Editorial

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The long way to standardization of practices: HbA_{1c} as archetypal example

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Standardization of laboratory tests is a highly desirable process as it guarantees the delivery of comparable results among methods and laboratories, thus avoiding the risks of incorrect interpretations and of inappropriate clinical decisions. However, achieving this goal is not so easy a task, even though standardization procedures are clearly defined and widely accepted, e.g. according the ISO 17511 guidelines [1].

Apart from the analytical aspects related to the measurement itself, which refer to biochemical and metrological concepts, all the other steps of the standardization process have to be taken into account, from pre-analytical but mainly to post-analytical phases [2]. Indeed, standardization is a multifactorial process which involves many stakeholders [3].

Standardization of HbA_{1c} assays is an excellent example of global complexity. Even though the reference method was published in 2002 by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on HbA_{1c} standardization [4], the field implementation in clinical laboratories and in medical practice at the physicians' and patients' levels is still ongoing around the world [5].

This global implementation is a strategy of paramount importance because the HbA_{1c} assay, which was for many years used in current practice only for diabetes monitoring, is now recommended in the diagnosis of diabetes mellitus [6]. Due to the increasing incidence of the disease worldwide and its severe degenerative complications, the availability of reliable HbA_{1c} assays providing comparable results is a public health priority and a major goal in order to improve patient care worldwide [7].

When the establishment of a reference method procedure, the processing of reference materials, the homogeneous calibration of tests by manufacturers and the establishment of a robust international network of reference laboratories are achieved, the analytical aspects ensuring the quality of results of HbA_{1c} assays at the clinical level are mainly related to the evaluation of method performances and the establishment of quality targets. Such initiatives have demonstrated their efficiency: well-admitted quality targets have been established and the global quality of methods used for HbA_{1c} assay has improved in a large number of countries [8, 9]. However, ensuring the completion and the success of the overall standardization process remains a challenge in many cases.

The example given in the paper published by English et al. in this issue of *Clinical Chemistry and Laboratory Medicine* illustrates pretty well the current situation of HbA_{1c} assay standardization and the eventual complexity of the process [10]. It describes a recent campaign of the IFCC-Committee for Education in the Use of Biomarkers of Diabetes (C-EUBD) in China. This Committee ensures the implementation of the HbA_{1c} standardization process, and organizes education actions in the field of diabetes mellitus worldwide, in the continuation of the activities of the previous IFCC working group on HbA_{1c} standardization. It faces on that occasion other types of challenges, which may turn out to be potential barriers [3]. They are related to national or local scientific, operational, economic and legislative specificities, which make the simultaneous rallying of different stakeholders necessary to overcome them, according to strategies taking into account the specificities of every country.

The campaign reported in this paper was based on a multicenter study involving a number of stakeholders, and especially key opinion leaders and policy makers of China, as well as manufacturers. This quality assurance program demonstrated the feasibility of large-scale trials using fresh frozen whole blood samples and good global performances of the HbA_{1c} assay methods evaluated, which showed the adequate use of standardized methods. This is interesting information, but this is not the major outcome of this study. An important achievement is the demonstration that it was possible to generate a first network of laboratories in China performing a standardized measurement of HbA_{1c} with methods which meet IFCC criteria for analytical performance and provide comparable results aligned to the international reference values [9]. This is the first step to further structured actions such as the establishment of a national quality

scheme, which is necessary for ensuring the correct use of HbA_{1c} results for the diagnosis of type 2 diabetes [11]. Another major indication given by this paper is the possibility to engage multiple stakeholders in a common approach of method standardization aiming at improving the quality of diabetes testing and thus patient care. Such approaches must be multiplied not only in China but all over the world, first, to give a new lease of life to standardization initiatives [3], second, to ensure the validity of clinical decision making proposed by the new diagnostic and therapeutic strategies involving the use of HbA_{1c} values.

An example is given in a second paper of this issue, in which Duff et al. address the importance of optimizing the frequency of HbA_{1c} testing in the follow-up of patients with diabetes [12]. This study reports that, in suboptimally controlled diabetes mellitus, HbA_{1c} testing every 6 months was as effective as quarterly testing. This result, which supports international recommendations [6], may be important in terms of public health, as, if a less frequent testing is adequate, the global treatment scheme is less costly for the society and less constraining for the patients. However, the other prominent information of this paper is that the vast majority of patients do no reach the commonly recommended HbA_{1c} targets in 1 year. This finding challenges the ability of health systems and professionals to adequately achieve an optimal patient care, especially with respect to the risk of development of the severe long-term complications of the disease, and underlines the necessity of critically reviewing the conditions of patient monitoring allowing reaching the best outcomes.

It should be noticed that in this paper neither the analytical aspects of the assay nor the meaning or interpretation of HbA_{1c} values are questioned. This clearly demonstrates that, thanks to HbA_{1c} assay method improvement and standardization, prescribers and patients trust in delivered values. This also reinforces the necessity to continue worldwide the efforts of networking in order to establish robust and sustainable quality assurance schemes, as reported in English et al.'s paper [10]. More generally, this "HbA_{1c} story" is an archetypal example of the complexity of global standardization approaches, which are not only matters of concern for laboratory people. In order to be effective, these approaches must involve from the beginning all stakeholders, who must be fully associated and convinced of the legitimacy of the process and of its interest in patient care, from heath regulators to clinicians and patients [3]. In many cases, the final standardization of practices is still on its long way.

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References

1. Panteghini M. Implementation of standardization in clinical practice: not always an easy task. Clin Chem Lab Med 2012;50:1237–41.
2. Plebani M. Harmonization in laboratory medicine: more than clinical chemistry? Clin Chem Lab Med 2018;56:1579–86.
3. Cobbaert C, Smit N, Gillery P. Metrological traceability and harmonization of medical tests: a quantum leap forward is needed to keep pace with globalization and stringent IVD-regulations in the 21st century! Clin Chem Lab Med 2018;56:1598–602.
4. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, et al. Approved IFCC reference method for the measurement of HbA_{1c} in human blood. Clin Chem Lab Med 2002;40:78–89.
5. Gillery P. New trends in the long and puzzling history of HbA_{1c}. Clin Chem Lab Med 2015;53:1297–9.
6. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41:S13–27.
7. Gillery P. A history of HbA_{1c} through Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2013;51:65–74.
8. EurA1c: The European HbA1c trial to investigate the performance of HbA_{1c} assays in 2166 laboratories across 17 countries and 24 manufacturers by use of the IFCC model for quality targets. Clin Chem 2018;64:1183–92.
9. Weykamp C, John G, Gillery P, English E, Ji L, Lenters-Westra E, et al. Investigation of 2 models to set and evaluate quality targets for hb a1c: biological variation and sigma-metrics. Clin Chem 2015;61:752–9.
10. English E, Weykamp C, Ji L, Siebelder C, Shan Z, Wang Y, et al. The global impact of the International Federation of Clinical Chemistry and Laboratory Medicine, Education and Management Division: engaging stakeholders and assessing HbA_{1c} quality in a multicentre study across China. Clin Chem Lab Med 2019;57:288–95.
11. Organisation WH. Use of Glycated Haemoglobin (HbA_{1c}) in the Diagnosis of Diabetes Mellitus (abbreviated Report of a WHO Consultation). Geneva, Switzerland: WORLD Health Organization, 2011.
12. Duff CJ, Solis-Trapala I, Driskell OJ, Holland D, Wright H, Waldron JL, et al. The frequency of testing for glycated haemoglobin, HbA_{1c}, is linked to the probability of achieving target levels in patients with suboptimally controlled diabetes mellitus. Clin Chem Lab Med 2019;57:296–304.

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