Editorial Commentary

Shaping the future of external quality assessment by integrating patient-based quality control programmes

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Introduction

External quality assessment (EQA) in medical laboratory diagnostics is not a purpose by itself. Instead, EQA exists to reduce the risk of incorrect measurement result release after validation or verification and compliant internal quality control (IQC) (1). Laboratories can either experience a false positive or false negative detection of bias by IQC or experience a drift in relation towards other laboratories using the same methods (2). Alternatively, methods can diverge from each other over time. Some of these drifts cannot be detected by (often non-commutable) IQC and thus require (commutable) EQA. Another major purpose of EQA is to monitor harmonisation status and successes of efforts therein.

EQA is not automatically superior to IQC in bias detection. To maximise its value, an ideal EQA scheme employs commutable materials, accompanied by metrologically traceable reference values. Tolerances around this target value should be based on the impact of measurement uncertainty on clinical decision-making. In addition, multi-sample evaluation in reports allows for the separation of bias and imprecision as separate sources of inaccuracy (3). Only EQA schemes which fulfil all these criteria are considered category 1 schemes as mentioned by Miller *et al.* in their description on EQA ambitions (4). Common shortcomings of classical EQA include the following: primarily, falsely assumed commutability, limiting the value of EQA to monitoring within-method agreement between laboratories. Next, target values based on metrologically traceable reference values and clinically relevant tolerances are not always available. In these cases, measurement results can only be compared to consensus values, either overall or method-group based. Further, low frequency and time lag between measurement and report can result in late detection of shifts in bias. Lastly, lack of multi-sample evaluation, resulting in limited analysis of root-cause of failure.

In patient-based real-time quality control (PBRTQC), a laboratory monitors the moving average of patient results to be able to detect sudden shifts in bias sooner than with traditional IQC (5). If laboratories serve a similar patient population and use the same units and clinical decision limits, their medians and flagging rates are expected to be comparable. Therefore, PBRTQC can not only be used for IQC, but also for EQA, a practice referred to as

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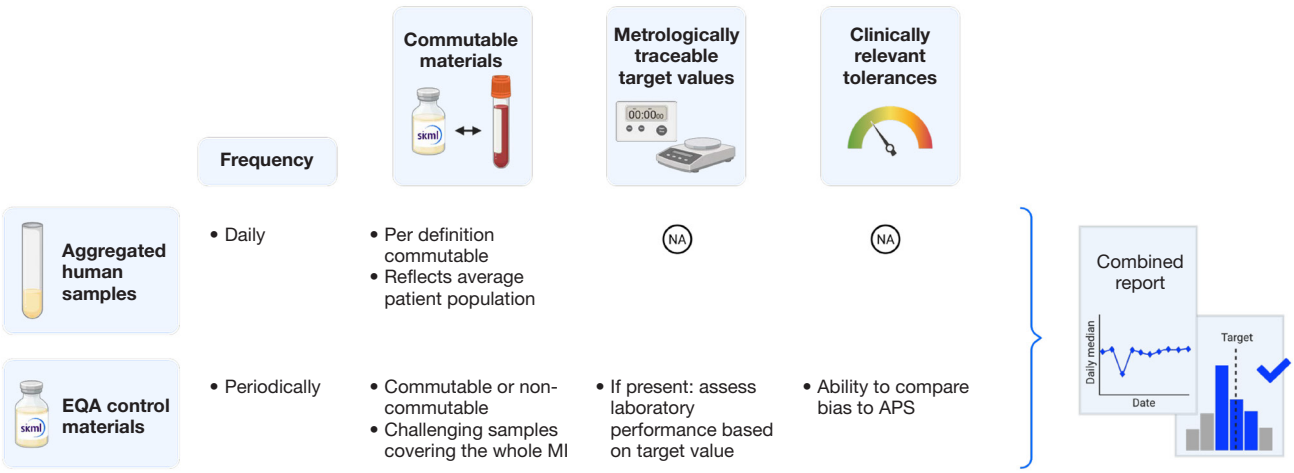

Figure 1 Properties of aggregated human sample data (PBEQA) compared to control materials (classical EQA). PBEQA results can be added to EQA reports to improve insight into instrument performance and/or assay drifts over time. Created in BioRender. Bioch M. [2026]. Available online: https://BioRender.com/3izgxxl. APS, analytical performance specifications; EQA, external quality assessment; MI, measuring interval; NA, not applicable; PBEQA, patient-based EQA.

patient-based EQA (PBEQA) (5,6). This rationale led to the introduction of the Noklus Patient Median (NOPAM) programme by the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus) (7).

NOPAM is based on the concept that patient medians and flagging rates should be stable over time, and that any change is due to pre-analytical or analytical instability or error. Participating laboratories send in daily results for their patient medians and flagging rates (percentage of results above upper reference limit and under lower reference limit, optionally). In return, they are supplied with overviews for their laboratory instruments, differences between instrument groups and group overviews of variation over time. The programme also registers data of country, patient population, sample material, sample conditions, measurement method, reagent lot number, manufacturer, instrument model and type, and any locally used factors. Participants can receive analyte-specific warnings for sudden shifts in medians or flagging rates. Data collection started in 2014 and currently, the programme has more than eighty worldwide participants and includes approximately forty clinical chemistry and haematology measurands.

PBEQA programmes such as NOPAM have several advantages and can complement classical EQA to further advance the quality of laboratory diagnostic results. This invited editorial commentary reviews these advantages and discusses how they can complement classical EQA by filling the gaps where classical EQA falls short. But does this end the need for classical EQA? We will discuss this question by outlining the limitations of PBEQA, and close off with a reflection on the future of PBEQA and EQA in general.

Advantages of PBEQA

The main advantages of quality control using PBEQA compared to classical EQA can be summarized as following. Firstly, there is no need for concerns about non-commutability (*Figure 1*). These programmes employ aggregated patient data, which are commutable per definition; together with a pre-analysis which is also per definition the same as in patient samples. Therefore, trends observed within PBEQA are recognized to reflect the clinical situation. Secondly, PBEQA employs readily available data. Once implemented, it only takes limited effort to participate, especially if data can be sent automatically from the laboratory information system to the programme. Thirdly, by sending in daily results, PBEQA enables frequent monitoring. This increases the detection rate of sudden bias and decreases lag time between origin and detection of failure, thereby contributing to the goal of EQA to reduce the risk of incorrect measurement result release. Finally, PBEQA data can aid in initiating and monitoring harmonisation efforts and improvement of assay development. For example, PBEQA can provide insight into differences between methods, platforms, or in vitro diagnostic (IVD) manufacturers and differences

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Table 1 Summary of purposes of classical EQA and PBEQA, and the utility of their combination

Purpose	Classical EQA	PBEQA	Combined
Monitor harmonisation status and successes of efforts therein	+	+	++
Detect sudden assay drift	–	++	++
Assess laboratory performance for challenging samples	++	–	++
Monitor assay drifts compared to peer group	+	+	++
Monitor assay drifts over time	+	+	++
Assess trueness of laboratory results compared to reference value	++	–	++
Capable to detect sample-specific bias due to non-selectivity	++	–	++

++, the tool is especially useful for the purpose. +, the tool is partially useful for the purpose. –, the tool is not specifically useful for the purpose. EQA, external quality assessment; PBEQA, patient-based EQA.

between (the implementation of) metrological traceability chains. This data can be made available to all stakeholders in the process of harmonisation, amongst which IVD manufacturers and EQA providers.

How PBEQA can complement classical EQA

EQA providers can compare their results with PBEQA data and produce a combined report to provide more insight into laboratory performance (*Figure 1*) (8). Such a report can aid laboratories in effectively analysing the large amount of data available in PBEQA in the form of a periodic EQA report. However, it is important that laboratories continue to monitor their instrument performance in PBEQA on a daily basis to fully gain the benefit of the frequency of monitoring that PBEQA offers. This can be made practical and time-efficient by employing a warning functionality for sudden assay drifts, as already implemented by NOPAM. The combined results of EQA and PBEQA provide extended insight into assay drift over time or in comparison to a peer group (*Table 1*). Additionally, combined (PB)EQA results can enhance insight into the success of harmonisation and standardisation efforts and the consequences thereof in clinical practice (9).

PBEQA initiatives allow EQA providers to compare results between PBEQA and their own EQA schemes (7). Such comparisons are beneficial when discrepancies are found in method performance among different EQA schemes, when methods perform dissimilar over time, or when evaluating the impact of interferents on different methods. As PBEQA results are representative of the daily workload and result set of participating laboratories, they provide tremendous insight when evaluating EQA findings. For example, the SKML (Foundation for Quality Assessment in Medical Laboratory Diagnostics; Dutch EQA provider) signalled that chloride results produced on Roche machines had a negative bias in samples with low bicarbonate (10). When other EQA providers were asked to verify whether they could confirm this pattern, some did, where others did not. This heterogeneity is partially due to Roche-heavy method-group consensus or method-specific target values and partially due to EQA providers circulating samples with varying or unknown concentrations of bicarbonate. As most patient chloride results are generated for the intended use to calculate the anion gap in metabolic acidosis, and this concerns samples with low bicarbonate, NOPAM could confirm the SKML's findings in clinical samples.

Another important advantage of PBEQA is related to commutability. EQA schemes that show similar between-method differences in PBEQA are likely those that use commutable materials. Therefore, PBEQA can aid in prioritising formal commutability studies, which can be very cost- and labour-intensive. Commutability studies are especially desired for measurands with large between-method differences within a single EQA scheme or between different EQA schemes. Here, a commutability study can distinguish between non-commutability of EQA samples and inadequate assay performance as possible causes for between-method differences. On the contrary, measurands with method equivalence in EQA are unlikely to be assessed by non-commutable samples. In the case of a non-commutable sample, the non-commutability bias should exactly cancel out the between-method differences in patients. Such an outcome is theoretically possible, but practically unlikely.

Priority for commutability studies should be given to

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measurands with large between-method differences in classical EQA and even more if different EQA schemes are inconclusive about such differences. If this coincides with method equivalence in PBEQA, EQA samples have a high chance to be non-commutable. Alternatively, if this coincides with similar between-method variation in PBEQA, EQA samples have a high chance to be commutable. PBEQA can therefore give insight into probable (non-)commutability of EQA samples and aid in prioritising formal commutability studies.

Limitations of PBEQA

Unfortunately, PBEQA programmes experience limitations due to biological factors. To begin with, the power of PBEQA is dependent on the between-subject biological variation. Large variation comes with large confidence intervals and thus subtle differences that can be relevant at the within-person level are easily missed. Similar issues arise for measurands where seasonal differences are to be expected. Although the found patient medians can be compared to a similar period, this requires insight and may limit between-laboratory comparison when these patterns are geographically different. Furthermore, equivalence of patient medians between participants is influenced by differences in patient population, exclusion of subpopulations and test utilisation.

PBEQA cannot substitute classical EQA, because it lacks some of the advantages of classical EQA (*Figure 1*). First of all, PBEQA is unable to provide information about performance across the entire measurement range, or give insight into specific patient groups or challenging samples (6). Furthermore, PBEQA does not include target values with metrological traceability to reference measurement procedures and/or reference materials. A third important shortcoming of PBEQA is its inability to detect sample-specific biases due to suboptimal selectivity and/or the presence of interferents. Bias caused by non-selectivity is dependent on the concentrations of the particular cross-reacting pseudo-measurands and therefore sample-specific by nature. Thus, such effects are averaged out when the median of multiple samples is used as in PBEQA, especially if the frequency of occurrence of such an interference is low. For example, the difference in selectivity between the albumin methods of bromocresol green (BCG) and bromocresol purple (BCP) is shown in PBEQA, but more pronounced in certain patient cohorts such as nephrotic syndrome patients (11-13). Lastly, PBEQA is not able to provide insight into laboratory imprecision or measurement uncertainty.

Development possibilities for PBEQA

PBEQA programmes could further increase their EQA utility by considering the following additions. First, register calibrator and metrological traceability data. This is important as data of different platforms may belong to different metrological traceability chains, limiting their comparability. Second, allow only units of preference in data input and reporting to aid in the process of unit harmonisation. Third, register any locally applied factors, and correct for those factors when comparing results between methods. Fourth, register clinical decision limits together with flagging rates to allow for qualitative comparison. Lastly, arrange automatic data upload to facilitate laboratory participation.

Eventually, the utility of PBEQA programmes will be largest when all relevant measurands are incorporated into the programme. For new measurands to be incorporated, priority should be given to those that are not universally defined, where commutability is difficult to establish experimentally, or where harmonisation efforts are ongoing. Top priority should be given to measurands with apparent between-method biases in classical EQA and/or differences therein between EQA providers. This especially applies to measurands with claimed identical metrological traceability and method-independent clinical decision limits in medical guidelines.

The future of EQA

In the era of patient mobility and digitalization, patients' results are more and more often exchanged between hospitals. Bias and selectivity issues diminish equivalence of results between methods and thereby hinder exchangeability of results and equivalence in clinical decision-making (14,15). Together, PBEQA and classical EQA provide extensive insight into method bias; however, these programmes are currently not equipped to provide insight into differences in selectivity. The development of a tool that can provide insight into such selectivity issues would therefore be highly desirable to aid harmonisation and standardisation efforts, especially when this can be incorporated in classical EQA where laboratories measure the same samples.

The value of classical EQA could be expanded by focusing on single donor samples with a specific medical

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case and question. EQA can test for performing the correct determinations, obtained results, and conclusions, actions, or interpretation based on these results. Since the distribution of single donor samples can be challenging due to sample volume availability, this must be limited to measurands where selectivity issues are to be expected. Possibilities to obtain large-volume single donor samples include apheresis or exchange transfusion procedures. Alternatively, samples from the same donor could be pooled together to create a greater volume, or smaller volume samples could be sent to a subset of laboratories. Pooled samples cannot be used for methods with differences in selectivity, because this leads to the averaging of sample-specific biases, creating the illusion of equivalent methods. Instead, classical EQA could introduce single donor samples containing known or suspected interferents or pseudo-measurands to actually assess sample-specific biases. Here, communication is pivotal to educate laboratories to not act on these biased results. Instead, they can learn that their measurement systems are not fit for intended uses where this interferent is relevant.

Another future ambition for EQA is to change the revenue model to a system where participants pay for the service itself instead of for the number of samples to be distributed. The business model of EQA should not be sample or data driven, but information driven. This would allow the change from a cost- and throughput-based industry to a value-based industry, as promoted by the EFLM in its transition towards value-based laboratory medicine (16).

In conclusion, PBEQA programmes add value to external quality control, but cannot replace classical EQA programmes. PBEQA benefits from commutable samples and quick observation of assay drift, but is limited by lacking value assignment and quality control of other-than-average samples. Both limitations can be addressed by employing classical EQA together with PBEQA, a solution that is recommended by the authors to implement in the near future.

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Footnote

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