Higher HbA1c Measurement Quality Standards are Needed for Follow-Up and Diagnosis: Experience and Analyses from Germany

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ABSTRACT

Measurement of HbA1c is an essential laboratory measure for the follow-up and therapy decision-making in patients with diabetes. HbA1c is one of the measurands in laboratory medicine that have to be successfully checked according to the criteria of the guidelines of the German Medical Association (Rili-BAEK) in external quality assurance using the reference method value concept, when applied in patient care. The allowed deviation of ± 18 % in external quality assessment (EQA) and ± 10 % in internal quality control has been ultimately met by virtually all the different manufacturers and methods. However, such broad limits for permissible deviations are not suitable in view of medical requirements in patient care. The low-level acceptance criteria also depends on the previously used EQA materials used in Germany. In fact, HbA1c measurement results that are imprecisely measured or come from incorrectly calibrated devices are difficult to identify. With implementation of unprocessed fresh EDTA blood, the situation has changed. Until now systems with unit use reagents for point-of-care testing (POCT) of HbA1c are not mandatory to participate in EQA schemes in Germany. This paper outlines why there was a need to narrow the acceptance limits listed within the Rili-BAEK for HbA1c's internal (to ± 3 %) and external (to ± 8 %) quality controls in EQA schemes for Germany, which will take place after a transition period in the next years. Higher quality in HbA1c measurements will help to avoid misdiagnosis of diabetes as well as potential over- or undertreatment of patients at risk for diabetes.

Abbreviations

INSTAND "Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien e.V." (Society for Promotion of Quality Assurance in the Medical Laboratories)
EQA External quality assessment
oGTT Oral glucose tolerance test
POCT Point-of-care testing
Rili-BAEK Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations

Introduction

The publication of the "Diabetes Control and Complications Trial (DCCT)" and other prospective long-term studies such as the "UK Prospective Diabetes Study Group (UKPDS)" have established HbA1c as the essential laboratory measurand for making diabetes therapy decisions and follow-up [1–3]. Over the course of many years, the HbA1c measurement was primarily used for monitoring diabetes. Since 2010, this value has become part of parameters beside plasma glucose values to diagnose diabetes [4–6]. Using the HbA1c value for follow-up presents high requirements of the parameter measurement quality as changes > 5 mmol/mol are regarded as clinically relevant and should lead to therapy adjustments. A significantly higher degree of analytical accuracy and precision is necessary when it is used for the diagnosis of diabetes. The use of HbA1c as an instrument for the diagnosis of diabetes was introduced by the American Diabetes Association, and other associations, like the IDF and the WHO, and a HbA1c limit value of ≥ 48 mmol/mol for the diagnosis of diabetes [7–11]:

- Is the degree of biological variation of the HbA1c concentration too broad for a confident diagnosis, even when the actual measurement takes place under ideal conditions (i. e., only a small measurement error occurs, etc.)?
- Is the analytical reliability of the different available HbA1c measuring systems sufficient and adequately standardized for its use?
- Are the HbA1c measuring systems intended for diagnostic use by the manufacturer? This question has been addressed by the US FDA. There were no claims for diagnosis until clinical organizations started recommending HbA1c for diagnosis. Then manufacturers used the claim outside the US. In the US, the FDA requires additional approval to make this claim and several manufacturers now have the diagnostic claim.
- Are the criteria for the permitted deviation in the guidelines, for example, of the German Medical Association (Rili-BAEK) in Germany, for the internal and external quality controls sufficient for quality assurance?
- An HbA1c value of ≥ 48 mmol/mol as a diagnostic decision limit is solely based on epidemiological data for detectable retinopathy.

In Germany HbA1c is one of the measurands in laboratory medicine, which has to be checked in external quality control using the reference method value in accordance with the guidelines of the Rili-BAEK, when applied in patient care [12]. The analyzers for HbA1c available on the European market are generally metrologically traced back to primary reference material and a high analytical reliability is thereby ensured. All systems on the market in Europe must have a CE mark, after a transition period they must fulfill the newly enhanced requirements of the (IVDD) European in-vitro regulation [13]. Therefore, in Germany no system should be on the market that is not sufficiently calibrated.

For many years the permissible deviation of ± 18 % in external quality assessments (EQA) and of ± 10 % for internal quality controls has been met by virtually all the different manufacturers, methods and laboratories. However, these broad limits for the permissible deviation as well as the EQA material used so far (see below) made it difficult for users in Germany to safely identify incorrect measurement results or incorrectly calibrated analyzers in the HbA1c analysis [14, 15]. In an assessment compliant with Rili-BAEK, the measurement result may lie between 43 mmol/mol and 63 mmol/mol for an external quality control of an HbA1c value of 53 mmol/mol.

This review outlines why there was a need to narrow the HbA1c acceptance limits for the internal and external quality controls for HbA1c in Rili-BAEK in Germany.

HbA1c for Diagnosis and Therapy of Diabetes

In diabetes care, the HbA1c concentration is used as the major measurand for assessing metabolic control and is therefore an important component of differentiated therapeutic decision making [6, 16]. Individual targets are determined and monitored, at least in part, using the HbA1c values. The HbA1c value is usually an important surrogate endpoint in clinical studies to evaluate the efficacy of a new drug and the success of different therapeutic strategies.

Following ADA and WHO, the clinical recommendations by the German Diabetes Association (DDG) permit diagnosis of diabetes using HbA1c values. The current version of this recommendation states that "... the specificity of a HbA1c value ≥ 48 mmol/mol is significant enough to diagnose diabetes with satisfactory level of certainty. At the same time, the sensitivity of an HbA1c value of < 39 mmol/mol is significant enough to make the diagnosis of diabetes sufficiently improbable" [6].

If the HbA1c value is notably high, e. g. 66 mmol/mol, the diabetes diagnosis is conclusive. In the HbA1c range of 42 to 97 mmol/mol, it is not unusual to observe deviations between laboratories of 18 mmol/mol and higher [17]. However, in the range of an HbA1c value of 37 to 48 mmol/mol many of the patients studied (50 %) showed pathological plasma glucose values in an oral glucose tolerance test (oGTT). In this case, the HbA1c measurement does not conclusively exclude diabetes. Other measurands (fasting/oGTT plasma glucose values) should be included for diagnosis [18]. Therefore, it can be stated that solely using the HbA1c value to diagnose diabetes often results in at least discrepant results in comparison to fasting/oGTT plasma glucose values. These critical statements on using the HbA1c to diagnose diabetes do not imply that the other measurands such as fasting plasma glucose and the 2-h value after an oGTT are significantly more suitable for the diagnosis [6]. The oGTT also presents a gamut of methodical difficulties [19, 20]. When using plasma glucose criteria for the diagnosis of diabetes, it is possible to identify other patient subtypes than when

using an HbA1c limit value of ≥ 48 mmol/mol. Therefore, the internationally accepted algorithm for the diagnosis of diabetes using HbA1c or fasting plasma glucose or the 2-h value during an oGTT will detect different diabetic populations with all possible epidemiological and therapeutic problems and interpretations.

The lack of clearly defined reference intervals as a basis for defining conclusive diagnostic criteria has made the current situation more problematic. The different pre-analytic influences on the HbA1c value must also be considered [21–24].

The variation of the HbA1c values is most probably also influenced by the quality of patient metabolic control: poor metabolic control results in shorter erythrocyte life span, which thereby might result in a lower HbA1c value than it actually should be; however, the scientific knowledge about this is scarce [25, 26].

In practice, a clear and pragmatic approach must be reached for diagnosing diabetes. In this context, it is also important for the users (i. e., general practitioners, diabetologists/endocrinologists, gynecologists, cardiologists, nephrologists, and clinical chemists) to be properly trained in recognizing the limits of the laboratory tests. Some manufacturers use claims such as "can be used to diagnose diabetes" to promote their HbA1c measuring system, which is scientifically not acceptable.

Standardization

The HbA1c concentration is one of the few clinical-chemical parameters that has been standardized on an international level. In order for various measurement methods and measuring systems to achieve comparability, in 1996, the National Hemoglobin Standardization Program (NGSP) established that the value was permitted to be traced back to DCCT equivalents; this was an important harmonization step, but not a standardization. To achieve a higher order of accuracy of measurement, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a reference system for HbA1c with a network of reference laboratories from which one reference measurement procedure and reference material for recalibration of analyzers emerged [27]. This is in line with a metrological approach.

Standardization in accordance with IFCC had an overall positive effect with regard to the comparability of HbA1c values. The experience of using the HbA1c measurement to diagnose diabetes and the - in part - contradictions to oGTT listed above have unraveled over the last 5 years that there is significant room for analysis quality improvement by both the manufacturer and user.

Internal Quality Control

HbA1c measurements, as all quantitative determinations performed in medical laboratories, are governed by internal quality control, e. g. in accordance with the Rili-BAEK in Germany [12]. This applies to clinical-chemistry analyzers in the core laboratory as well as to point-of care (POCT) systems. For laboratory systems, successfully performed two quality control samples on a daily basis are mandatory for the approval of analyzers, reagents and personnel. By contrast, point-of-care systems with unit-use reagents in which only daily electronic/physical standards are used, need to be analyzed once per week using a control sample. The HbA1c value is permitted to have a relative deviation of ± 10 % from the individual value to the target value of the control material for all systems. The control materials for internal quality control are mostly offered by the device manufacturers in order to correspond with their analyzers. How equivalent this material is to a patient sample remains to be determined, since these are in part processed and stabilized lyophilisates or liquid samples. The internal quality control serves to assure the level of analysis quality in the medical laboratory on a daily basis and directly contributes to the patient safety. With this aspect in mind, the broad HbA1c acceptance limits for internal quality control should be adjusted to the current requirements for safe diagnosis and therapy. A narrowing of the allowed relative deviation of the individual value from the target value to ± 3 % would be effective. This target value is based on medical requirements. The coefficient of variation as a measure for the scatter of the measurement results should not be > 2 %. This corresponds to a Minimal Difference of 1.9 mmol/mol Hb at 48 mmol/mol. Since 2008 the Rili-BAEK is not listing the coefficient of variation in the internal quality control scheme in Germany, but the "acceptable relative deviation of the individual value or the relative quadratic mean value". This value covers not only the imprecision, but also the bias of a measurement system [28].

External Quality Control

For HbA1c, the external quality control and the quarterly mandatory participation in EQAs is regulated for example in the German Rili-BAEK. The assessment of the EQA occurs using the reference method value. The concept of the Rili-BAEK differs from the approach used in other countries. With the approach used in Germany the EQA assessment for HbA1c is based on a target value, which was obtained using a measurement principle of higher metrological order. This reference method value with particularly high accuracy comes as close to the "true value" as currently technically possible. This concept comes with a "standardization", which is method-independent and clear criteria for acceptance limits can therefore be defined. At the moment, a maximum permitted deviation of participant results is defined at ± 18 % from the target value [12]. Just as for internal quality control, the Rili-BAEK criteria for external quality control are also much too broad from a medical requirement perspective.

In other countries, other concepts are used for rating in EQA. There the assessment of EQA results is generally based on the consensus value concept. The median is calculated using the complete collective of all EQA participants as a basis or from the respective partial collectives of different analytical methods and systems. Participants can deviate from this median within a maximum defined limit. Accuracy and comparability of the values over time are not ensured for consensus values from method-dependent partial collectives. Lower acceptance limits can be more easily realized as problems with poor commutability of the EQA material can mostly be excluded. Commutability is understood to be the ability of a control material to give equivalent results on an analyzer as with native patient material. The specifications for external quality control for HbA1c measurements are ± 6 % in many countries, such as the USA, Netherlands, England and Switzerland; in China, the acceptance limits for external quality controls are ± 8 %.

In accordance with the German concept, HbA1c can only be billed to health insurance companies as a laboratory-medical service in conjunction with successful participation in EQAs. A narrowing of the acceptance limits for this measurand in external quality controls increases the pressure on users and manufacturers but should not lead to disregarding the objective necessity of quality improvement – especially in view of the medical requirements in patient care.

In Germany, manufacturers and users of POCT systems are not obliged to participate in EQAs. In contrast, all devices in Switzerland are subjected to testing. In the interests of high transparency, the POCT systems for HbA1c measurement in Germany should also compulsory participate in EQA and all data should be made public.

Control Material for EQA – The Problem of the Sample Matrix

Making commutable control material available is one of the challenges for EQA organizers. To date in Germany, processed control materials for which commutability has not been guaranteed have been used in HbA1c by EQA organizations. For this reason, the quality of the different HbA1c systems could not be optimally assessed [29].

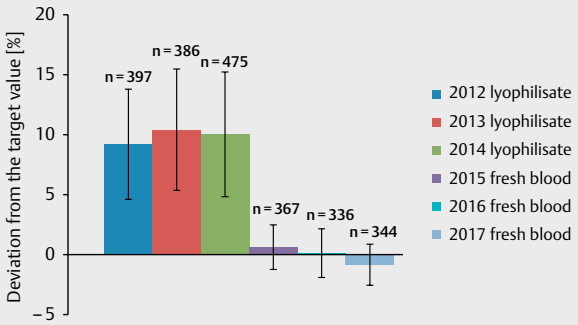
With the recent introduction of unprocessed fresh EDTA blood as an EQA material, the situation has changed fundamentally. This material is as close to patient blood as possible. Artificial matrix effects are thereby largely avoided (▶ **Fig. 1**). In practice, care should be taken to shipment of the control blood samples and the HbA1c measurement should be performed by the participating laboratory within two days after the samples arrive in order to avoid stability problems and aging effects on the control samples. Experience in recent years have shown that maintaining a tight time schedule when using whole blood samples is accomplishable [13]. The participants in the EQA get detailed instructions by both German EQA organizations for correct handling of the samples. However, so far no information is available how the routine measurements of patient samples are done in daily practice in the individual laboratories.

The heterogeneity of the HbA1c results of past EQAs is, to a great extent, a direct result of commutability problems. The unification of the material for control samples should per se contribute to smaller deviations than before in EQA measurement results. This makes it easier for manufacturers to comply with lower acceptance limits, which is important for implementing narrower limits in practice (see below).

With respect to the availability of control material for internal quality control the manufacturer of the HbA1c measurement systems should provide appropriate products.

Consequences of Narrowing the Requirements for Acceptance Limits

Recently it becomes clear that the acceptance limits for external quality control in the Rili-BAEK will be lowered from the current ± 18 % to ± 8 %, taking into account the current state of technology for most manufacturers and users. Using suitable control material results in almost no method-dependent differences as can



▶ **Fig. 1** Results obtained in HbA1c EQA using lyophilisates or fresh blood samples (EDTA blood). Deviation of the average of participant results from the reference method value in HbA1c EQA from May 2012 and 2013, January 2014 and May 2015, 2016 and 2017, given in percent (all data are from INSTAND EQA). The lyophilisate samples used come from different manufacturers, the fresh blood samples from individual donors. The HbA1c concentration range lies between 33.1 and 37.4 mmol/mol. The averages were calculated from the results obtained using analyzers from Abbott, Beckman-Coulter, Biorad, Roche, Tosoh and Menarini.

be seen in the EQA result from January 2018, for example (▶ **Fig. 2**). With an acceptance limit of ± 8 % instead of the previous ± 18 % for deviations from the reference method value, the pass rate of HbA1c measurement systems will decrease from 93 % to 83 %. This rate most probably can be increased by taking more care of the systems in daily practice.

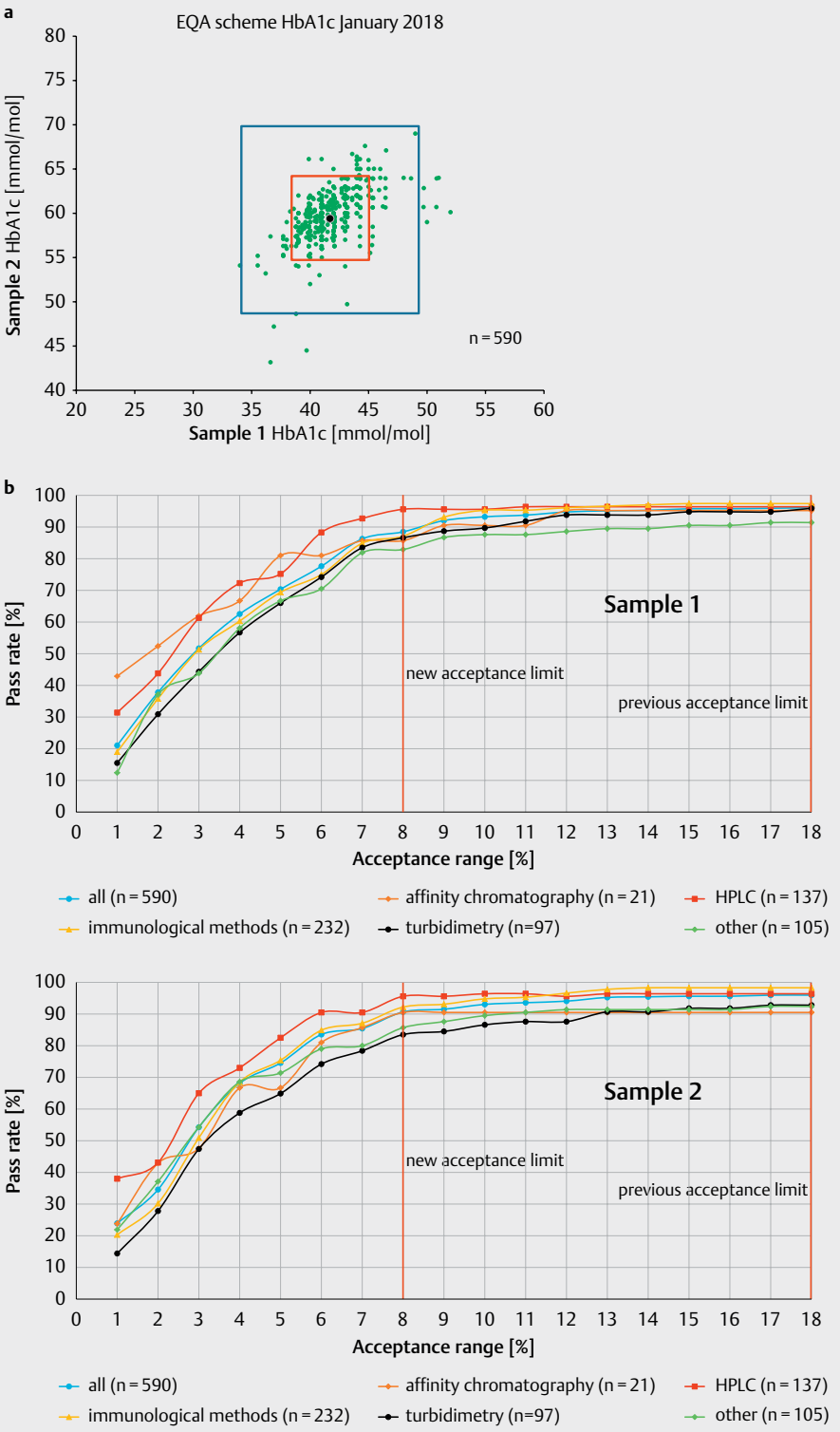
HbA1c Measurement with Laboratory Methods and POCT Systems

The specifications to-date for internal and external quality controls are relatively easy to fulfil for most users of the laboratory systems currently on the diagnostics market. There are significant differences in particular between the POCT systems themselves which appear to fulfill the tighter quality requirements to varying degrees [30, 31].

A higher requirement of measurement quality thereby can be expected to present a higher hurdle for some POCT systems than for laboratory systems. In order to keep the advantages of POCT systems such as point-of-care use and immediate availability of measurement results, it is necessary that these systems have the same specifications for EQAs than laboratory systems. There should also be no differentiation between diagnostic use and therapeutic follow-up use of HbA1c. In order to improve measurement and treatment quality, all HbA1c measuring systems available on the market – including POCT systems – should have the same quality standards to improve patient safety.

Costs of the HbA1c Measurement

The costs associated with the increased effort when narrowing the EQA limit values should be covered by the health care insurance companies. This means that the medical requirements of a high measurement quality should be reflected in the cost reimburse-



▶ **Fig. 2** HbA1c EQA results for fresh blood samples from INSTAND (January 2018). The Youden plot (Fig. 2a) presents the results from samples 1 and 2 of the complete collective (green dots) of 590 participants and the reference method value (black dot). The HbA1c target value of sample 1 is 41.7 mmol/mol and from sample 2 is 59.4 mmol/mol. The acceptance limit for the deviation from the target value of ± 18 % is displayed as a blue frame; the acceptance limit of ± 8 % is displayed as a red frame. Clear outliers were removed, that is, samples for which there was a mix-up or error in the units. Fig. 2b shows these results again separately according to the different analysis methods used in the EQA. (Note: These figures serve as examples. The results can vary minimally with a different EQA).

ment. For a reliable diagnosis and proper therapy, a high quality HbA1c measurement is of significant clinical and health-economic importance; for example by avoiding misdiagnosis and additional diagnostic procedures, like the oral glucose tolerance test.

Compared to other European countries, Germany has an exceptionally low reimbursement level for laboratory diagnostics, although we are not aware of any international comparison. This presents a difficulty for new developments and for realization of new quality demands in view of personalized or stratified medicine. An overview of the cost situation and other aspects (such as market share of manufacturers or laboratory/POCT systems) in a European and International context is still missing.

Summary

The Commission for Laboratory Diagnostics in Diabetology has supported decreasing the tolerance limits in EQA schemes for HbA1c measurements in Germany by the BAEK for reasons of medical necessity in one step from ± 18 % to ± 8 %. Decreasing tolerance limits for the internal quality control from ± 10 % to ± 3 % should also occur in one step in parallel. With higher quality in HbA1c measurements, less patients will receive an incorrect diagnosis of diabetes and suffer potentially from false, and even dangerous therapeutic decisions. Market considerations and what is possible from a technical standpoint should not be more important than medical requirements. For this reason, there should not be any differences in quality control criteria for central laboratory or point-of-care analytics, i. e. no differences based on the intended use. As far as we know, there is no publicly-accessible information on whether, and to what extent, HbA1c measurements in Germany are used for diagnostic purposes. The issue of the limit value of HbA1c of ≥ 48 mmol/mol remains unsolved especially in times of evidence-based medicine. However, information about the HbA1c market are not sufficiently documented and published. The discussion in this position paper refers primarily to the HbA1c measurement; however, it is also valid for glucose measurement and other biomarkers in diabetes diagnostics and therapy.

Narrowing of the tolerance limits in quality assurance will have consequences for all parties involved in HbA1c measurement – manufacturers, distributors, EQA organizations, laboratories, medical as well as non-medical assistance staff and, last but not least, the patients. There is a need for these to work together to achieve a consistently high quality for this measurand which is so far the key parameter for diabetes care and clinical diabetes research.

From our point of view, the topic “Quality of the HbA1c measurement” is of relevance for all parties involved in treatment of patients with diabetes. Systematic evaluations and presentations of the EQA results should take place. Other countries might also need to improve their regulation of laboratory testing like the regulations are updated now in Germany. All countries should employ an adequate EQA. There should be stronger involvement by International and European expert associations in the area of diabetology (ADA/EASD) and Clinical Chemistry (IFCC) in the topic of HbA1c measurement.

Conflict of Interest

LH is a shareholder of Profil Institut Stoffwechselforschung GmbH, Neuss and of ProSciento, San Diego, USA. He is advisor for a number of companies that develop new diagnostic and therapeutic options for diabetes therapy. He is the chair of the “Kommission für Labordiagnostik in der Diabetologie (Commission for Laboratory Diagnostics in Diabetology).

PK has no conflicts of interest (CoI) with respect to this manuscript. She is an employee of INSTAND, Düsseldorf, Germany.

GF is the medical head and director of the IDT (Institut für Diabetes - Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm (Institute for Diabetes Technology, Research and Development, Ulm University)), which performs clinical studies on medical products for diabetes therapy either of its own initiative or on behalf of various companies. GF/IDT has received or receives remuneration or consultancy fees from Abbott, Ascensia, Bayer, Berlin-Chemie, Becton-Dickinson, Dexcom, LifeScan, Menarini Diagnostics, Novo Nordisk, Roche, Sanofi, Sensile, and Ypsomed.

DGK has no CoI with respect to this manuscript. He is an employee of the Institute for Clinical Chemistry, Hannover Medical School.

WK has no CoI with respect to this manuscript.

RL declares the following potential conflicts of interest: Advisory Boards: Lilly Deutschland, Novo Nordisk Pharma; remuneration: AstraZeneca, Bayer Vital, Berlin Chemie, Lilly Deutschland, Novo Nordisk Pharma.

LM in an employee of the MVZ DaVita Dormagen GmbH. He received honoraria for oral presentations /consulting activities from: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Meyer Squibb, Eli Lilly, Kassenärztliche Bundesvereinigung, Merck Inc., MSD Sharp & Dohme, Novo Nordisk, Praxisnetz Dormagen, Servier. He declares to see no CoI with respect to this manuscript.

UAM has received no personal honoraria or coverage of travel costs from pharmaceutical companies since 2010. His working group received support for their scientific work by Fresenius Medical Care, VDBD, Diabeteszentrum Thüringen e.V., Haemopharm, NOVO Nordisk, Abbott, Pfizer Pharma, European Association for the Study of Diabetes. DMW received honoraria for oral presentations and advisory boards from the following companies: Amgen, AstraZeneca, Boehringer Ingelheim, MSD, Novo Nordisk, Sanofi. He is current president of the German Diabetes Association.

JR has no CoI with respect to this manuscript.

MS has no CoI with respect to this manuscript. He is the CEO of INSTAND, Düsseldorf, Germany.

HW has no CoI with respect to this manuscript.

MN has the following potential CoI: Advisory Boards: Becton Dickinson; Honoraria for oral presentations: Boehringer Ingelheim, Roche Diagnostics, Siemens; EQA-scheme consultant at INSTAND e.V.; Member of the Board of the DGKL and the of the Foundation Advisory Board of the Reference Institute for Bioanalytics, Member of the advisory council of the Bundesärztekammer and of D1 of the guideline of the German Medical Association on Quality Assurance of Laboratory Medical Analysis.

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