of patients will align with the frequency of lupus nephritis, e.g., ~40–50%. Another possibility is to set 2 limits of positivity, a higher limit primarily for diagnostic use and a lower limit for separating healthy individuals from inflammatory disease controls and patients with inactive SLE (Figure 1). The gray area between the 2 limits can then be used for the followup of anti-dsDNA–positive SLE patients to monitor a serologic response to therapy or a recurrence of disease activity (21). A similar strategy is recommended for longi-

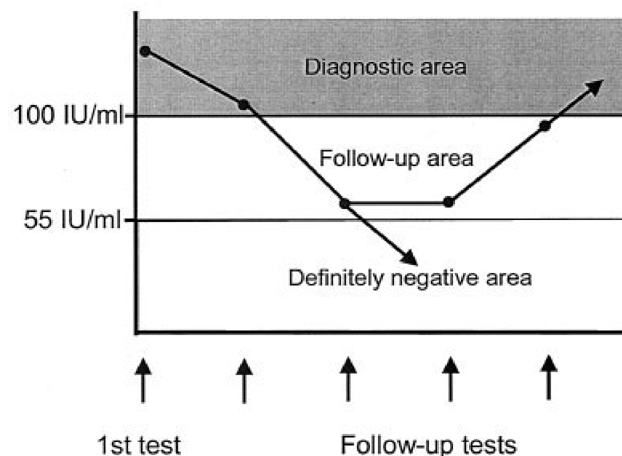

Figure 1. Example of cutoffs for diagnostic and followup purposes.

Table 2. Conditions in which neutrophil-specific autoantibodies are common

Rheumatoid arthritis
Felty's syndrome
Ulcerative colitis
Chronic active hepatitis
Sclerosing cholangitis
Systemic vasculitides (ANCA)*
Drug-induced lupus or vasculitis (ANCA)*

* ANCA = antineutrophil cytoplasmic antibodies.

tudinal studies in systemic vasculitis patients with associated antineutrophil cytoplasmic antibody (ANCA) (25).

As equipment becomes more sophisticated and assays gradually become more sensitive, the diagnostic specificity is lost and readjustment toward a higher specificity should be undertaken. For example, new recommendations were recently suggested regarding indirect immunofluorescence (IIF) testing for autoantibodies, particularly antinuclear antibodies (ANA), using HEp-2 cell substrates (26). For years, the cutoff for normal results was considered to be an ANA titer of 1:40. This multicenter international study revealed that 32% of normal individuals were positive at this titer. Thus, a titer of 1:160 was recommended as a more acceptable cutoff between normal and abnormal sera. Also, sera used as standards for a particular methodology need reevaluation from time to time, as exemplified by the reevaluation of Arthritis Foundation/Centers for Disease Control and Prevention reference sera for immunoblotting purposes (27).

In a routine clinical laboratory setting, a staged approach to serologic testing can be very productive. For example, when screening for anti-dsDNA antibody, the first step may be to use a sensitive enzyme-linked immunosorbent assay (ELISA). Then, if that test result is positive, assays that have high diagnostic specificity, such as the Farr or the *Crithidia luciliae* IIF assays, may be employed. The ELISA is easy to automate and thus less labor intensive, allowing manpower to be redeployed to the IIF test or the radiometric Farr test, which take more experience to interpret. It should be noted that only the IIF-positive (or Farr test-positive) results are reported as an anti-dsDNA positivity. For safety reasons, the use of the Farr test is declining, and several manufacturers do not produce such kits anymore. Hence, another assay that can reveal intermediate-to-high–affinity anti-dsDNA antibodies is highly warranted.

This screening cascade is well known for IIF testing for ANA and neutrophil-specific autoantibodies (NSA). The latter group of autoantibodies encompasses the vasculitis-associated ANCA as well as NSA. NSA is detected only by IIF and is associated with many chronic inflammatory diseases (Table 2) (13,28). Strong efforts should be made to report the presence of the clinically important ANCA quite differently from NSA (25,29).

For certain HEp-2 IIF results, a screening cascade is not necessary, a fact that can be highlighted in a posttest algorithm. For example, some IIF patterns of ANA on HEp-2 cells, such as the anticentromere pattern, relate closely to Raynaud's phenomenon and limited scleroderma (30). When the characteristic anticentromere pattern has been found, further characterization of these antibodies is not necessary (31). The same protocol holds true for anti-proliferating cell nuclear antigen antibodies, which are related to SLE (16), and many other ANA that can be seen only by the IIF-ANA technique. In contrast, sera containing ANA that produce a homogeneous nuclear or a speckled nucleoplasmic staining pattern should be studied further for specific ANA directed against individual antigens (such as dsDNA, chromatin components, DNA topoisomerase I, Sm, U1 RNP, SSA/Ro, SSB/La, etc.) for the results to become clinically useful (16). The clinician with first-hand knowledge about a particular patient's tentative or established diagnosis should make the decision as to which specific antibody testing should be performed. This approach will secure that positive ANA screening is optimally adapted to the diagnosis and that the costs of testing will be contained.

Patients presenting with repeated arterial or venous thrombosis, recurrent abortions, and, often, thrombocytopenia should be suspected of having antiphospholipid syndrome (APS) (32). One way to support this diagnosis is to obtain a prothrombin and activated partial thromboplastin time. In the event that the patient has a lupus anticoagulant, the partial thromboplastin time will be abnormal. The presence of the lupus anticoagulant will require additional measurements using at least 1 of several confirmatory tests. These tests include the activated Russell viper venom time or the kaolin clotting time (33). In some instances, it is easier to measure the products of prothrombin degradation, as is done in many commercial laboratories. The ascertainment of the APS diagnosis requires presence of a lupus inhibitor or some form of antiphospholipid antibody (aPL; e.g., anticardiolipin of the IgG or IgM isotype) (9). IgA anticardiolipin antibody is not routinely measured or even available in most hospital laboratories. However, this isotype should be measured if lupus inhibitor is absent and IgG and IgM anticardiolipin antibodies are normal, but the suspicion of APS remains. A positive test result of an isotype for an anticardiolipin antibody can be confirmed by measuring the antibody to a protein antigen called the β_2-glycoprotein I (β_2GPI) (34). Antibody isotypes against this antigen are important because some investigators believe that this antibody predicts clotting with better sensitivity. The β_2GPI is one protein cofactor against which the aPL is directed (35). There are many others (34), but this one seems to have particular importance. It is assumed that lupus inhibitor activity is caused by antibodies to β_2GPI or prothrombin complexed to phosphatidyl serine (34).

The presence of these antibodies constitutes part of the criteria for the diagnosis of the APS, but the clinical criteria must be satisfied before one can set the diagnosis. The mere presence of serologic abnormalities, like anticardiolipin antibody, lupus anticoagulant, or antibodies against β_2GPI, is not sufficient to begin anticoagulation or antiaggregation. The presence of aPL must be demonstrated at least twice with an interval of at least 6 weeks to satisfy the Sapporo criteria (9). Until now, it has been very difficult to standardize the various aPL assays.

Tentative diagnosis	ANA-IIF	a-dsDNA	a-Sm	a-U$_1$RNP	a-SSA/SSB	a-Scl-70	a-Jo-1	a-riboRNP	ANCA-IIF	MPO-ANCA	PR3-ANCA	a-Cardiolipin	a-β_2GPI	IgM RF	a-CCP
Systemic lupus erythematosus	■	▲	▲	●	▲			▲				▲	●	●	
Primary Sjogren's syndrome	■	●	●		▲			●				●		●	
Systemic sclerosis*	■			▲		▲						●			
Mixed connective tissue disease	■	▲	▲	▲				▲				●		●	
Polymyositis/ dermatomyositis†	■			▲			▲					●			
Anti-phospholipid syndrome‡	■											■	▲		
Rheumatoid arthritis														■	■
Primary small vessel vasculitis									■	▲	▲				
Connective tissue disease§	■	●	●	●	▲	●	▲		■	●		■	▲	■	

■ Primary screen test ▲ Secondary test ● Additional test (optional)

Figure 2. An algorithm to aid in the ordering of autoantibody tests based on a tentative diagnosis. *Ideally should include systemic sclerosis panel testing for anti-RNA polymerase I and III, anti–U3 RNP and anti-To/Th RNP antibodies. †Ideally should include polymyositis/dermatomyositis panel testing for anti–aminoacyl–transfer RNA synthetases, anti-SRP, anti–Mi-2, anti–PM-Scl, and anti-Ku antibodies. ‡Should also include lupus anticoagulant. §Only the 4 primary screening tests should be performed initially and only in patients that are strongly suspected of having a connective tissue disease. ANA = antinuclear antibody; a-dsDNA = anti–double-stranded DNA; a-Sm = anti-Smith; a-U$_1$RNP = anti–U1 RNP; a-SSA/SSB = anti–SSA/SSB; a-Scl-70 = anti–Scl-70; a-Jo-1 = anti–Jo-1; a-riboRNP = anti-ribosomal RNP; ANCA = antineutrophil cytoplasmic antibody; IIF = indirect immunofluorescence; MPO = myeloperoxidase; a-Cardiolipin = anticardiolipin; a-β_2GPI = anti–β_2-glycoprotein I; IgM RF = IgM rheumatoid factor; a-CCP = anti-cyclic citrullinated peptides.

Clinical practice guidelines

Because of the complexity of modern autoimmune serology, laboratory directors should make suggestions concerning the appropriate and economic use of serologic testing. If a limited number of clinicians are involved in ordering diagnostic tests and the laboratory services a finite number of departments, it is easier to achieve consensus on testing strategies. When a large laboratory provides service to more extensive areas or populations, written guidelines are required to ensure a rational testing scheme and to avoid unnecessary testing. For example, providing a simple guide to all clinicians involved can easily accomplish this goal. In the Department of Autoimmunology at Statens Serum Institut in Copenhagen, all regions of Denmark (family practitioners, and specialists plus hospital departments) are provided a broad range of autoantibody tests relevant to all areas of medicine. Hence, it has been necessary to produce an extensive guide suggesting which screening tests should be used for a patient to be evaluated for a particular tentative diagnosis. This guide also outlines additional tests that are necessary to support a diagnosis and estimate prognosis. Figure 2 shows the principles in the guide relating to rheumatology. A positive screening test result may lead to the referral of a patient to a specialist, who will then plan the further investigation program, including additional serologic testing. It is important to realize that the pretest probability of detecting a useful diagnostic laboratory result increases dramatically with each clinical feature that has been incorporated into the tentative diagnosis (36).

When an autoantibody is found, the positive result is communicated to the clinician as a printed report or a duly secured digital report sent directly to the doctor's personal computer. A description of the most common diagnostic associations related to this antibody is included with the result, e.g., "Anti-dsDNA antibodies are found in about 40% of patients with SLE. A clear rise in antibody level may precede a disease relapse." Information related to the sensitivity and specificity of a positive result is tabulated in the guide in a printed and Internet-based version of both the guide and the handbook to aid in the interpretation.

Laboratory measures

It is very important that all laboratory results can be validated. In Europe, it has been recommended that borderline positive results must be confirmed or refuted by use of a second well-established, independent technique to ensure that only certified positive results are reported to the physician or clinic. If controversy about the result persists, the laboratory can recommend retesting on a new serum sample in 1–2 months. Strong and intermediate positive results of a single credible technique can be reported without independent confirmation by a second technique. To aid in the interpretation of laboratory results, the chosen limit for positivity must be stated on the report. Ideally, the ranges of low, intermediate, and strong positivity should also be mentioned.

With the increasing use of low-cost, automated, high-throughput technology in a nonspecialized laboratory, a borderline positive result is often reported without confirmation by a second technique. Such results should be reported with a note of caution to the clinician that the result may have little significance in supporting a diagnosis unless corroborative testing is performed. In North America, regulatory agencies expect that borderline positive tests should be regarded as positive until proven otherwise through repeat or followup testing at appropriate intervals.

A major problem is that easy-to-use, high-throughput techniques are being implemented in the laboratory without proper clinical validation. Screening for ANA by use of ELISA plates that have adsorbed complex mixtures of native and recombinant autoantigens or nuclear extracts is now used by many laboratories instead of ANA screening by IIF. Data show that many patients with Sjögren's syndrome, scleroderma (SSc), and polymyositis/dermatomyositis (PM/DM) score negative for ANA using such composite ELISA techniques (37). HEp-2 IIF screening of these false-negative sera reveals that most contain antibodies to nucleoli, nuclear matrix, proliferating cell nuclear antigen, nuclear envelope, nuclear pores, coiled bodies, promyelocytic leukemia domains, mitotic spindle apparatus, or other cytoplasmic organelles and structures, e.g., mitochondria, Golgi apparatus, signal recognition particles, or ribosomes (Table 3) (38). Recent studies have shown that these autoantibodies are readily recognized by experienced technicians (39) and may prove to be useful in clinical diagnostics but are missed by ELISAs for ANA screening (37). Until additional improvements in the ANA-screening ELISA can be achieved, IIF-ANA should remain the gold standard.

Table 3. Some autoantibodies that are detectable by IIF using HEp-2 cell substrates and are associated with various rheumatic diseases*

Cellular target structure	Associations
Nuclear matrix	Several CTDs
PCNA	SLE
Centromeres	SSc
Multiple nuclear dots (PML)	Primary biliary cirrhosis
Coiled bodies	SSc, primary SS
Nuclear envelope	SLE, RA, primary SS, APS
Nuclear pores	Primary biliary cirrhosis
Nucleoli	SSc, primary SS, PM-SSc overlap
Centrioles	SSc
Mitotic spindle poles	Several CTD
Mitotic spindle fibers	SLE
Midbodies	SSc
Ribosomes	PM, SLE
Signal recognition particles	PM
Mitochondria	Primary biliary cirrhosis
Golgi apparatus	Several CTDs, cancers
Actin cables	Chronic active hepatitis

* IIF = indirect immunofluorescence; CTDs = connective tissue diseases; PCNA = proliferating cell nuclear antigen; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; PML = promyelocytic leukemia; SS = Sjögren's syndrome; RA = rheumatoid arthritis; APS = anti-phospholipid syndrome; PM = polymyositis.

New assays to determine the presence of autoantibodies in certain connective tissue diseases have produced some controversial results. Several studies have suggested the presence of certain specific ANA in diseases in which they were not previously described. Upon further analysis, these conclusions were probably based on an uncritical use of laboratory assays. For example, some reports state that anti-DNA–topoisomerase I (topo I) is found in a subgroup of patients with SLE (40). When highly specific classical techniques (e.g., double immunodiffusion) are used, these results have not been confirmed. There are several possible explanations for these discrepancies. The antibodies might target another epitope on the enzyme, an ELISA could produce false-positive results because of small amounts of DNA in the antigen preparation, or a serum may contain DNA in DNA/anti-DNA immune complexes that bind to a natural ligand, such as topo I. Under somewhat similar circumstances, ANCA with apparent specificity for myeloperoxidase (MPO) have been reported in strains of mice that develop a lupus-like syndrome. Nonspecific ionic interaction between the anionic DNA or nucleosomes in biologic fluids and the highly cationic MPO antigen fixed to the ELISA plate may be interpreted as MPO-ANCA although the antibodies are actually anti-dsDNA antibodies (41). The fact that a certain subgroup of lupus-prone mice (MRL/Mp-lpr/lpr) do actually produce MPO-ANCA and develop small-vessel vasculitis makes the picture rather complicated (42).

Another controversy arises when a serum tests positive by *Crithidia luciliae* assay for anti-dsDNA and negative by another anti-dsDNA assay; or a positive anti-dsDNA result may be reported in a serum that is negative on the HEp-2 substrate (43–45). Accordingly, the strengths and shortcomings of new tests must be scrutinized and there must be agreement on how to interpret discrepant results before the test is introduced for clinical use. Positive or negative results that are out of context with known clinical parameters should always arouse suspicion that a test system may be unreliable and will require reevaluation.

A good example of improved performance of an old IIF assay is the HEp-2 cell line transfected with Ro-60, complementary DNA resulting in overexpression of human Ro-60 in the nuclei of 15–20% of the cells allowing detection of anti-SSA/Ro-60 antibodies in the ANA screening test (46). This method reliably reveals the presence of anti-SSA/Ro antibody, one of the most common ANA in clinical practice, which often is missed on routine IIF ANA (47). Another example of recent improvement of an old test is the use of an ELISA for anti-cyclic citrullinated peptides (a-CCP) in exchange for the IIF antikeratin test (48). This new assay is reported to be 98% specific for the diagnosis of rheumatoid arthritis (RA) among inflammatory disease control patients. The first version of the ELISA for a-CCP had a sensitivity ~70% (48). Additional studies have indicated a similar sensitivity in patients with early RA where the presence of a-CCP at the onset of disease has been associated with more severe radiologic damage during followup (49).

Because new autoantibodies are continually being described, it is best not to report results on autoantibodies that lack proven clinical value until their value has been clearly established. This approach mandates rigorous, multicenter studies of newly discovered autoantibodies to establish their clinical relevance or value. To give an example, anti-SSA/Ro-52 are known companions to anti-SSA/Ro-60 and anti-SSB/La antibodies in patients with SLE or primary Sjögren's syndrome (50), but they may also be associated with myositis-specific autoantibodies in PM/DM and SSc patients (51,52). Anti-SSA/Ro-52 antibodies of the IgG class may carry a pathophysiologic potential to induce congenital heart block in newborns of mothers that harbor this antibody after transfer of the antibody through the placenta. This serious perinatal complication is seen in about 1% of pregnancies of anti-SSA/Ro-52–positive women (53), many of whom also have anti-SSB/La antibodies (54). Both antibodies have been suggested to be involved in the mechanisms that lead to damage of the atrioventricular node and the Hiss bundle (53,54). The great majority of mothers having babies with congenital heart block have anti-SSA/Ro-52 antibodies, and at least 60% of these also have anti-SSB/La, as shown by routine techniques for their detection. More sensitive methods show presence of both of these antibodies if one of them has been found by a routine method. The clinical value of finding anti-SSA/Ro-52 in isolation or in addition to a myositis-associated antibody is as yet uncertain.

Importance of early diagnosis

Rheumatologists have shown a historic interest in establishing an early diagnosis of RA, which allows institution of efficient therapy that may actually stop or significantly

retard disease progression (55,56). However, before administering a treatment that may have associated risks, the diagnosis of RA and the prognostic group to which the patient belongs should be established. In diagnosing early RA, characteristic clinical manifestations, as well as genetic and laboratory markers that may support the diagnosis and indicate prognosis, are important (14,20). For example, presence of a-CCP in a patient with recent-onset arthritis suggests that the patient has early RA and should be followed closely (49). An inaccurate diagnosis can cause damage to patients either by inappropriate treatment or through side effects of medications. RA is just one of many chronic diseases where early recognition and a correct diagnosis is mandatory to prevent organ damage and avoid drug-induced toxicity.

The long-term prognosis of any systemic rheumatic disease depends on accurate categorization of each patient into a prognostic subgroup (10–15,20,30,57,58), and on correctly applied early therapy. An inaccurate or delayed diagnosis in any chronic disease leads to unwanted long-term health care costs and to continued suffering for the patients and their families.

ANA often play a very special role in the recognition of early rheumatic disease where the initial clinical manifestations are few and not yet diagnostic. In this initial phase of clinical workup, the choice of ANA screening technique is especially critical. Practically nothing is known about the efficacy of ANA ELISAs for detecting autoantibodies in early disease, whereas at least something is known by the use of IIF ANA and some specific ANA, studied as a consequence of detecting ANA in the screening procedure (30,59). Particularly in the early workup of clinical diagnostics, the finding of an autoantibody may be most helpful (14,49,59–61).

There is a serious deficiency in our present knowledge as to the actual costs incurred through inappropriate laboratory testing. The costs of laboratory diagnostic studies can easily be calculated. In Scandinavia, the estimated cost of all types of in vitro diagnostic testing in laboratories is between 2% and 3% of the total budget for health care. Diagnostic imaging techniques are now being used much earlier in spite of their much higher expense. Frequently, their clinical value with regard to the long-term prognosis has not been clearly elucidated. In the light of this significant expense, it is difficult to explain why low-cost and high-quality autoimmune serology is not given a higher priority by health care economists. The prospects for health care financing are intimately linked to an accurate early diagnosis and treatment. Inappropriate laboratory testing (e.g., panel testing) is both costly and potentially misleading in the diagnostic workup. An estimation of long-term costs related to early accurate diagnosis and therapeutic intervention compared with a missed or a wrong diagnosis, with or without treatment, has to be performed to highlight the value of high-quality laboratory diagnostics.

Conclusion

In contemporary medical practice, changes in laboratory diagnostics and new technologies are constantly introduced, which may be a concern if certain central matters (such clinical utility) are not debated thoroughly between clinical and laboratory directors. It is important to avoid alienation of users and deliverers of potentially important information that should be used to set an early and precise diagnosis and estimate a likely prognosis. In rheumatology, autoantibodies are considered reporters of overt or subclinical organ or tissue damage. The antibody profile can serve as a rational tool for focusing the attention to involved tissues or organs using classic diagnostic tools, such as histopathology, imaging techniques, and organ-function testing. Clinical guidelines to ease the communication between clinicians and laboratories can be formulated, mutually accepted algorithms for test ordering be used, rules for reporting results be agreed upon, and algorithms for optimal use of laboratory results be adopted. A tradeoff between sensitivity and diagnostic specificity always has to be negotiated before a test is put into the laboratory program, since cutoff values for positivity that are furnished by manufacturers of kits mainly separate a certain nosographic entity from the healthy population. This is not ideal for differentiating between clinically related diseases. Therefore, patients willing to donate blood for use to optimize differential diagnostics are absolutely necessary to accomplish cutting-edge diagnostics in rheumatology. Easy-to-use technology should not replace older, well-established technology until the clinical utility has been thoroughly scrutinized. Only if there is agreement that the new technique is better or at least as good as the old one for patient care can a change be advised.

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Applications Invited for Editor of *Arthritis & Rheumatism*, 2005–2010 and Editor of *Arthritis Care & Research*, 2005–2009

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