



How to achieve harmonisation of laboratory testing — The complete picture



Aasne K. Aarsand^{a,b,*}, Sverre Sandberg^{a,b,c}

^a Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway

^b Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS), Haraldsplass Deaconess Hospital, Bergen, Norway

^c Department of Global Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Norway

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ABSTRACT

Harmonisation is likely to be an important contributor to ensure high quality laboratory testing, thus potentially improving patient outcome. Efforts for harmonisation must be made in the total testing process, from test requesting to communication of the laboratory test results and its consequences to the patient. In this article, suggestions are given about what level of harmonisation is possible at the various steps of the testing process, who could be responsible for facilitating and monitoring the effects of harmonisation, and what are likely barriers to achieving harmonisation. Harmonisation can be achieved at local, national and international levels, and will be most challenging when it involves more than one profession as in the extra-analytical phases. Key facilitators will be laboratory associations, regulatory bodies and accreditation systems, whereas barriers are likely to be reimbursement systems or economic factors, opinion leaders and manufacturers. A challenge is to try to turn barriers into facilitators. Harmonisation effects can in most settings be monitored by external quality assurance organisations provided that schemes are expanded to cover all relevant steps and phases. We must combine our efforts, both within our profession as well as in cooperation with others, to achieve harmonisation of the total testing process, in the best interests of the patient.

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1. Introduction

The goal of harmonising laboratory testing is to contribute to quality health care and ultimately improve patient outcome. So far, the focus of our profession has to a large extent been to harmonise and standardise the processes within the four walls of the laboratory and less focus has been put on what is going on outside. We have thus not seen the “complete picture”, but concentrated on what we considered our main responsibilities and core activities. However, ultimately, and for the patient, it is the final consequences of the laboratory test result(s) that matter. This means that all the different phases of the total testing process (TTP), from requesting of laboratory tests to interpretation and communication of the results, should be given equal consideration. These phases have been described by many authors and most recently in [1–3]. The TTP includes test requesting, identification (at several

stages), collection, transportation, preparation and analysis of samples, interpretation and reporting of the analytical results, and finally actions based on the results and their communication. Some authors categorise the different parts into pre-pre-analytical, pre-analytical, analytical, post-analytical and post-post-analytical phases [1,3]. The value of this approach can be discussed, and clinicians may find it amusing since we make the laboratory the centre of the world. However, for our purpose it may be a valuable concept as it clearly identifies what we as laboratory professionals can influence directly and for which parts we depend on others. At this point in time, the laboratory profession has a golden opportunity to look outwards and influence those parts of the TTP that traditionally have not been directly under our control. This may be challenging as the farther we move “out” from the central laboratory and the analytical process, the more we have to fight for our view among other professions and show how our input is essential for best practise [4,5]. In everyday life, communication and cooperation with other professions are equally important. Failure to communicate can result in significant errors as they often occur at the interface between professions with different or unclear responsibilities [6].

Implementation of best-practise and evidence-based guidelines, assuming that systems for monitoring laboratory performance allowing for detection of errors in all phases of the TTP are available, has the potential of being an important tool to help us provide quality health care on a large scale. So what is lacking in making us achieve this? Some basic

Abbreviations: IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; AACC, American Association for Clinical Chemistry; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; EQA, External quality assurance.

* Corresponding author at: Laboratory of Clinical Biochemistry, Haukeland University Hospital, NO-5021 Bergen, Norway. Tel.: +47 55 97 31 27, +47 55 97 31 70; fax: +47 55973115.

E-mail addresses: aasne.aarsand@helse-bergen.no (A.K. Aarsand), sverre.sandberg@isf.uib.no (S. Sandberg).

work must be performed for all the different steps of the phases in the TTP prior to harmonisation being possible. This work can be categorised into three stages, applicable to each phase, as shown below:

1. Characterisation and estimation of prevalence of errors [7,8].
2. Development of systems for registering and monitoring errors, and the establishment of quality indicators and performance requirements [9,10].
3. Harmonisation of methods for registering and monitoring errors and of quality indicators and performance requirements [11,12].

How much has been accomplished for the different phases and steps varies, with the analytical phase having come the farthest way. There are also additional areas that need to be developed, for example how the laboratory should act when a laboratory error in any phase of the TTP occurs, and the harmonisation of these actions.

Successful harmonisation of all the different phases and steps depends both on the availability of evidence-based knowledge as well as systems that can initiate, monitor and maintain the results of the harmonisation. Some steps of the TTP can be harmonised internationally, while others will best be harmonised locally or nationally. There are several parties that can be drivers and stakeholders in this process. Laboratory associations like the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the American Association for Clinical Chemistry (AACC) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) can play essential roles, with national associations having impact nationally or locally. Regulatory bodies and accreditation systems can be facilitators by setting requirements and developing standards that focus on harmonisation of the TTP. External quality assurance (EQA) providers already play an important role in harmonisation, but need to improve on the analytical side e.g. by taking greater care in selecting commutable EQA materials, and by turning their attention to the extra-analytical phases. For the different phases where the laboratory profession can have a significant impact, we will give suggestions as to what level of harmonisation is possible, who could be responsible for initiating, facilitating and monitoring the effects of harmonisation, and the barriers to achieve this successfully (Table 1).

2. Pre-pre- and pre-analytical phases

2.1. Test requesting and request forms

It has been shown by many studies that test requesting varies substantially, with some analyses being over-requested while others are under-requested [13–18]. Test requesting is thus an area with great potential for harmonisation. Some variation in requesting patterns is to be expected, as test requesting and test profiles will depend on local prevalence of disease. But differences will probably more often be effects of “strong” opinion leaders, insufficient knowledge, inadequate reimbursement systems and lack of resources in the laboratory. Test requesting will usually be under the control of the requesting physician, who decides after having examined the patient what analyses are to be performed. In this setting, the laboratory's key to influence test requesting patterns is the request form, which must be made to optimise evidence-based laboratory use from both a medical and economic viewpoint. In specific clinical situations, selection of tests may also be more directly under the laboratory's influence, for example when predetermined test profiles (e.g. automatically selected for a patient admitted with “suspected myocardial infarction”) or problem-based requesting (e.g. “thalassemia?”) are offered. In all settings, the electronic request form is an excellent opportunity to improve test requesting and to facilitate harmonisation. Here information about the tests of interest and recommendations on their use can easily be provided to the requesting physician, and submitting clinical information can be made compulsory for tests where this is necessary for adequate interpretation of results. Furthermore, problem-based requesting,

algorithms including reflex and reflective testing [19–22] and restrictions on repetitive testing [23,24] can easily be implemented.

To our knowledge, only a few established quality indicators for test requesting are currently in use. An example is “the number of appropriate requests, with respect of clinical question from general practitioners, as a percentage of the total number of requests that reports clinical question from general practitioners” [9]. Generally, these may be difficult to harmonise internationally. Another indicator associated with test requesting is “the number of requests with clinical questions from general practitioners as a percentage of the total number of requests from general practitioner” with optimum quality scored as >87% [9]. However, such comments are only of use if they are registered and used by the laboratory specialist in the evaluation of test results, which is certainly not always the case.

The procedure on how to reach consensus on what tests to perform when investigating a specific clinical condition or to include in test profiles can be harmonised nationally [25,26] and probably internationally. To harmonise test requesting by clinicians for each individual patient will be challenging and may in some settings be unrealistic, and the laboratory profession's ability to influence test requesting patterns will differ from country to country. When feasible, it will require the combined efforts of international and national clinical and laboratory organisations, regulatory bodies and reimbursement systems. A relevant recent example is the worldwide recommendation of HbA1c for the diagnosis of diabetes mellitus [27,28]. Harmonisation of test profiles and problem-based testing is likely to be achievable either within one country or within several similar countries. Here national laboratory organisations should play a major role. There is for example an on-going initiative by the Association for Clinical Biochemistry to harmonise commonly used test profiles in the United Kingdom [26]. On a smaller scale, laboratory specialists should take responsibility to harmonise test requesting both within their hospital and in their local environment. The most important tools for harmonisation of test requesting are by education of, and communication with, those who request tests and at the same time by optimising the request forms, either in paper format or electronically [22,23]. As a principle, implementation of problem-based requesting should be encouraged, in particular for complex laboratory testing or for clinical questions where physicians will be unfamiliar with the tests in question. Monitoring of test requesting and request forms can be performed by EQA organisations [29] and national laboratory societies. An obvious barrier to achieve evidence-based and harmonised requesting patterns throughout an area is competition among laboratories. This is especially challenging for private laboratories as they often economically depend on high requesting rates, and some laboratories may therefore present their request form in a way enabling them to make the best profit. Reimbursement systems may thus serve as a powerful barrier against harmonisation of test requesting, but may also serve as a facilitator if appropriately constructed. The structure and content of such a financing system should therefore be addressed as part of the harmonisation process.

2.2. Patient identification

It has been claimed that the most frequently occurring errors in the TTP are related to patient identification and sample treatment [30,31]. Correct identification of the patient is a major point where failures can have serious consequences. It has been suggested that along with handling of critical results, correct identification should be given the highest priority in the extra-analytical phases [32]. An IFCC working group has suggested that optimum performance should be a patient identification error percentage of less than 0.4% [9]. Identification errors also include mismatching of the patient identity given on the sample tube and the request form as well as adding an incorrect requesting physician [10,32]. Procedures on how to avoid identification errors and how to collect samples can be harmonised internationally and written up in guidelines and standards. A working group under the ISO Technical

Table 1
The likely achievable levels of harmonisation are shown for the different phases and steps of the total testing process where the laboratory profession can have a significant impact. The potential for harmonisation will vary with different laboratory tests and the prevalence of the associated diseases. Successful harmonisation to the likely achievable level will furthermore depend on the ability of organisations and stakeholders to cooperate and on healthcare systems being advanced enough to incorporate the required changes. In many cases the listed barriers can be turned into drivers/facilitators and vice versa.

The total testing process			Harmonisation			
Phase	Steps	Responsible	Likely achievable level	Drivers/facilitators	Barriers	Structures for monitoring
Pre–pre and pre-analytical Procedures related to laboratory testing both outside (e.g. test requesting, sample drawing at the GP's office) and under the direct control of the laboratory manager	Test requesting	Clinician with the involvement of laboratory specialist	International procedure on how to achieve harmonisation of test ordering Local, national and international harmonisations of commonly used test profiles	International and national clinical and laboratory societies/organisations Government/regulatory bodies Reimbursement systems	Strong (clinical) opinion leaders Reimbursement systems	Regular consensus meetings (local, regional, national) addressing which tests to request in different conditions EQA organisations
	Request forms (closely linked to the test requesting process) including test profiles and problem-based requesting	The laboratory with the involvement of clinicians	Local and national, in particular for problem-based requesting	National laboratory societies	Strong opinion leaders Competition between laboratories Reimbursement systems	Regular consensus meetings (local, regional, national) addressing which tests to request in different conditions EQA organisations or national laboratory societies
	Patient identification	Laboratory, hospital ward/outpatient clinic, GP's office	International for principles for identification, with local adaptations	Accreditation bodies	IT resources	EQA organisations
	Sample material, collection, preparation, transportation	Laboratory, hospital ward/outpatient clinic, GP's office	International for sample materials and their preparation International for statistical and practical methods used to examine stability Local or national concerning concrete results for e.g. stability of different constituents	International and national laboratory societies/organisations Manufacturers	Strong opinion leaders Competition among laboratories	International and national laboratory societies EQA organisations
	Interferences, e.g. by haemolysis, lipids, bilirubin	Laboratory	International, but method-dependent	International and national laboratory societies/organisations Manufacturers		EQA organisations
Analytical Procedures under the direct control of the laboratory	Methods and quality control systems	Laboratory	International	International laboratory organisations (e.g. the harmonisation initiative by AACC	Manufacturers Disagreement between opinion leaders	EQA organisations

Post-analytical Procedures under the direct control of the laboratory sometimes in cooperation with clinicians	Verification of results				Laboratory and IT resources	EQA organisations
	Reflective/reflex testing	Laboratory in cooperation with clinicians	Local, national, international	Accreditation bodies		
Post-post-analytical Procedures related to laboratory testing outside the direct influence of the laboratory manager	Units and reference intervals	Laboratory	Local, national and international	International and national laboratory societies	Strong opinion leaders	EQA organisations
	Interpretation and commenting on test results	Laboratory, sometimes in cooperation with clinicians	Local and national	National laboratory societies Competition between laboratories		EQA organisations
	Laboratory report forms and reporting of critical results	Laboratory in cooperation with clinicians	Local, national and international	International and national laboratory societies Competition between laboratories Regulatory bodies Accreditation bodies	Laboratory and IT resources	EQA organisations National laboratory societies
	Interpretation of test results in the clinical context and actions	Clinicians in cooperation with laboratory specialists	Local, national and international	International and national clinical and laboratory societies Government/regulatory bodies	Strong opinion leaders Clinical and IT resources	Clinical and laboratory societies EQA organisations

Committee 212 is presently preparing a guidance document on quality practise in collection and submission of primary samples for medical laboratory examinations. In certain cases, for example depending on resources, local modification may be necessary.

2.3. Sample material, preparation, collection and transportation of samples, sample stability and interferences

Harmonisation of many of these classical pre-analytical steps should be achievable at an international level, with international and national laboratory societies being both facilitators and providing the structure for monitoring together with EQA organisations. As a starting point, it should be agreed upon how best to examine stability of samples. The availability of freely accessible databases run by (inter)national laboratory societies or EQA organisations and containing data on stability for different constituents could further facilitate local or national harmonisation. Sample transportation from e.g. GPs' offices or by a pneumatic tube system [33–36] may be difficult to harmonise, but the criteria set for acceptable transportation time, degree of haemolysis, insufficient fill volume etc. can be harmonised. Quality indicators and performance criteria for the pre-analytical phase should be agreed on internationally [12]. The monitoring of these and other pre-analytical steps such as identification should be performed by EQA organisers, with separate schemes being developed in line with EQA of the analytical phase.

3. Analytical phase

In recent years, improvements in the analytical phase have been evident and many authors now claim that the analytical phase only contributes to a small fraction of the errors in the TTP. Even though we very much agree that great attention should be given to the extra-analytical phases, focus on the analytical phase is still important. Especially for less frequently performed, specialised tests, analytical performance has been reported to vary substantially [29]. Variations in measurement procedures may influence clinical decisions and thereby treatment of patients as recently reported for prostate specific antigen [37,38]. Whereas standardisation of measurement procedures is the optimal way of assuring similar test results throughout the world, this is difficult and cumbersome to achieve for all tests. An initiative for harmonisation of clinical laboratory measurements procedures for which there are no higher order reference measurement procedures or primary reference materials has therefore been initiated by the AACC [11,39]. If successful, this will lead to harmonisation of test results for important measurement procedures, avoiding clinical decisions based on erroneous assumptions. The success of this project may be dependent on funding and good cooperation with manufacturers. Additionally, rules for internal quality control including performance requirements and their harmonisations must be addressed. Monitoring of the harmonisation process for the analytical phase can be performed by EQA organisations. However, organisations have to seriously assess the programmes they offer, especially with regard to the quality control material. It is extremely important that commutable control material is used so that performance between methods can be assessed [40–44]. In addition, harmonisation of methods for evaluating participants in EQA programmes is necessary. The European Organisation for External Quality Assurance Providers in Laboratory Medicine [45] is working to achieve this aim in Europe.

4. Post-analytical phase

4.1. Verification, reflex and reflective testing

Adequate verification routines for analytical results are necessary to ensure good laboratory practise. Though it is likely that most laboratories have such routines in place, studies indicate that which tests and which test results are included varies [46,47]. Our experience, based

on running a European post-analytical EQA scheme for automated haematology, indicates that verification routines and corrective actions for complex testing such as automated haematology are poorly harmonised, to the extent that it may affect quality of patient care [48]. Similar challenges are likely for related procedures such as auto-validation rules and routines for reflex and/or reflective testing. For all these post-analytical procedures, consensus has to be reached on when for example auto-validation or reflective testing is indicated, for which tests and for what type of results. This type of testing can be harmonised within certain areas or countries, but is likely to be difficult to achieve on an international scale as the disease spectrum and prevalence of disease vary among countries. Accreditation bodies have the potential to be facilitators for harmonisation of verification procedures, whereas national laboratory societies could be drivers for implementing harmonised routines for reflex and/or reflective testing. However, both processes are likely to be slowed down by the lack of laboratory and IT resources. National laboratory societies and/or EQA organisations could monitor the harmonisation efforts.

4.2. Units and reference intervals

From a clinician's point of view, it is difficult to understand why reference intervals and reporting units are inconsistent between laboratories, and in particular that action limits also may vary within local areas with homogenous populations. Principles on how to establish and harmonise reference intervals have been proposed [49–51]. To achieve harmonisation of reference intervals, as a minimum within a country or a region that has a population with similar prevalence of disease, must be a clear goal for our profession [52]. However, the extent to which this is achievable in different countries will also depend on the success of the previously mentioned harmonisation project for measurement procedures. In the Nordic countries, common reference intervals have been established through the Nordic Reference Interval Project (NORIP), with each laboratory being monitored by EQA schemes to assess if it can use the common reference intervals for its reporting [53–55]. Countrywide initiatives for harmonisation of reference intervals are also currently on-going in for example the United Kingdom [56], financed by a grant from the Department of Health. Follow-up and continuous monitoring of the appropriate use of reference intervals can be performed by EQA organisers.

4.3. Interpretative commenting

It has been shown that interpretative comments are welcomed by clinicians, being time-saving and improving the accuracy of their diagnoses [57–59]. Several studies show that although most of the interpretative comments given by laboratory specialists are appropriate, inconsistencies in comments are observed when laboratory specialists are presented with the same case histories [60,61]. Most importantly, some comments may be directly misleading. It has therefore been suggested that interpretative commenting should be limited to a few specialists in each laboratory [60]. From our point of view, interpretative commenting, in particular for complex testing or for laboratory tests that the requesting physician is unlikely to be able to interpret adequately, should be an integrated and central part of laboratory specialists' daily activities. However, it is absolutely essential that the quality is improved and that practise is harmonised, a process where national laboratory societies can play an important role. Improved quality can be achieved by education, availability of best-practise and evidence-based guidelines and by establishing or expanding EQA programmes to assess this post-analytical activity. Some EQA schemes already include or focus on interpretative commenting [10,29,62,63]. Equally important is that when a laboratory applies for accreditation or is audited against ISO 15189 or similar standards, assessors must examine the EQA results for interpretative commenting in line with results from analytical EQA programmes.

4.4. Laboratory report forms and reporting of critical results

The laboratory report form in its paper or electronic version is important as our primary tool for communicating the laboratory test results and related information to the requesting physician. Harmonisation may therefore improve the quality of this communication by ensuring that laboratory report forms contain all the information that is essential for the requesting physician to make optimal use of the laboratory test results [64]. The quality of laboratory report forms can be evaluated through EQA schemes, for example by inclusion in already established schemes [29,65]. Reporting of critical values or critical results is another key element in communication with the requesting physician [32]. A recent review shows that the reporting of critical values is very heterogeneous, both when it comes to procedures on how to report and what results to report to whom [66]. In a study from India, adequate reporting was achieved for only 1/4 of critical results (17% of the total production), due to different reasons with incomplete request forms a major cause [67]. Reporting of critical results is a field where efforts must be made to improve the quality at many levels [68]. International laboratory societies can be facilitators for this process by making guidelines on how decisions on critical results can be made, including communication and agreement with clinicians. As a European–Australian cooperation, the EFLM has established a Task and Finish Group to deal with these questions [69]. Harmonisation of which test results are to be reported as critical results is likely to be achievable nationally or locally, as this will depend on how the local healthcare systems are organised. The process could be facilitated and monitored by national laboratory societies.

5. Post-post-analytical phase

In the post-post-analytical phase, the laboratory test results are interpreted and actions are initiated in the clinical context, and these are communicated to the patient. This part of the TTP is not in any way under the laboratory's control. It must nevertheless be a major concern for us, since if laboratory test results are not followed up adequately, our efforts in contributing to quality healthcare for the patient are wasted. Two recent systematic reviews show that a substantial proportion of laboratory test results, both in ambulatory (7% to 62%) and hospitalised patients (20% to 62%), is not addressed, with potentially serious negative outcomes [70,71]. Additionally, it is generally of concern whether the interpretation of the laboratory tests and the actions taken upon these are adequate. In a series of papers based on case histories circulated internationally, we have addressed how clinicians, mostly general practitioners, interpret laboratory test results including changes in a monitoring situation [72–74]. In general, our data indicates that there is a large intra- and inter-country variation in interpretation and subsequent actions, that concepts of analytical and biological variation are not well known and that adherence to guidelines is very variable. The need for harmonisation in the post-post-analytical phase is clear, and as laboratory specialists we can play an important role in the education of our users to improve on the quality of this phase. The most immediate solution is locally, by providing clinicians with harmonised best-practise interpretative comments to ease their work, by streamlining our reporting to make it user-friendly and by providing guidance to clinicians both in writing and by direct communication. On national and international levels, we must work together by collaboration between clinical and laboratory societies to provide recommendations and guidelines.

6. Conclusions and future perspectives

To achieve harmonisation of the TTP is an ambitious goal, but the many international and national harmonisation initiatives give us hope for the future. We have in this article, as a starting point for discussion, suggested achievable levels of harmonisation for the different

steps and phases of the TTP. We have also identified likely facilitators and barriers, and suggested how harmonisation efforts can be monitored. There may be many opinions on this point, and we welcome the discussion. An example of how harmonisation can be achieved for large parts of the TTP and how the laboratory profession can have impact at many levels is the introduction of HbA1c as a diagnostic criterion for diabetes mellitus in Norway. Similar initiatives have been taken in other countries. In 2009, an international expert group published recommendations on the use of HbA1c for this purpose [28], followed by other key players in the field [27,75,76]. By this time, the reference measurement procedure for HbA1c was already established. In Norway, these recommendations were reviewed by a working group composed of clinical and laboratory specialists [77], resulting in the Norwegian Health Authorities instructing that HbA1c should be used as the primary diagnostic tool for diabetes mellitus nationally [78]. However, laboratories are only allowed to report HbA1c results to be used for diagnosis if they fulfil analytical performance requirements, the monitoring of which are performed by the national HbA1c EQA scheme. In this EQA scheme, laboratories report results from both EQA control materials as well as internal quality controls. The EQA organisation then informs in individual feedback reports to the laboratories if they fulfil the analytical performance requirements set to use HbA1c for diagnostic purposes, and offer help if not [79].

Generally, successful harmonisation is likely to depend on the ability of laboratories, organisations and stakeholders to cooperate as well as on available funding and resources both in the laboratory and in the clinical fields. Additionally, for parts of the TTP, some basic work is required before it is possible to take the harmonisation process further. This includes error identification and characterisation, development of systems for monitoring of errors as well as establishment of harmonised quality indicators and performance requirements. Another important aspect that needs more focus is how should the laboratory act when a laboratory error occurs, and the harmonisation of these actions. It is of course easiest for the laboratory to reject a sample because an error has occurred, for example if rules for stability have been exceeded, and there is thus uncertainty about the result [3,80]. Nonetheless, sometimes more harm than good can be done to the patient by not reporting an uncertain result than by reporting it and stating the uncertainties involved.

The speed with which we may expect to arrive at our goal is likely to be higher for frequently performed laboratory tests where standardisation and/or harmonisation of many steps are already in place. Additionally, as increased quality and harmonisation of laboratory procedures will require resources and funding, harmonisation may be more easily achieved in some parts of the world than others. A challenge and great opportunity is to turn barriers into drivers or facilitators, e.g. such as with reimbursement systems or strong opinion leaders. Accreditation standards can also be efficient drivers and facilitators. While many laboratories in Europe are accredited against the ISO standard 15189 and this standard refers to the TTP, the extra-analytical phases are less prescriptive compared with similar items in the Joint Commission International and the College of American Pathologists standards used in other parts of the world [32].

To monitor harmonisation efforts and effects, EQA organisations are in most settings a natural choice [10], either by expanding existing schemes to assess other relevant phases of the TTP or by setting up new schemes. We have as part of a European project set up a case-based worldwide EQA scheme assessing most of the TTP for porphyria-related metabolites [29]. The specialised laboratories that in most countries perform the full range of porphyria-related tests, select diagnostic strategies based on available clinical information, perform the relevant analyses and finally in the laboratory report provide a diagnosis including clinical advice. Our EQA scheme accordingly assesses all these pre–(pre) analytical, analytical and post–(post-) analytical aspects. With increased availability of electronic requesting, problem-based and reflex or reflective testing is likely to be increasingly implemented, and EQA schemes

must be developed to reflect this trend. For common analytes and pre-/post-analytical procedures, schemes should be run by local EQA organisers and national meetings could be organised to address results.

Harmonisation of the TTP will be a great challenge for the international laboratory community in the years to come. All parts and steps of the TTP are equally important, as whether the final result actually benefits the patient, depends on the weakest part of the chain. We must renew our efforts to achieve harmonisation of those parts we can directly control and those that are, or typically have been, outside our control, in the best interests of the patient.

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