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REVIEW ARTICLE

Accreditation of histocompatibility and immunogenetics laboratories: Achievements and future prospects from the European Federation for Immunogenetics Accreditation Programme

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The importance of demonstrating adherence to good practice in the provision of clinical services is well recognised, and there are many legislative and regulatory requirements that aim to ensure that services are appropriately reviewed and certified. Therefore, for regulatory purposes, laboratories must provide assurance of the quality of the services they provide. Additionally in the field of transplantation, where donor organs and stem cells are exchanged across national boundaries, adoption of a common set of standards by laboratories across many different countries is an important factor. The European Federation for Immunogenetics (EFI) Accreditation Programme was established to provide assurance that Histocompatibility & Immunogenetics laboratories providing services for transplantation, transfusion, and disease association testing meet the requirements of the specialty specific EFI standards. The first H&I laboratories achieved EFI accreditation in 1995, and currently there are over 260 EFI accredited laboratories in 36 countries. The programme depends on the voluntary participation of the inspectors, who are all experts in the field of H&I, and who, over the last 22 years, have performed over 1400 onsite inspections of laboratories. Inspection findings show the areas that are most frequently found to be deficient in meeting the requirements of the standards, and this can be used to inform educational and other activities with the aim of improving laboratory compliance with the standards. The EFI standards have been regularly updated to reflect the changes in the field with 19 versions over the last 22 years, and the data from the accreditation programme show how laboratories have changed their practices to incorporate new techniques that support patient care.

KEYWORDS

accreditation, clinical trials, European Federation for Immunogenetics, external proficiency testing, harmonisation, histocompatibility & immunogenetics, HLA, quality management, regulatory bodies, standards

1 | INTRODUCTION

In the review article "A short history of HLA" published in 2009,[1] Erik Thorsby gives an account of the discoveries in the HLA field, from the 1958 seminal paper by Jean Dausset,[2] to the many advances of the following 50 years.

This review was invited and edited by the Reviews Editor Katharina Fleischhauer.

TABLE 1 Aims of the European Federation for Immunogenetics (EFI)

1. To support the development of immunogenetics in Europe as a discipline of medicine and promote research and training in this field
2. To provide a forum for exchange of scientific information and to reinforce the skills and knowledge of young scientists and others working in the field
3. To create a formal organisation of workers in the field of immunogenetics, histocompatibility testing, and transplantation
4. To develop recommendations for the standardisation of techniques, quality control, and criteria for accreditation and to support their implementation
5. To promote the organisation and use of immunogenetic databases
6. To develop relations with organisations with similar aims

Of particular interest are the pioneering years when scientists in Europe and the United States of America, struggled to define HLA antigens, alloantibodies, and the genetics of the HLA system. Investigators were successful because they came together in Histocompatibility Workshops to share sera, cells, techniques, and knowledge, and it is widely recognised that international collaboration was one of the main factors that allowed the field to evolve so rapidly.

As the role of HLA became established, the pioneering years gave way to the creation of HLA-typing laboratories that adopted a common nomenclature and standardised techniques, allowing the development of solid organ and haematopoietic stem cell transplantation programmes, at first on a local basis and subsequently on a more global scale.

International cooperation remained a hallmark of the field and progressed from the Committee of Experts in Histocompatibility in the 1970s, to the more formal organisation of immunogeneticists and tissue typing experts in 1981, to the creation, in 1985, of the European Foundation for Immunogenetics which shortly after was renamed European Federation for Immunogenetics (EFI), whose purposes are summarised in Table 1.

One of the main goals of EFI is to manage an accreditation programme for histocompatibility and immunogenetics laboratories, based on the standards agreed upon by the community of experts, and the aim of this review is to report the achievements of the programme after more than 22 years from its implementation.

2 | TYPES OF ACCREDITATION PROGRAMMES

The purpose of laboratory accreditation is to certify that a laboratory is meeting the requirements of a given set of standards, the rationale being that if these standards are met there is a level of assurance that the service provided is appropriate and of an acceptable level of quality.

Generic medical laboratories can be accredited to a set of standards that can be applied generically to laboratories working in different pathology disciplines. The most common example relevant to Histocompatibility and Immunogenetics laboratories is accreditation to ISO 15189 Medical laboratories—requirements for quality and competence. Accreditation to these standards provides assurance that the laboratories operate within a defined quality management system and that the service meets the requirements of the users.

For Histocompatibility and Immunogenetics (H&I) laboratories, there are also specific accreditation schemes, organised by professional bodies in the field of immunogenetics. The schemes offered by the EFI and the American Society for Histocompatibility and Immunogenetics (ASHI) fall into this category.[3,4] They use specific standards that are regularly reviewed and updated taking into account the latest clinical and technical advances in immunogenetics and transplantation; in the last 22 years, a total of 19 versions of the EFI standards have been released, evidence of how histocompatibility, immunogenetics, and transplantation are fast developing fields.

A key feature of EFI and ASHI accreditation is that the standards define minimum requirements for the testing essential to support specific clinical activities. These requirements are based on published evidence showing the relevance of testing in relation to patient outcomes. This level of detail is not contained within the ISO standards that are generic across multiple disciplines.

3 | THE EFI ACCREDITATION PROGRAMME

The EFI accreditation programme is schematically illustrated in Figure 1. The Accreditation Committee (AC) meets twice a year to review the situation of the programme, plan inspector workshops, discuss the inputs from other EFI committees, notably the Standard and External Proficiency Testing committees, and exchange views on plans and projects that regard accreditation of H&I laboratories. Moreover, the AC members examine the cases of laboratories which were accredited in the previous semester and those who present difficult situations that require a decision by the AC, guaranteeing the consistency of the accreditation process.

The programme relies on the much appreciated work of just over 100 voluntary inspectors, who must work in EFI accredited H&I laboratories, and this highlights the main strength of the EFI Accreditation programme, of being a professional, specific accreditation among peers, differentiating it from the generic ISO-based systems.

The requirement that inspections be carried out by two inspectors, of which one from the laboratory's region, implies at least two advantages: assurance that conflict of interest is kept to a minimum and second, that there is a significant exchange of experience among inspectors and laboratory staff benefitting both. In this view, the EFI accreditation programme can be considered a powerful tool for continuing education.

Accreditation by EFI or ASHI to H&I specific standards is available to laboratories worldwide. This is of particular

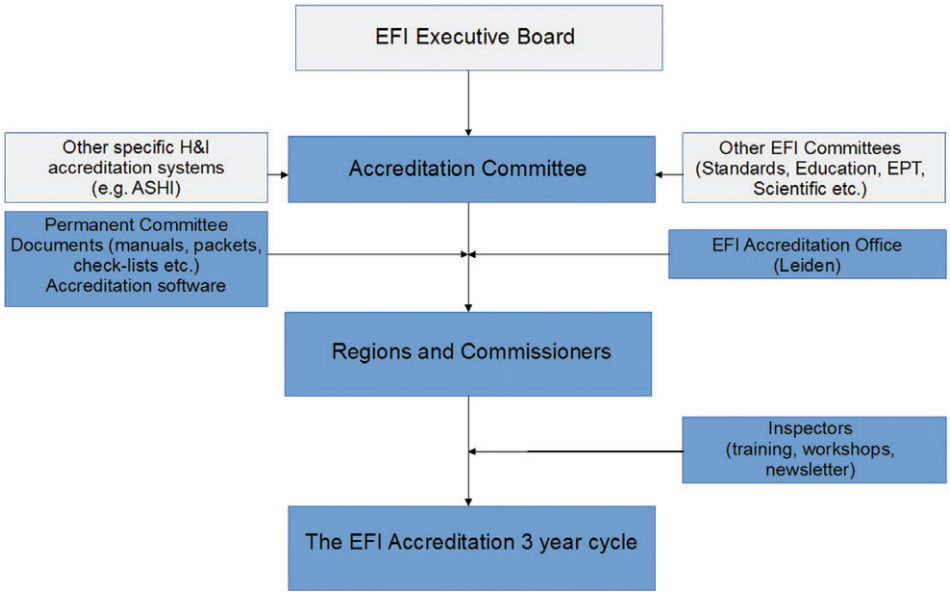

FIGURE 1 The EFI accreditation system. Showing the relationship between the EFI committees (in grey) and the activities and individuals involved in the accreditation programme (in blue)

relevance in the field of transplantation where the provision of donor material for transplantation is not necessarily restricted by national boundaries and where donor allocation is in part or in whole informed by the results provided by H&I laboratories. Accreditation of these laboratories to the same set of H&I specific standards therefore provides assurance that the testing of donors and patients is performed to the same set of minimum requirements and that the information used to inform donor selection/allocation meets the clinical requirements defined in the standards. The need for accreditation to H&I specific standards has achieved widespread recognition in the field of haematopoietic stem cell transplantation (HSCT)[5]. The role of accreditation in ensuring quality and comparability of the HLA-typing data held by unrelated stem cell donor registries has long been recognised. Hurley et al.[6] emphasise the importance of accurate results in registry data and the need for the testing to be performed in laboratories accredited to specific standards relating to the individual methodologies used to obtain the results. Tiercy et al.[7] suggest that for standardisation reasons all quality control measures should be covered by the accreditation programme. The need for EFI or ASHI accreditation in HSCT has been recognised by the Foundation for the Accreditation of Cellular Therapy and the Joint AC for ISCT and EBMT (FACT-JACIE) and is specifically mentioned in the FACT-JACIE International Standards for Haematopoietic Cellular Therapy.[8]

In solid organ transplantation, EFI or ASHI accreditation is required by some national allocation programmes and most notably by the Eurotransplant programme that facilitates the allocation and distribution of deceased donor organs between eight countries in Europe.[9]

4 | ACHIEVEMENTS OF THE PROGRAMME

From 1995 (the year EFI Accreditation programme was implemented) to 2010, the number of participating laboratories increased steadily, before reaching a plateau (Figure 2). At present, there are 264 accredited laboratories and their distribution among 36 European and non-European countries is depicted in Figure 3. The number of accredited laboratories in the latter countries is gradually increasing. It is of note that five laboratories have both EFI and ASHI accreditation.

Data on the categories of accreditation obtained by laboratories during the last 12 years of the programme indicate the activities laboratories are supporting and also how techniques have changed during that time to meet the needs of the clinical services. Figure 4 shows that the highest proportion of laboratories is accredited for related HSCT and for disease association studies. Both these categories have increased in terms of the percentage of labs providing these services with over 85% of laboratories accredited for these categories in 2017. Unrelated HSCT support is accredited in 66%, renal transplantation in 61%, and non-renal organ transplantation in 53% of laboratories in 2017.

HLA-typing techniques have advanced during this time with a notable decline in the use of complement dependant cytotoxicity testing and growth of the more accurate DNA-based typing techniques (Figure 5). The requirement of the EFI standards for laboratories supporting HSCT to be able to type at high resolution to achieve optimal donor selection is reflected in the increase in the proportion of laboratories accredited for high-resolution typing. In 2017, 88% were accredited for high-resolution class II typing and 81% for class I typing compared with 71% and 54% in 2005. These data confirm that laboratories supporting related and unrelated HSCT are able to meet the requirements for class I or class I + II typing as defined in the standards.

In its three-year cycle, the EFI accreditation programme requires one inspection every three years; in the period 1995 to 2017, a total of 1414 inspections were carried out, each requiring two inspectors. Currently, there are 110 active

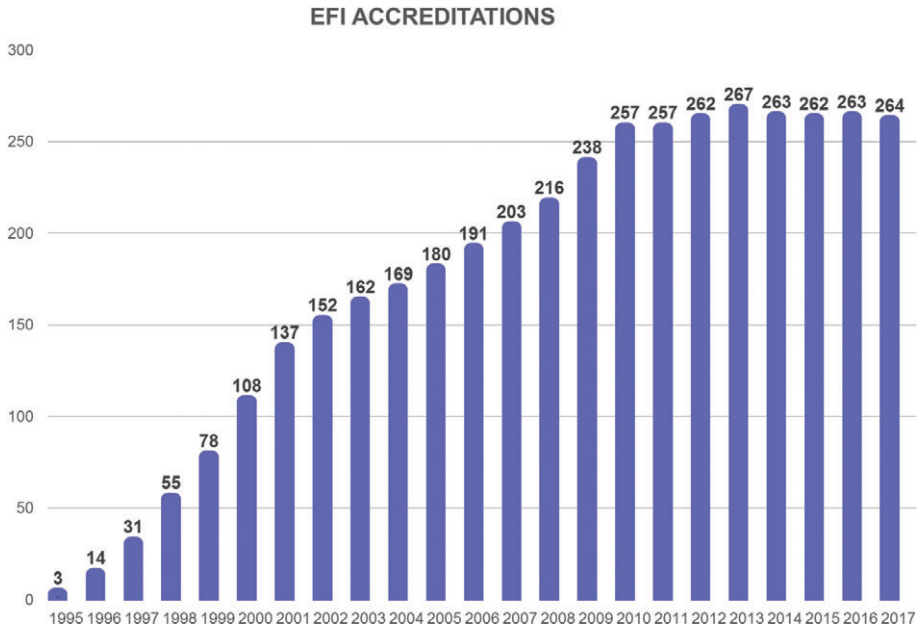

FIGURE 2 EFI accredited laboratories from 1995 to 2017. Showing the total number of EFI accredited laboratories in each year from the start of the accreditation programme in 1995 from the records of the EFI accreditation database

inspectors who have performed an average of 1.9 inspections per year. Of the 264 accredited laboratories, 97 (36.7%) have at least one EFI inspector among their staff.

Analysis of the findings from inspections shows that there are specific areas of the standards which the laboratories find most difficult to comply with. The two areas that consistently produce the highest number of deficiencies are standards relating to quality assurance and to nucleic acid analysis. More detailed analysis of the period 2012 to 2016 shows that the specific standards that laboratories fail to meet most often are also largely consistent from year to year as is shown in Table 2. The area which has the highest number of findings against it during this period are the standards relating to external proficiency testing with significant numbers of laboratories failing to participate in a recognised external proficiency scheme for every technique in use in the laboratory. In some cases, this is due to difficulty in accessing a scheme, with customs regulations in some countries preventing the import of samples for testing. In a small number of cases, early implementers of new technologies are using these techniques before a formal scheme has been established. In

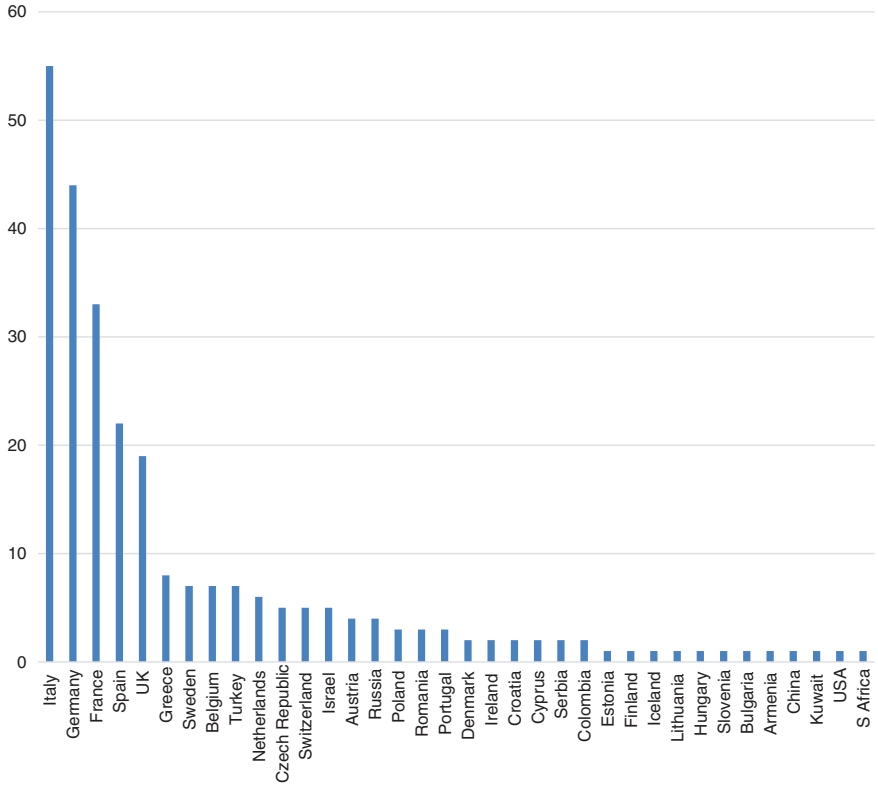

FIGURE 3 Distribution of EFI accredited laboratories among countries. Showing the total number of EFI accredited laboratories by country in 2017 from data in the EFI accreditation database

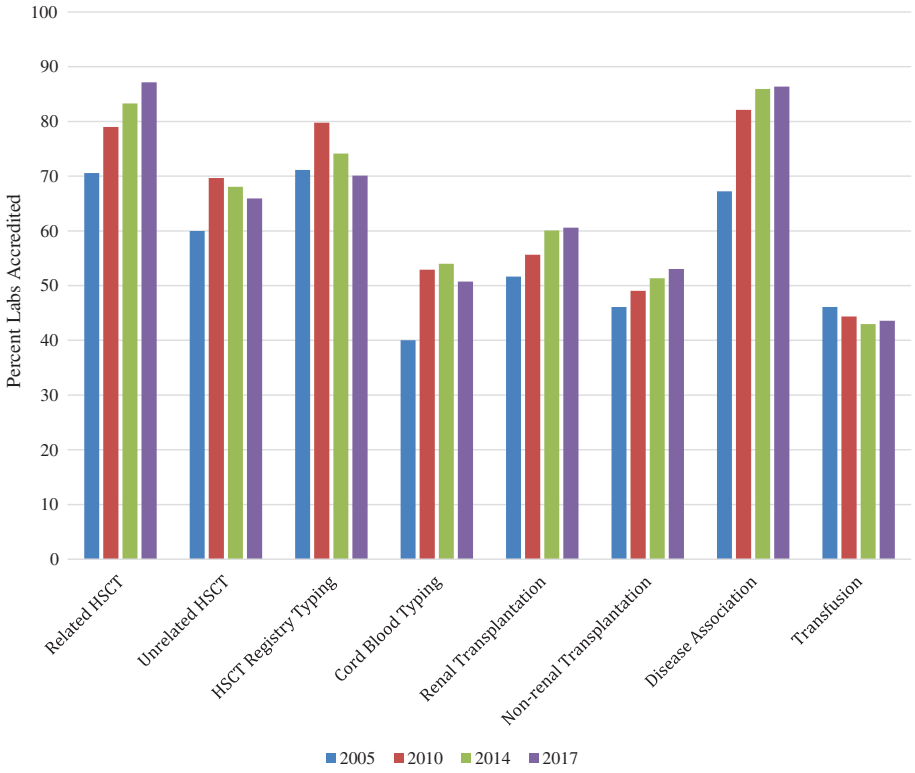

FIGURE 4 Distribution of accredited clinical categories among laboratories. Showing changes in the percentage of accredited laboratories holding accreditation for specific clinical categories in the period 2005 to 2017 as recorded in the EFI accreditation database

these cases, laboratories can participate in interlaboratory exchanges to control their testing. While most of the findings have been common over the period, problems with equipment maintenance found in 2012 were not common in subsequent years while failure to adequately validate computer software and issues with reporting results which did not feature in the top 10 in 2012 were both common failings in 2014 and 2016.

Although data concerning laboratory activity collected with the EFI packets are not specifically intended for statistical analysis, in 2013 members of the AC conducted a preliminary study on the global activity of the accredited laboratories which yielded interesting results[10] and which could be more easily reproduced in future thanks to the accreditation software.

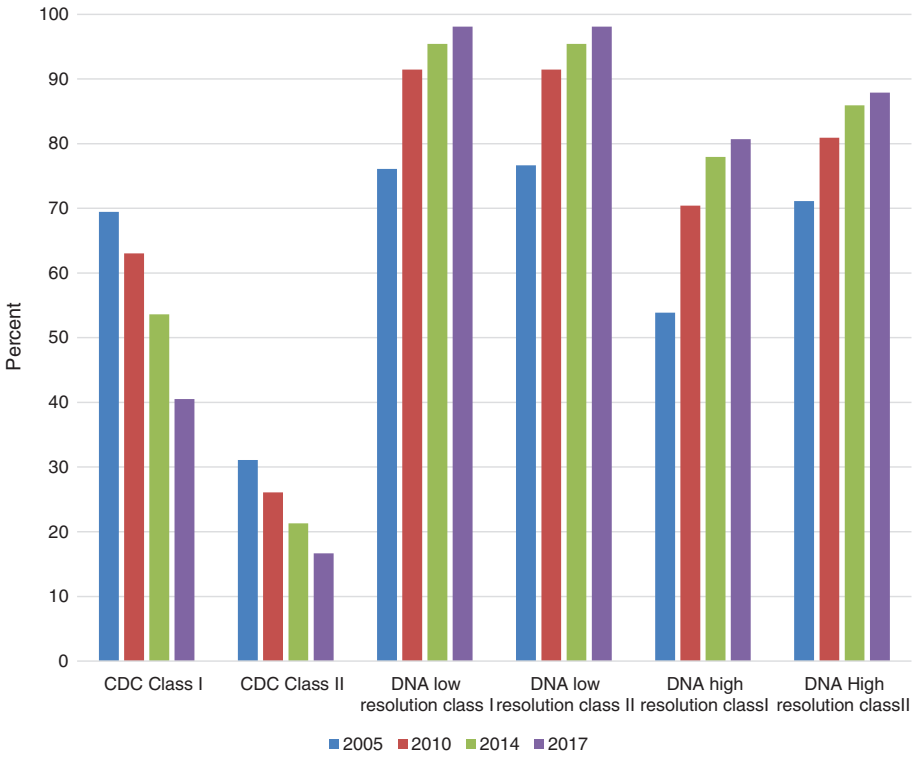

FIGURE 5 Distribution of accredited HLA-typing techniques among laboratories. Showing changes in the percentage of accredited laboratories with accreditation for different HLA-typing techniques in the period 2005 to 2017 as recorded in the EFI accreditation database

TABLE 2 Most common deficiencies with EFI standards found during inspections

	2012		2014		2016	
	No. of labs with deficiency	Rank of finding	No. of labs with deficiency	Rank of finding	No. of labs with deficiency	Rank of finding
External proficiency testing	29	1	22	1	23	2
Equipment maintenance	26	2				
Continuous monitoring of processes	22	3	13	4=	29	1
Procedure manual	21	4=	14	3=	8	8=
Temperature monitoring	21	4=	10	5=	11	5=
Competence evaluation	18	5	16	2	8	8=
Software validation			14	3=	16	3
Reports			13	4=	12	4
High-resolution typing ambiguities	14	8	10	5=	11	5=

Figures give number of individual findings plus ranking in top 10 plus, for example, in 2012, 29 laboratories had a deficiency in external proficiency testing and this was ranked first in the most common findings.

5 | FUTURE PROSPECTS

Immunogenetics, histocompatibility, transplantation, and autoimmunity are rapidly changing areas of science and medicine. New deep sequencing methods allow not only routine HLA allele level typing, but also the assessment of multiple other genetic systems which are increasingly being recognised as relevant to the immune response.[11,12] Similarly, from the serological point of view, increased sensitivity of methods used for the detection of specific alloantibodies relevant to solid organ and haematopoietic stem cell transplants are improving the safety of transplantation. In this challenging *scenario*, by continuing to work with the Standards Committee, the EFI Accreditation System can be seen as a framework for clinically significant advancements to be processed and brought to the routine laboratories.

In the majority of countries, cell and tissue donation, banking, and transplantation are highly regulated. The WHO states that National Health Authorities must ensure an appropriate legislative framework which defines international practice guidelines that must be applied in the interest of patient safety.[13] In the European Union, issues related to safety and quality of HSC are regulated by the legally binding European Directives 2004/23/EC, 2006/17/EC, 2006/86/EC. Moreover, a guide to the quality and safety of tissues and cells is available to provide assistance to transplant centres on how to manage appropriate quality improvement systems.[14] The EFI accreditation system is harmonised with the above-described regulatory frameworks because it ensures that one important aspect of organ/HSCT transplantation, that is, determining histocompatibility, is performed according to the highest possible standards.

To continue to develop the harmonisation of H&I testing and the clinical activities it supports, the principle of international collaboration given to EFI by its founding members should be strengthened. In order to achieve an ever growing homogeneity of histocompatibility and immunogenetics laboratories globally, cooperation with similar programmes such as ASHI should be ensured.

EFI intends to continue to make the programme available to a wider community, supporting the growth of an expanding number of laboratories both to European as well as to non-European countries. Finally, EFI is available to study ways to interact with mutual advantage, with National Accreditation Bodies.

The balance of the first 22 years of the EFI Accreditation programme is more than positive, and the number of accredited laboratories worldwide indicates the widespread acknowledgement that histocompatibility and immunogenetics specific accreditation provides benefits to the laboratories and most importantly, to the patients those laboratories serve.

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Conflict of interest

The authors have declared no conflicting interests.

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