

EASI—The European Autoimmunity Standardisation Initiative

A New Initiative that Can Contribute to Agreed Diagnostic Models of Diagnosing Autoimmune Disorders throughout Europe

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ABSTRACT: The European Autoimmunity Standardisation Initiative (EASI) was founded 6 years ago with the intention of improving diagnostics in chronic rheumatic disorders by strengthening the collaboration between clinical and laboratory scientists responsible for autoimmune diagnostics at any given level of the health care systems in Europe. Thorough clinical work-up is frequently not the basis for the usage of laboratory tests. Old established test methods may be exchanged for new methods without the differences being communicated. Often, the optimal way of reporting laboratory results to the clinic has not been agreed upon between clinicians and laboratory scientists. An EASI international

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team consisting of expert rheumatologists/internists/laboratory scientists from Denmark, France, Germany, Israel, Italy, the Netherlands, Spain, and the United Kingdom meets once a year to discuss how interactions between laboratories and rheumatology clinics could be improved in practical terms, how algorithms for cost-effective and rational autoantibody testing could be harmonized, and what an international concept of standardization in this area could look like. In national EASI teams, which were founded in many European countries, clinical and laboratory experts also meet regularly to discuss how European guidelines may lead to practical improvements in their recent country-specific approaches. To enable the exchange of information and experiences, representatives of the different teams of the EASI Network will meet annually in the EASI Forum. All EASI teams will present and discuss the results of their activities with other experts in the field in an EASI Conference, which will be held biannually at the International Congress on Autoimmunity.

KEYWORDS: autoimmunity; standardization; guidelines; laboratory diagnostics

INTRODUCTION

Autoimmune diseases (AID) are a very large and complex group of disorders, which can be organ specific (affecting one organ only, such as Grave's disease, primary biliary cirrhosis, or insulin-dependent diabetes mellitus) or systemic (affecting different organ systems of the whole body, such as systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis).^{1,2} They are characterized by a broad variety of clinical symptoms, which in the initial phases of the diseases may often be faint and uncharacteristic, and here the finding of characteristic autoantibodies in the patients' serum can lead to recognition of early disease.^{3,4}

A thorough medical examination of a patient must precede analysis and interpretation of combined clinical and serological data.⁵ Decisions on technologies and reporting routines should be based on a close collaboration between clinicians and laboratory specialists. Experiences in the different European countries, however, demonstrate that due to changes in the health care systems and the organization of laboratories, clinicians and laboratory specialists are working more and more in isolated units.

The European Autoimmunity Standardisation Initiative (EASI) was founded 6 years ago with the initial intention of improving diagnostics in chronic rheumatic disorders by strengthening the collaboration between clinical and laboratory scientists responsible for rheumatology diagnostics at any given level of the health care systems in Europe.

SITUATION OF THE DIAGNOSTIC OF AUTOIMMUNE RHEUMATIC DISEASES

An analysis of how such diseases are diagnosed in several European countries resulted in the identification of three areas, where changes in the actual work-up could lead to an earlier, better, and faster diagnosis of patients and an overall reduction of health care costs.

Communication between Clinicians and Laboratory Needs to be Improved

Through the introduction of new techniques and methodologies in clinical and laboratory practice and the efforts taken by most of the European health care systems to increase efficiency and reduce costs, clinical and laboratory units are organized to work more and more independently, sometimes even isolated from each other. Initially, this leads to a less frequent communication between the parties and finally can result in an exchange of information solely by electronic media. Through the loss of direct contacts between the laboratory, the clinician, and the patient the importance of interactive diagnostics becomes weaker.

A stronger communication and cooperation network between the different groups would lead to an earlier, more precise and faster diagnosis of patients, would allow a rational follow-up, and sometimes an earlier treatment, all of which would reduce the overall health care costs.

Testing Algorithms Are Not Standardized

Thorough clinical work-up is frequently not the basis for the usage of laboratory tests. Old established test methods are often exchanged by new methods without recognition of the differences such exchange may confer to the clinical use of test results. Often, the optimal way of reporting laboratory results to the clinic has not been agreed upon between clinicians and laboratory scientists.

There are no standardized algorithms used by the different laboratories for easing the rational use of laboratory tests. Such algorithms should be locally customized taking into account the various methods available and the results that can be derived by using these tests should be studied.

A standardization/harmonization of testing algorithms across Europe could lead to a more efficient usage of the laboratory tests.

***International Standards for Test Kits, Methodology,
and Use of Results Are Needed***

Only few assay systems used in the determination of autoantibodies are based on international standards (such as WHO WO 80 for anti-dsDNA⁶ or MRC 65/93 or 66/387 for antithyroglobulin (Tg) or anti-TPO (thyroid peroxidase), respectively). Most of the test systems refer to arbitrary units resulting from internal calibrations by the manufacturers or the laboratory itself.

Comparability of results, however, is even not given if international reference preparations are used due to the very different reaction conditions many of the assay systems are using. FARR assays, *Crithidia luciliae* immunofluorescence (CLIF) tests, or regular enzyme-linked immunosorbent assay (ELISA) systems, which are all calibrated against the WHO WO 80 standard, can give very different results in the various detection systems for antibodies against dsDNA, depending on their ability to determine antibodies of high or low avidity to the dsDNA target.⁷⁻⁹ For the determination of Tg/TPO antibodies, the situation is similar as described by Wood or Tozzoli.^{10,11}

Actually, there are no international guidelines available on how to standardize autoimmunity test kits. A common concept to standardize assay systems internationally could increase the clinical value of the test systems, improve the accuracy of the diagnosis, and could guide the manufacturers of assay systems.

THE PRACTICAL APPROACH

An EASI international team consisting of expert rheumatologists/internists/laboratory scientists from Denmark, France, Germany, Israel, Italy, the Netherlands, Spain, and the United Kingdom was formed to discuss how interactions between laboratories and clinics could be improved in practice, how algorithms in autoantibody testing could be harmonized, and what an international concept of standardization of diagnostic strategies in this area could look like.

In national EASI teams, which were founded in many European countries, clinical and laboratory experts from different clinical areas also now meet regularly to discuss practical improvements in their country-specific approaches.

All EASI groups build a close EASI Network, which allows a frequent exchange of information and experiences and enables a close cooperation across borders on particular EASI projects (see FIG. 1). Newsletters and an Internet platform as well as individual e-mail conversation are used to make communication as easy and fast as possible. To review the common activities

The EASI Network

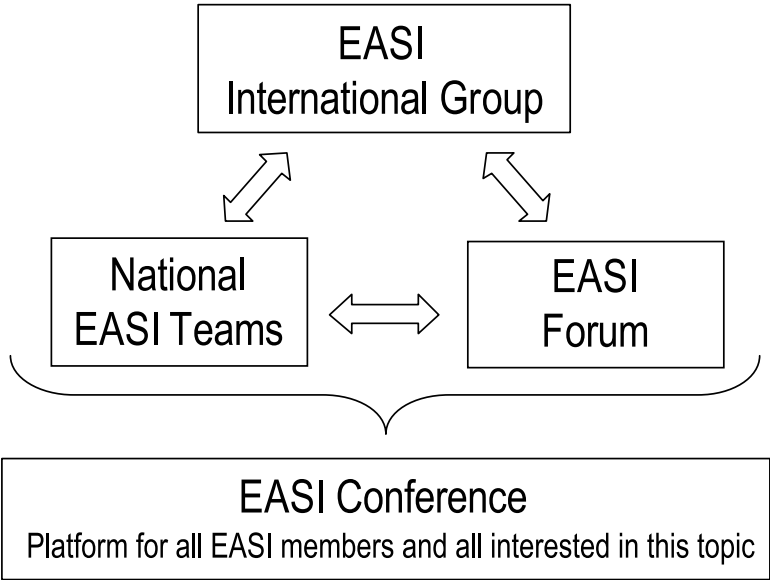


FIGURE 1. The EASI Network. All National EASI Teams and the International EASI Group build a close network to exchange information and experiences frequently. EASI Forum: Meeting of the coordinators of the different groups, who meet annually to coordinate the projects of the network. EASI Conference: The results of the EASI activities and projects are presented biannually at the International Congress on Autoimmunity.

regularly and to plan new European projects, the coordinators of all EASI teams meet annually in the EASI Forum.

Beside the communication within the different teams, EASI also presents and discusses the results of their activities with other experts in the field. Therefore, EASI Conferences are organized biannually during the International Congress on Autoimmunity.

ACTIVE TEAMS OF THE EASI NETWORK

International, Austria, Belgium, Denmark, Finland, France, Germany, Spain, Sweden, Switzerland, Norway, and the Netherlands.

ACTUAL PROJECTS OF THE EASI NETWORK

Publication of Guidelines for Family Doctors

A paper describing diagnostic screening algorithms for systemic rheumatic AID is being prepared by the EASI international team meant for use by family practitioners.

Booklet(s) for Family Doctors

Authors from the different EASI teams will write in a joint collaboration the chapters of the booklet, covering each of the rheumatic/AID. Beside the EASI team members, also external collaborators will join the booklet authors.

Future booklets should cover all areas in autoimmunity. Each of the chapters will focus on one disease and on the symptoms of the different disease phenotypes, recommend markers, which can help to make the right diagnosis and phenotype and describe algorithms that are recommended for use.

Multicenter Study

A multicenter study about the performance of the different methods used for autoantibody testing should be initiated. All assay systems, which are commercially available, should be included.

The study should be run in cooperation with IUIS (International Union of Immunological Societies)/WHO/AF (Arthritis Foundation)/CDC (Centers for Disease Control and Prevention) International Autoantibody Standardization Committee, and the European Autoantibody Consensus Group.

The study should be divided into

1. A routine study with samples randomly selected by the laboratories from their daily practice.
2. Clinical study with samples from clinically well-defined samples. All samples will be collected following the required ethical regulations.
3. Control samples (blood donors and disease samples from non-AID).

BOOKS AND PAPERS PUBLISHED BY THE EASI NETWORK

- Wiik, A., Cervera, R., Haass, M., *et al.* 2006. European attempts to set guidelines for improving diagnostics of autoimmune rheumatic disorders. *Lupus* 15: 391–396.

- Cervera, R. & Plaza, A. 2006. Eds. Guías de práctica clínica y de laboratorio: Autoanticuerpos y enfermedades autoinmunes. Ergon.
- Chyderiotis, G., Claudel, E., Fabien, N. *et al.* 2006. Eds. Autoanticorps utiles au diagnostic et au suivi des maladies auto-immunes systémiques.

REFERENCES

1. SHOENFELD, Y., M.E. GERSHWIN & P.L. MERONI. 2006. Eds. Autoantibodies, 2nd ed. Elsevier. Amsterdam.
2. CONRAD, K. & U. SACK. 2002/2003. Eds. Autoantigens, Autoantibodies, Autoimmunity. Papst Science Publishers. Berlin.
3. REICHLIN, M. 1998. Systemic lupus erythematosus. *In* The Autoimmune Diseases, 3rd ed. N.R. Rose & I.R. Mackay, Eds.: 283–298. Academic Press. New York.
4. GALPERIN, C. & M.E. GERSHWIN. 1998. Systemic sclerosis (scleroderma). *In* The Autoimmune Diseases, 3rd ed. N.R. Rose & I.R. Mackay, Eds.: 317–342. Academic Press. New York.
5. WIJK, A. 2005. Anti-nuclear antibodies: clinical utility for diagnosis, prognosis, monitoring, and planning of treatment strategy in systemic immunoinflammatory diseases. *Scand. J. Rheumatol.* **34**: 260–268.
6. FELTKAMP, T.E., T.B. KIRKWOOD, R.N. MAINI, *et al.* 1988. The first international standard for antibodies to double stranded DNA. *Ann. Rheum. Dis.* **47**: 740–746.
7. McMILLAN, S.A. & A.C. FAY. 1988. Evaluation of five commercial kits to detect dsDNA antibodies. *J. Clin. Pathol.* **41**: 1223–1228.
8. WERLE, E., M. BLAZEK & W. FIEHN. 1992. The clinical significance of measuring different anti-dsDNA antibodies by using the Farr assay, an enzyme immunoassay and a *Critzhidia luciliae* immunofluorescence. *Lupus* **1**: 369–377.
9. RIBOLDI, P., M. GEROSA, G. MORONI, *et al.* 2005. Anti-DNA antibodies: a diagnostic and prognostic tool for systemic lupus erythematosus? *Autoimmunity* **38**: 39–43.
10. WOOD, W.G. & R. HANKE. 2004. Comparability of method results and performance in a national external quality assessment scheme between 1993 and 2003 using thyroid associated antibodies as examples. *Clin. Lab.* **50**: 209–221.
11. TOZZOLI, R., N. BIZZARO & E. TONUTTI. 2002. Immunoassay of anti-thyroid autoantibodies: high analytical variability in second generation methods. *Clin. Chem. Lab. Med.* **40**: 566–573.