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Bayesian approach to guide termination of retrospective retesting after detection of a systematic quality control failure

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ABSTRACT

Background: When a systematic error is detected in the analytical process, ideally, one seeks to retest only patient samples between the onset of the error and the time the error was detected. In practice, the onset of error is often unknown, and patient samples are retrospectively retested back to the last acceptable QC sample. This can be wasteful of reagents and operator time.
Methods: An alternative approach that is based on the expected number of spurious results is described to determine when retrospective retesting should terminate. Assuming each patient sample was independently measured by an analytical process with an underlying Gaussian distribution, a Bayesian model that takes into account the difference between the original and retest result of each patient sample was developed.
Results: We are able to significantly reduce the number of samples retested, while ensuring that the average number of spurious results observed under the proposed retesting procedure was similar to or only marginally higher than the baseline number of spurious results when the assay was in control.
Conclusion: Patient samples measured after the systematic error have high probabilities of being retested under the proposed retesting procedure.

1. Introduction

Good clinical laboratory practice requires a laboratory to have in place a quality system that controls the analytical process to minimize variation, and ensure that the results produced meet certain quality specifications [1]. Internal quality control (QC) programs are tools that help monitor the performance of the analytical process. It involves periodic measurement of internal QC samples, which are materials that mimic the human specimen, in the same manner as a patient sample. The internal QC results are interpreted using control charts (e.g., Levey–Jennings charts) and appropriately defined statistical control limits (e.g., Westgard QC rules).

An internal QC result that falls outside of predefined control limits (e.g., 3SD from the QC mean) is considered *out of control*. The QC run is rejected and patient sample testing should be discontinued immediately. The cause of the out of control condition should be identified using checklists and troubleshooting processes. This requires careful consideration and examination of the analytical processes to exclude any systematic error that may have resulted in a deterioration of the analytical process. On the other hand, the out of control QC result may be a false alarm due to random error [2]. Several statistical tools have been described to guide laboratory practitioners in selection and interpretation of QC rules to identify true out of control situations from false QC rejections [2–14].

Once the cause of the out of control condition is identified, it should be rectified as soon as possible to bring the analytical process back in control before testing of patient sample can resume. If the systematic error exceeds the required quality specification (e.g. total allowable error), the analytical process is considered to be performing *out of specification* and an increased number of spurious patient results is expected.

A well-designed internal QC program should provide early warning flags for out of control situations, where timely remedial actions can be taken before they accumulate and become out of specification. However, even with well designed internal QC programs, out of specification conditions may arise when there is a large abrupt systematic error in the analytical process, or when the analytical process has relatively poor process capability compared to the quality specification (i.e., a low sigma value process) such that a relatively small deterioration in the analytical performance would compromise the patient results.

After the offending cause has been corrected, the laboratory would ideally identify and retest all patient samples that may have been affected and hence, have increased likelihood of being spurious. The laboratory error and the corrected results should be communicated to the clinician in a clear and timely manner to avoid inappropriate management of the patient [15–17].

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There is currently limited literature to guide laboratory practitioners in the retesting of suspect patient samples. Most practitioners retest all patient samples between the out of control QC sample and the last known in control QC sample, which implies the retesting of all patient samples until when the analytical process was last shown to be in control. Under this approach the number of unaffected patient samples that are retested can be high, resulting in waste of resources.

2. Materials and methods

When an assay is in control, a small number of patient results may deviate from their true value by a margin greater than a certain quality specification (e.g. total allowable error, or accuracy target) due to analytical imprecision/random error. They are considered spurious results (Fig. 1A). When *a single event* (e.g. calibration shift) leading to a systematic error occurs, the introduction of analytical bias and/or additional analytical imprecision will significantly increase the number of spurious results (Fig. 1B and C). Ideally, the laboratory should identify and correct the systematic error before retesting only the affected patient samples, as they are more likely to contain spurious results. However, the point in the analytical run where the systematic error occurred is often unknown.

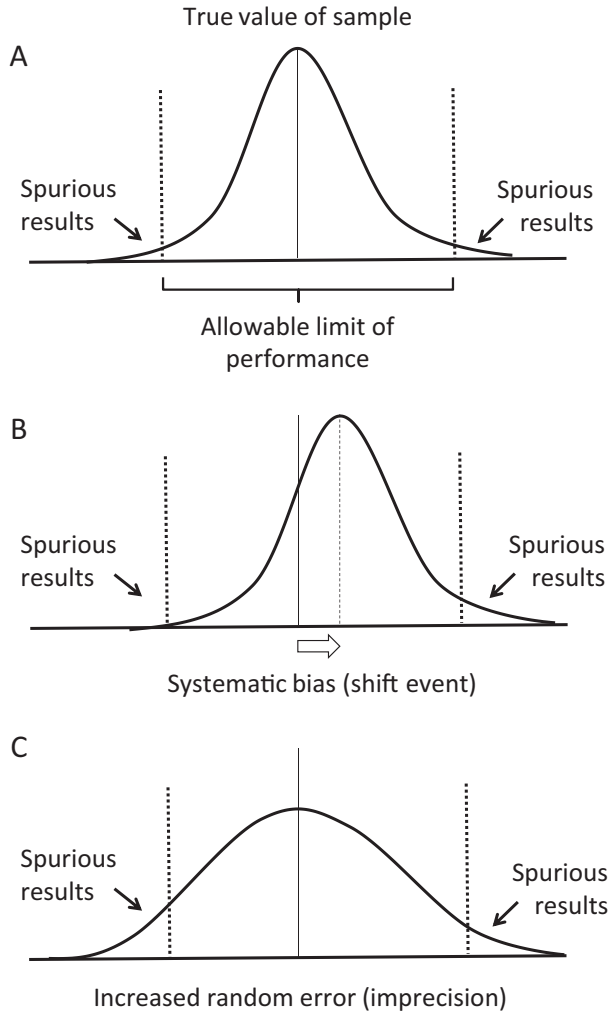

Fig. 1. Panel A shows that even when an analytical process is performing within specification, a number of patient results may deviate from their true value by an amount greater than a certain quality specification (e.g. total allowable error or accuracy targets) due to random error (imprecision). The number of results that does not meet the quality specifications (i.e. spurious) may increase when bias (panel B) and/or additional analytical imprecision (panel C) is introduced as a result of systematic error.

2.1. Retesting procedure

We suggest estimating the analytical performance of the assay after the systematic error by repeat measurements of the QC samples *before* troubleshooting the underlying problem. After correcting the systematic error, the patient samples are retrospectively retested and amended until the expected number of spurious results is reduced to no greater than α times the expected number of spurious results if all patient samples were measured using an in control assay. The retesting process should start with the most recent (closest to the failed QC) patient sample and progressively move backward. The in control analytical performance can be estimated using historical QC results.

2.2. Assumptions

Consider a situation where there is *a single event* (e.g. calibration shift) that resulted in a systematic error that introduced an analytical bias β, and possibly an increased imprecision, causing the process to perform out of specification. This is referred to as the *shift event*. Before the shift event, each measurement of the patient sample i is independent and normally distributed with mean μ_i and standard deviation $\sigma_i = CV \times \mu_i$, where μ_i is the true value of the patient sample i, and CV is the analytical imprecision expressed as coefficient of variation of the assay before the shift event. After the shift event, each measurement of the patient sample i remains independent and normally distributed with mean $\mu_i(1+\beta)$ and SD $\sigma_i = CV_e \times \mu_i$, where CV_e is the CV of the assay after the shift event. For simplicity, the bias is assumed positive (i.e., $\beta > 0$). Note that the proposed approach can be easily modified for situations with negative bias.

Suppose N patient samples were tested between the 2 QC samples. The earliest patient sample is referred to as the first patient sample and the most recent patient sample (i.e., just before the failed QC sample) as the N-th patient sample (Fig. 2). Let i^* denote the patient sample that was tested immediately before the shift event. In theory, one would retest the (i^*+1)-th to N-th patient samples, however, i^* is often unknown in practice.

Given that the shift event occurred between the two episodes of QC samples, the shift event could have occurred in any one of the $N+1$ periods:

Period 0	Period 1	Period 2	…	Period N
Before patient Sample 1	After patient Sample 1	After patient Sample 2	…	After patient Sample N
$i^* = 0$	$i^* = 1$	$i^* = 2$	…	$i^* = N$

In the absence of additional information, it is reasonable to assume that the shift event is equally likely to occur in each of the $N+1$ periods stated above (Laplace's principle of insufficient reason):

$$P(i^* = i) = \frac{1}{N+1} \text{ for } i = 0, 1, 2, \ldots, N.$$

However, the difference between the original and retest measurement of each patient sample provides additional information that can be used to improve our estimation of the location of i^*, using a Bayesian approach.

2.3. Bayesian-based statistical approach

First, we describe how the distribution for i^* can be estimated by comparing the original and repeat measurements. Next, we illustrate how the expected number of spurious results can be computed and used to determine the termination of the retrospective retesting procedure.

Here, we use serum calcium test as an example. Using the accuracy target of 3% for serum calcium, specified by the External Quality Assurance program of the College of American Pathologists, a reading x_i is