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A simple matrix of analytical performance to identify assays that risk patients using External Quality Assurance Program data

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ABSTRACT

Objectives: We propose a simple way to reliably rank assays for improvement according to patient risk, based solely on EQA imprecision and biological variation data. Because the underlying technique aligns the imprecision class of an assay from EQA data, peer performance can be used to assess achievable imprecision and the risk ranking can not only prioritise improvement but also highlight laboratory QC operating parameters that are easy to manage and provide reliable, acceptable performance.

Design and methods: A modified Failure Modes Effects Analysis (FMEA) is applied to produce an analyte risk rating based on three factors, each of which is graded: 1) the ease of detecting analytical errors based on the ratio of allowable limits of performance to imprecision (Assay Capability) compared to absolute standards and to peers, 2) the predicted frequency of errors in patient monitoring based on the ratio of within-individual biological variation to laboratory imprecision, and 3) the clinical importance of the assay as a surrogate marker for harm arising from an error.

Results: We provide laboratory examples to illustrate these models.

Conclusion: The proposed models using only EQA data can objectively identify assays at risk of failing against biological variation goals for monitoring patients and suggest parameters for reliable performance.

1. Introduction

Maintaining the quality of clinical assays continues to challenge pathology laboratories despite improvement in data handling and analyser capabilities. To achieve commutable and precise results requires suppliers providing appropriate calibrators, the laboratory using an effective QC system and careful interpretation of External Quality Assurance results. EQA results will identify if either the laboratory or the relevant analyser method group performs worse than other laboratories in terms of bias and imprecision.

Laboratories need to identify assays which are poorly performing and adopt QC practices that maintain results that are clinically acceptable. Using EQA performance can give strong guidance and identify those particular assays which warrant closer attention.

The aim of Quality Control (QC) is to ensure that laboratory test results are fit for their intended use. But laboratories manage assays using a QC system with a single analytical goal for an analyte, even though the clinical goal changes with the patient circumstance. For example, the goal for patient monitoring is individual biological variation, while for patient diagnosis it is total error based on individual and group biological variation (BV). The adopted analytical goal for an analyte might be regulatory (e.g. CLIA), derived by expert group (e.g. RCPA QAP Chemical Pathology Program) or determined by the laboratory itself. Methods of assessing laboratory performance should focus on both the suitability of the selected operating parameters so they ensure compliance with the analytical goal (e.g. target SD and QC rules/algorithms) and outcome measures of performance (e.g. imprecision). Methods for calculating patient risk from errors in test results cannot rely on analytical goals alone; they need to include clinical goals and the harm arising from the errors.

Quality Control strategies do not usually consider patient risk, they are concerned with detection of analytical error. The aim of QC strategies was to develop QC rules (algorithms) and QC sample frequencies that allow high error detection rates usually a 90% probability of detecting a statistically significant shift in QC results (Ped), combined with a low probability of false error detection (Pfr). These analytical goals were usually based on stable imprecision which is not always adequate for the relevant biological goal for patient care. The analytical error detection rates were determined using power function rules [1,2] or computer programs such as QC Validator [3]. Parvin [4] introduced the variable, expected number of patient reports with an unacceptable error condition E (Nu) which is the product of the increased probability of a result having an unacceptable amount of error due to an error state and the average number of results reported during an error state. There are many different QC rules and frequencies that meet a given E(Nu).

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This variable is an example of a quality goal focussing on predicting and minimising outcomes that would affect patients, rather than merely detecting analytical/statistical outliers.

In this paper, we wish to explicitly consider risk to the patient, not just analytical error. There is a requirement under ISO 15189 [5] and CLSI EP 23A [6] standards/guidelines that any clinical laboratory must also have targeted processes in place that reduce patient risk. Risk is a function of the clinical application, e.g. diagnosis or monitoring, and whether or not an immediate intervention in treatment may follow from an unexpected result. Risk is also dependent on the frequency of errors for a test and how effectively the current processes identify these errors. These components of risk will be used in the discussion to present a simple risk based model that laboratories can use to identify high risk assays on which they should concentrate quality monitoring efforts.

The idea relies on three concepts, Assay Capability (Cpa) [7], a 3 × 3 matrix of achievable imprecision, and a calculation of a risk score, using a modified Failure Mode Effects Analysis. We will base our model on EQA results. Laboratories often undervalue EQA results by only considering short-term survey feedback. EQA results should be analysed over longer time intervals than just a survey cycle. Long-term EQA results are in fact quite stable and can reflect the performance of the laboratory over the life of an instrument [8]. We will apply the idea to EQA data but it can equally be used with QC data if peer QC imprecision data is available.

1.1. External Quality Assurance Programs

It is important to be aware that different EQA programs have different approaches depending on whether they are part of a regulatory system (Proficiency Testing) or Aspirational (Quality Assurance) [9]. The differences have been summarised by the IFCC, see Table 1 [10].

There can be problems with EQA samples because of their nature. When investigating a problem identified by an EQA sample the following must be considered: clerical errors, methodological problems (carryover, reagent or calibrator variation), equipment problems, human errors with preparation of the EQA material, and problems with the EQA material (commutability issues) [11].

Miller et al. described the key factors for interpreting PT/EQA results as a knowledge of the commutability of the samples used and the process used for target value assignment. A commutable PT/EQA sample demonstrates the same numeric relationship between different measurement procedures as that expected for patients' samples. Non-commutable PT/EQA samples frequently have a matrix-related bias of unknown magnitude that limits interpretation of results [12]. The techniques used in the following analysis require an EQA program with commutable samples and robust target setting procedures.

Table 1
Summary of differences between Proficiency Testing and External Quality Assessment.

Proficiency testing External Quality Assessment Schemes (EQAS)	• Laboratory performance evaluation for regulatory purposes • Laboratory performance and method evaluation • Educational
External Quality Assessment Programmes (EQAP)	Inter-laboratory comparisons designed and operated to assure one or more of: • Participant performance analytical, interpretive, clinical advice • Method performance evaluation • In vitro diagnostic device vigilance • Education • Training and help

2. Methods

For the rest of this paper we will concentrate on calculating risk for assays based on performance in an EQA program. We have selected the RCPA QAP Chemical Pathology program which uses paired, linearly related samples and an estimate of imprecision is calculated from the standard error of the linear regression line fitted to all data points [13].

2.1. Assay Capability — detection of analytical errors

The first concept to understand as we develop a model of risk is Assay Capability. Capability is an objective measure of the ability of an assay to meet pre-defined requirements and is defined as the analytical goal divided by assay imprecision. This can be expressed as Cpa = AG/CVa (equivalently AG/SD), where AG is the Analytical Goal and CVa is the Coefficient of Variation (imprecision) of the assay in question [14].

The analytical goal can be chosen from a number of sources including BV, State of the Art and expert opinion [15]. We will use the AG concept based on biological variation which is given for a desirable target as:

$AG = [k \times 0.5 \times CV_i] + [0.25 \times \sqrt{(CV_i^2 + CV_g^2)}]$ [16] where k = 1.65 for 95% confidence; CVi = within individual biological variation; CV_g = between individual biological variation.

The assumption of zero systematic bias is valid in the case of many routine clinical chemistry tests [17] and is also valid for the analysis of most tests if the result is compared to the method or group performance. The AG could be based on biological variation, group performance in an EQA (standard deviation of group), or an arbitrary error limit, such as with CLIA regulations. The Assay Capability value indicates the number of standard deviations inside the analytical goal, so the higher the value the better the assay. We recall that the aim of any QC strategy is to have well defined QC rules which have at least a 90% probability of error detection (Ped) with low false rejection (Pfr) which requires selecting an appropriate QC algorithm matched to laboratory imprecision.

2.2. 3 × 3 matrix (of achievable imprecision)

The 3 × 3 matrix displays achievable imprecision for every laboratory assay in a single graphic. It shows analytical laboratory performance against peers and against performance standards, with the position of the assay in the matrix showing responsibility for improving poorly performing assays (see Table 2).

As is the case with many other External Quality Assurance Programs, the RCPA QAP Chemical Pathology End-of-Cycle report [13] is useful in establishing laboratory performance on a test-by-test basis, showing a laboratory's imprecision, the imprecision of the top 20th percentile for all laboratories, the imprecision of the 50th percentile for laboratories, the median imprecision for a method group, as well as the allowable limits of performance. However, such formats do not give insight into a laboratory's overall performance, particularly for a laboratory having a wide variety of instrumentation.

Using Assay Capability (Cpa) we constructed a 3 × 3 matrix to visualise the performance of individual laboratory assays against better performing laboratories in an EQA program. We chose the 20th percentile as the comparator group because we considered that this was an aspirational performance goal achieved by a reasonably large number of laboratories. There are a number of possible analytical goals that could have been chosen as imprecision goals, for example the CLIA guidelines. We selected the analytical goals of the RCPA QAP (the Allowable Limit of Performance). The advantages of these goals are that they are based on BV and State of the Art. It is not possible to use just BV for all analytes because some are not endogenous, e.g. drugs. In programs where there were insufficient members in a method group to accurately calculate the 20th percentile, we propose using the average for the method group as the comparator. This substitution is one of expediency and