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Estimating the cost of quality of errors in the analytical phase

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ABSTRACT

Background: Cost of quality (COQ) can be defined as the difference between the current cost of providing laboratory services and the cost that would be incurred if there were no errors in the measurement process. Errors due to analytical imprecision and bias are not traditionally included in COQ. The objective of this study was to develop methods to estimate the COQ due to errors in the analytical phase.

Methods: We consider 2 types of error events: errors in patient results and run failures due to violation of a quality control (QC) rule. We provide a general and a simplified model for estimating the cost of analytical errors in patient results and a separate model for estimating costs due to QC failures.

Results: An example calculation is provided. The COQ for 12 mass spectrometry assays using the simplified cost model for estimating analytical errors and the cost model for run failures is presented.

Conclusions: The models provide a way to estimate COQ associated with analytical error, which have not been previously incorporated into clinical laboratory standards or published literature. Estimating COQ and using those data to prioritize improvement efforts can be challenging for laboratories but are important for value-driven patient care.

1. Introduction

Clinical laboratories are under increasing pressure to demonstrate value. Thus, laboratories are seeking ways to reduce costs and improve quality. To do this, they must have systems to identify and measure the costs associated with poor quality. Cost of Quality (COQ) programs provide a way to measure costs and prioritize quality improvement efforts [1–5].

COQ can be defined as the difference between the current cost of providing a product or service and the cost that would be incurred if there were no errors [6]. There are a number of ways to categorize costs, but the most common method is the Prevention-Appraisal-Failure (PAF) method [7]. Prevention costs include items such as training, preventive maintenance, and validation of new laboratory processes. Appraisal costs are incurred by the activities that ensure that the laboratory's processes conform to requirements. For example, quality control and calibration would be classified as appraisal costs. Failure costs are divided into 2 categories: internal and external. Internal failures are errors that are caught inside the laboratory. Internal failure costs are the costs associated with correcting these errors. External failure costs are associated with errors detected outside the laboratory. Although COQ is a well-established concept, it is relatively new to clinical laboratories [1–5].

Prevention costs and appraisal costs are relatively easy to measure. These costs can be estimated by the time that personnel devote to these activities. Failure costs are more difficult to estimate. Failure costs depend both on the failure rate and the cost per failure. Studies have shown that errors are most frequent in the pre-analytic phase and are least frequent in the analytical phase [8]. However, the frequency of failures depends on definition of failure.

Every laboratory result has some element of error due to analytical imprecision and bias. Traditionally, these errors are not included in the COQ unless they are detected. For example, the time spent on an investigation regarding an unusual result would be counted as a failure cost. However, most results have errors that are undetected. Even if they are small, these errors pose some risk to patients and can incur costs. It would be useful to have a method to estimate the COQ associated with measurement errors. The objective of this study was to develop methods to estimate the COQ due to errors in the analytical phase.

2. Theoretical development

We consider 2 types of error events: 1) errors in patient results, and 2) run failures due to violation of a QC rule. Both of these events contribute to costs and would be included as failure costs in the overall

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COQ. Our objective is to develop a model to estimate the annual cost of these events. We consider 2 definitions of COQ: an absolute cost and a relative cost. The absolute COQ is determined by comparing the current COQ relative to a state of perfect quality (i.e., COQ = 0). The relative COQ compares the current COQ to the COQ in an achievable future state in which the COQ is reduced but not eliminated.

2.1. General model for estimating the cost of analytical errors in patient results

An analytical error occurs when the observed patient result, x, deviates from the true result, x_0. We will begin by developing a general model for estimating the expected cost of errors and then make several simplifying assumptions to develop a simple model based on process capability. Our cost model depends on three factors: the magnitude of analytical errors (measurement errors), the cost of the error, and the distribution of patient results.

Analytical errors are caused by bias and imprecision. The magnitude of bias and imprecision can depend on the true concentration level, x_0. For example, the coefficient of variation often varies with the underlying concentration. Thus, given a true value, x_0, the observed value, x, will have a distribution, $f_i(x|x_0)$, that depends on the underlying true value, x_0 (Fig. 1). The subscript i indicates that the distribution of measurement error applies to a particular assay, i. Although measurement errors are often normally distributed, we make no assumptions about the distribution of measurement errors, $f_i(x|x_0)$. $f_i(x|x_0)$ could take many forms and can be estimated from quality control (QC) data or validation studies.

Each analytical error is assigned a cost. The cost of the error could depend on the magnitude of the error, $|x - x_0|$, as well as the level, x_0. We designate the cost function as $c_{e,\,i}(x|x_0)$ to indicate that the cost can depend on the magnitude of the error as well as the true value. For example, several different cost functions are presented in Fig. 2. The cost functions in Fig. 2 are symmetric; however, it is not necessary for the cost function to be symmetric. For example, the cost function may be asymmetric near a decision limit. We are not aware of any definitive method for specifying the cost function. The cost function is subjective and depends on managerial judgement. The cost function should incorporate a risk-weighted average of all the potential consequences of an analytical error. For example, the cost function should incorporate

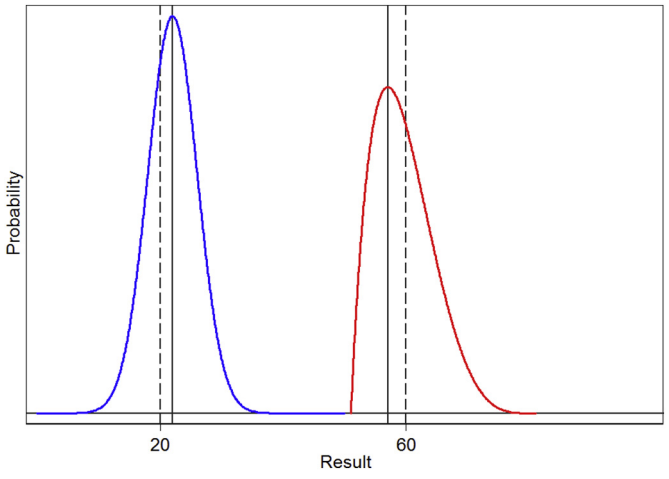

Fig. 1. Distribution of measurement error. The distribution of measurement error can vary with the magnitude of the underlying true result. The Fig. shows the distribution of measurements at 2 different concentration levels: 20 (blue) and 60 (red). The Fig. shows that the bias, SD, and shape of the distributions can differ. The blue distribution has a positive bias and is symmetric. The red distribution has negative bias and is positively skewed. The SD of the distributions is approximately equal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

factors such as the risk of PT failures, repeat testing, potential harm to patients, and lawsuits that may result from reporting an erroneous result. Thus, the cost function applies to patient results rather than QC results. We assume that these errors are generally undetected and represent external failures.

The expected cost of error depends on the cost function and is computed by averaging the cost of error of each patient result over the distribution of patient results. Equations to perform these calculations are provided in Appendix A.

2.2. Simplified model for estimating the cost of analytical errors

We make several assumptions to develop a simplified model. First, we assume that the cost of an error only depends on the magnitude of the error, $|x - x_0|$, and that the cost of an error does not depend on x_0. Also, we assume a "goal-post" cost function (Fig. 2); that is, errors are assigned costs only if the magnitude exceeds a threshold. We assume that the threshold is the total allowable error (TAE). Errors are classified as acceptable if the magnitude of the error is less than TAE and unacceptable if the magnitude of the error exceeds TAE. Unacceptable errors incur a fixed cost, $c_{u,\,i}$, whereas acceptable errors incur no cost (Fig. 2, goal-post cost function).

$$c_{e,i}(x) = \begin{cases} c_{e,i} \; if \; |x| > TAE \\ 0 \; if \; |x| < TAE \end{cases} \quad (1)$$

We also make simplifying assumptions regarding the distribution of observed results. First, we assume that the bias and imprecision are independent of x_0 so that the distribution of observed results, $f_i(x|x_0)$, is the same at all levels of x_0. We also assume that the observed results are normally distributed with a mean, $\mu = x_0 + b$, and SD, s, where b is the bias. The SD, s, would be estimated from QC data and the bias, b, would be estimated from proficiency testing challenges.

Under these assumptions, the proportion of unacceptable patient results and the associated cost would not depend on the underlying true value, x_0. Instead, the proportion of unacceptable results would be a constant proportion of the total number of tests performed and a constant cost, $c_{e,\,i}$, would be applied to each of the unacceptable results. Thus, the total expected cost of unacceptable errors can be estimated as:

$$\widehat{C}_{e,i}^{tot} = V_i * P_u * c_{e,i} \quad (2)$$

where P_u is the probability of an unacceptable result.

$$P_u = P(x > TAE \mid \mu = x_0 + b, \sigma = s) \quad (3)$$

The proportion of unacceptable results can be estimated from the capability (i.e., sigma value) of the assay. Capability, Σ, is defined as:

$$\Sigma = \frac{TEA - b}{s} \quad (4)$$

Based on the assumptions of the simple model, P_u is a function of Σ, $P_u = L(\Sigma)$, that can be looked up in a table or calculated (Fig. 3, Table 1).

The process capability depends on the bias and imprecision. Both of these quantities can be reduced over time through quality improvement efforts. We can compare the cost of unacceptable results before and after the improvement effort to determine the potential savings. To that end, we calculate the error rate of the current (observed) state and a hypothetical future state in which the rate of unacceptable errors has been reduced (but not eliminated) due to quality improvement efforts (Fig. 4). The capability of the current state is Σ_c and the capability of the future state is Σ_f. The probability of unacceptable results in the current and future states are $P_{u,\,c} = L(\Sigma_c)$ and $P_{u,\,f} = L(\Sigma_f)$, respectively.

The current capability is determined by the bias and observed SD. Bias can be estimated from external quality assessment and the SD can be estimated from QC data. The future capability can be estimated by predicting the change in bias and imprecision that could be achieved

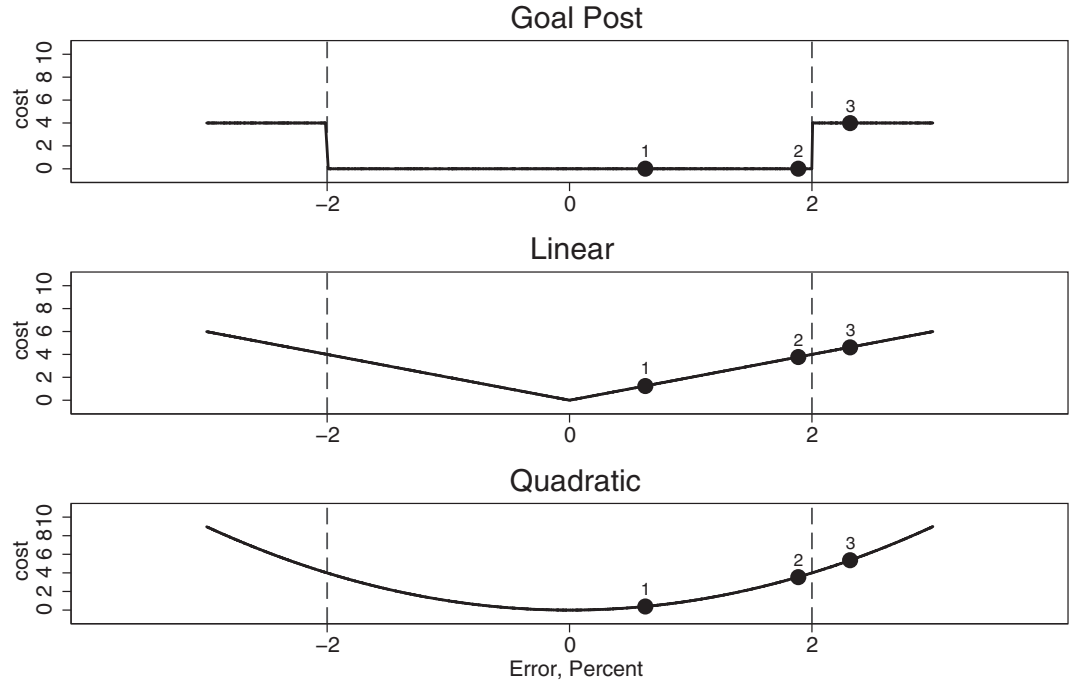

Fig. 2. Cost functions for errors. The Fig. shows different ways of assigning costs to errors. The simplest way to base costs on specifications such as total allowable error (TAE). In the "goal-post" cost function, a cost is assigned only if the error exceeds the TAE (± 2%). In the linear-cost function, costs are proportional to the magnitude of the error. In the quadratic-cost function, larger errors incur greater costs at an increasing rate. The three dots indicate the relative costs associated with different errors. In the goal-post cost function, errors 1 and 2 are assigned the same cost despite the fact that the errors have large differences in magnitude. Errors 2 and 3 have large differences in cost but have small differences in magnitude. In general, cost functions may depend on the location and can be asymmetric.

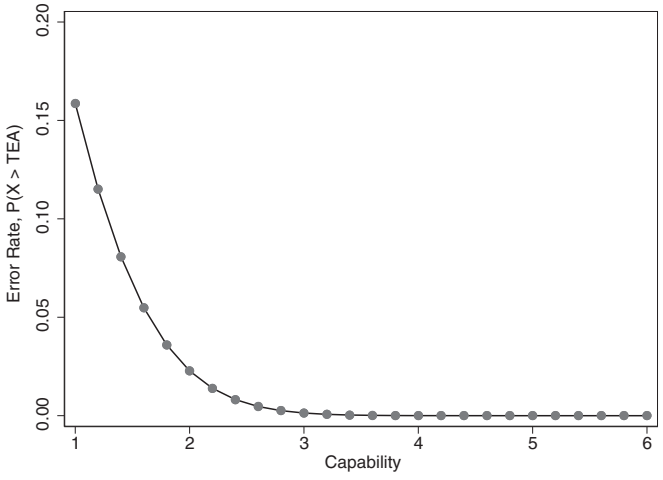

Fig. 3. The rate of unacceptable errors as a function of capability. Unacceptable errors are defined as measurement errors that are greater than the total allowable error (TAE).

Table 1
Error rate as a function of process capability. The table shows the fraction of results that would exceed the total allowable error (TAE) at different levels of capability.

Capability	p(X > TAE)
1.0	1.59E-01
1.2	1.15E-01
1.4	8.08E-02
1.6	5.48E-02
1.8	3.59E-02
2.0	2.28E-02
2.2	1.39E-02
2.4	8.20E-03
2.6	4.66E-03
2.8	2.56E-03
3.0	1.35E-03
3.2	6.87E-04
3.4	3.37E-04
3.6	1.59E-04
3.8	7.23E-05
4.0	3.17E-05
4.2	1.33E-05
4.4	5.41E-06
4.6	2.11E-06
4.8	7.93E-07
5.0	2.87E-07
5.2	9.96E-08
5.4	3.33E-08
5.6	1.07E-08
5.8	3.32E-09
6	9.87E-10

through quality improvement efforts (imprecision is the inverse of the SD). We will use the subscripts c and f to denote the current and future levels of bias and variation (e.g., b_c, b_f, s_c, s_f). The future imprecision can be estimated by using the concepts of long-term and short-term variation. The observed or long-term variation, s_L, is a combination of common cause and assignable cause variation. Short-term variation, s_s, is composed of only common cause variation and represents the variation of a well-controlled process. The concepts of assignable cause variation, common cause variation, short-term variation, and long-term variation are discussed in these references [9,10]. The objective of quality improvement is to remove assignable cause variation so that only common cause variation remains [11,12]. Thus, short-term variation can be used to estimate the common-cause variation that would remain after a successful quality improvement program and can provide an estimate of the future variation, s_f ($s_f \approx s_s$). The long-term variation corresponds to the current state ($s_c \approx s_L$). We are not aware of a good method to predict the future level of bias. For simplicity, we suggest assuming that the bias is eliminated ($b_f = 0$). Thus,

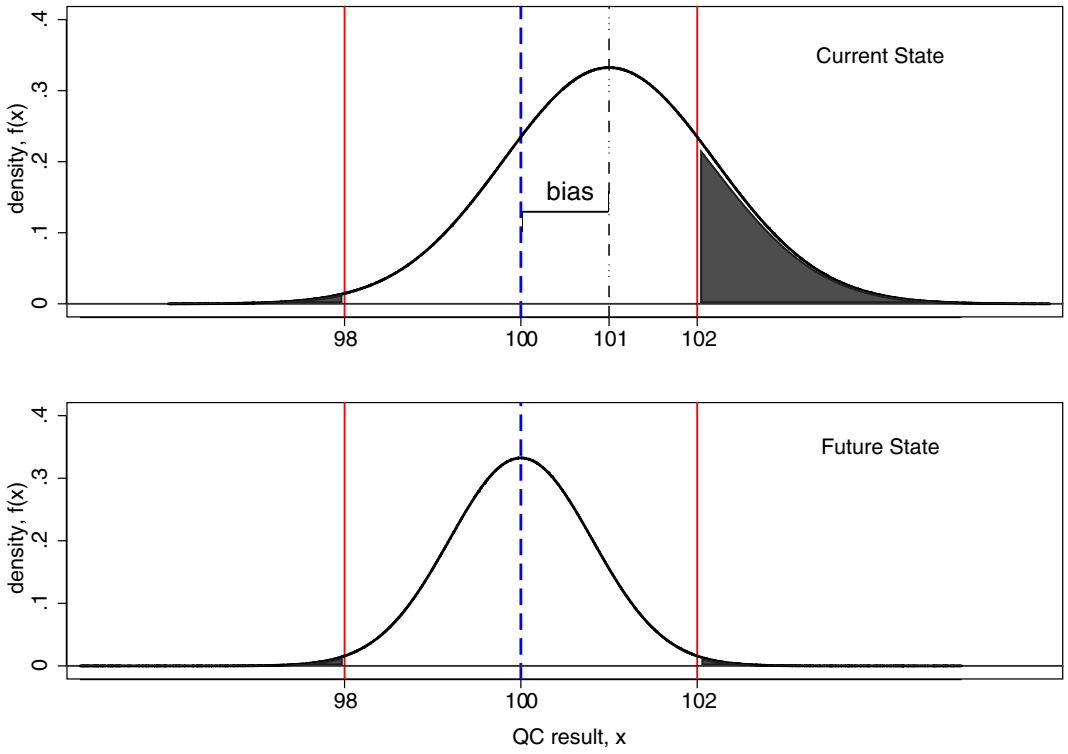

Fig. 4. Unacceptable error. The Fig. shows an assay with a target of 100 units and a total allowable error (TAE) of 2%. Unacceptable errors (i.e., errors greater than TAE) are shown as dark shade regions. In the current state, the bias is 1%, and the coefficient of variation (cv) is 2%. The capability of the current state is low (sigma = 0.5), and the rate of unacceptable errors is high. In future state, we assume that bias has been eliminated and that the CV is reduced to 1%. The capability is improved (sigma = 2), and the rate of unacceptable errors is 5%.

$$\Sigma_c = (TEA - b_c)/s_c = (TAE - b_c)/s_L \quad (5)$$

$$\Sigma_f = (TAE - b_f)/s_f = (TAE - 0)/s_S \quad (6)$$

The estimates of current and future capability can be used to calculate current and future rates of unacceptable errors:

$$P_{u,c} = L(\Sigma_c) \quad (7)$$

$$P_{u,f} = L(\Sigma_f) \quad (8)$$

The difference between the current and future rates of unacceptable errors represents the excess rate of unacceptable error:

$$\Delta P_u^* = (P_{u,c} - P_{u,f}) \quad (9)$$

The excess unacceptable error rate, ΔP_u^*, is the maximum reduction in the unacceptable error rate that could be achieved by quality improvement projects (variance and bias reduction). In practice, an organization would only capture a fraction, $\alpha \in [0,1]$, of the opportunity for improvement so that the estimated reduction would be:

$$\Delta P_u = \alpha \Delta P_u^* < \Delta P_u^* \quad (10)$$

The coefficient, α, would depend on the technological and organizational factors associated with a particular assay. The definitions of the current unacceptable error rate and the excess unacceptable error provide the basis for estimating the absolute and relative cost of unacceptable errors:

$$\widehat{C}_{e,i}^{tot,abs} = V_i * P_u * c_{e,i} \quad (11)$$

$$\widehat{C}_{e,i}^{tot,rel} = V_i * \Delta P_u * c_{e,i} \quad (12)$$

The absolute cost of analytical error, $\widehat{C}_{e,i}^{tot,abs}$, provides an estimate of the savings that would be obtained if all analytical error were eliminated. The relative cost of analytical error, $\widehat{C}_{e,i}^{tot,rel}$, provides an estimate of the reduction in quality costs (savings) that could be obtained if quality was improved to reach an achievable future state. Overall, given certain assumptions, Eqs. (11) and (12) provide relatively simple methods to estimate the cost of quality associated with analytical errors.

2.3. Estimating the cost of run failures

Run failures are defined as events in which QC monitoring produces a rule violation that requires investigation. Run failures incur costs due to time spent troubleshooting, recalibrating, rerunning samples, etc. The cost of a run failure will depend on the specific assay. We designate the cost of a run failure for assay i as $c_{rf,\ i}$. The cost of a run failure includes troubleshooting time, repeat samples, recalibration, review by supervisors, etc.

Many QC monitoring rules are available. These include simple rules, such as 2 or three SD (sd) limits, or more complicated rules such as Westgard multi-rules, cumulative sum control charts (CUSUM) or exponentially weighted moving averages (EWMA). All monitoring methods are subject to error (false rejection, failure to detect). Organizations choose a monitoring plan based on the risk associated with false rejection and failure to detect. We do not consider the choice of monitoring method and assume that an organization has chosen an optimal method based on its particular circumstances. However, given a choice of monitoring method and a retrospective data set, it is possible to compare the rate of rule violations that would have occurred under the current state of control to the rate of rule violations that would have occurred under perfect statistical control. At our institution, we use Westgard multi-rules and use the INSR statistic to compare the current failure rate, $F_{c,\ i}$ to the failure rate that would be expected if the assay were under statistical control, $F_{f,\ i}$ [13]. The total cost of run failures is given by:

$$C_{rf,i}^{tot} = N_i(F_{c,i} - F_{f,i})c_{rf,i} \quad (13)$$

Table 2
Data for example calculation for cost of measurement errors. The data are illustrative.

Statistic	Current	Future
Mean	987	987
SD	67.4	54.2
Coefficient of variation (cv), %	6.3	5.5
Bias %	6.8	3.0
Capability (sigma)	2.1	3.3
Unacceptable error rate, P_u	0.0179	0.0004
Avoidable error rate, $\Delta P_u^{\#}$	0.0179–0.0004 = 0.0175	
Annual volume, V_i	4579	
Cost per error, $c_{e,\,i}$ (Direct cost of test)	$14.79	
Total cost of error, $\widehat{C}_{e,i}^{tot,rel}$	4579 × 0.0175 × 14.79 = $1185	

where N_i is the number of QC challenges (i.e. failure opportunities) per year and $F_{c,\,i}$ and $F_{f,\,i}$ are the current future run failure rates. $F_{c,\,i}$ and $F_{f,\,i}$ can be obtained from QC records or estimated by applying QC monitoring rules to retrospective QC data. In this study, we applied the full set of Westgard rules (1_{3S}, 2_{2S}, 4_{1S}, 10x, and R_{4S}) to estimate the current and future run failure rates.

3. Methods

We used the simple model to estimate the cost of errors for 12 assays in our clinical toxicology laboratory. The assays include amphetamine (serum and urine), barbiturates (serum and urine), benzodiazepine (serum), cocaine (urine), methadone (serum), nicotine (serum), opiates (serum), PCP (serum), propoxyphene (serum and urine). These analyses are conducted in batches with at least one run per day. QC and calibration samples are included in every batch.

4. Results

We now provide a detailed example calculation using the simplified model (Table 2). In this example, the annual volume of the test is 4579, the direct cost is $14.79 and the current capability is 2.1. The estimated future capability is 3.3 which means the avoidable error rate is 0.0175. Thus, the estimated COQ is $1185.

We estimated the COQ for 12 mass spectrometry assays using the simple cost model for errors (Eq. (12)) and the cost model for run failures (Eq. (13)). These are presented in Tables 3 and 4. We used the direct cost of the test for $c_{e,\,i}$, assumed $\alpha = 1$, and assumed $c_{rf,\,i}$ = $100 per failure. The error costs (Table 3) depend on the annual volume of the assay as well as the unit cost and ranged from $1 per year to $2377 per year. The total cost of measurement error was $4727. The cost of run failures depends on the failure rate and the number of failure opportunities (QC runs). The total cost of run failures was $5464.

Table 4
Method to estimate the costs associated with run failures. The current number of run failures is determined from the run failure rate and the number of challenges per year. The annual run failure cost is determined by the product of the number of excess run failures (current – future) and the cost per failure. Run failure rates were based on the full set of Westgard rules (1_{3S}, 2_{2S}, 4_{1S}, 10×, and R_{4S}).

Assay	Run Failure Rate	Challenges/yr	Run Failures/yr				Annual Run Failure Cost, $/yr
			Current	Future	Excess	Cost/failure, $	
1	1.9%	365	7	1	6	100	0
2	1.0%	365	4	1	3	100	300
3	1.9%	365	7	0	7	100	0
4	3.4%	365	12	0	12	100	0
5	2.2%	365	8	0	8	100	86
6	2.8%	365	10	0	10	100	96
7	2.9%	365	11	0	10	100	82
8	1.8%	365	7	4	2	100	200
9	5.5%	365	20	2	18	100	1800
10	4.8%	365	17	5	12	100	1200
11	1.8%	365	6	2	5	100	500
12	4.3%	365	16	3	12	100	1200
Total	2.9%	4380	125	19	106	100	5464

5. Discussion

We developed a simple cost model to estimate the COQ in the analytical phase of the testing process and provided example calculations for 12 assays to show how the model could be applied. These data can be used to prioritize quality improvement efforts to reduce bias and imprecision. Of the 12 examples, a manager might select assays 8 and 9 for directed improvement efforts since they had the highest excess errors and excess cost per year.

There are a number of different frameworks for measuring COQ [7]. The most common framework is the Prevention-Appraisal-Failure (P-A-F) framework which was introduced by Feigenbaum [14]. In this framework, run failures would be classified as internal failures because they are detected. Measurement errors would be classified as external failures because they are usually undetected. These 2 costs are only 2

Table 3
Spreadsheet for tabulating costs associated with analytical error. An error is defined as a result beyond the total allowable error. Each error is assigned the unit cost for the test. The error rate is estimated from the current capability and the estimated future capability that could be achieved through quality improvement. The costs shown in the table can be considered costs of process capability.

Assay Information			Analytical Errors							
			Current State			Future State			Excess Errors/yr	Error Cost/yr
Assay	Volume	Unit Cost	Capability (Sigma)	Error Rate	Errors/yr	Capability (Sigma)	Error Rate	Errors/yr		
1	10,150	$7.02	2.15	0.02	160	4.44	0.00	0	160	1124
2	1185	$11.15	1.86	0.03	37	3.42	0.00	0	37	411
3	358	$8.24	2.03	0.02	8	2.43	0.01	3	5	40
4	856	$8.24	2.21	0.01	12	3.02	0.00	1	11	87
5	346	$13.73	2.55	0.01	2	3.60	0.00	0	2	25
6	637	$9.95	3.62	0.00	0	4.65	0.00	0	0	1
7	63	$19.94	2.18	0.01	1	3.61	0.00	0	1	18
8	105	$19.94	2.34	0.01	1	4.51	0.00	0	1	20
9	470	$12.55	2.02	0.02	10	2.79	0.00	1	9	112
10	5120	$8.02	3.95	0.00	0	6.63	0.00	0	0	2
11	1604	$10.57	1.87	0.03	49	3.22	0.00	1	48	510
12	28,653	$5.85	2.19	0.01	409	3.77	0.00	2	406	2377
Total	49,547				689			9	680	$4727

components of the cost of failure. The total COQ would incorporate prevention costs, appraisal costs, and other failure costs.

COQ has received relatively little attention in the clinical laboratory literature. A recent Clinical and Laboratory Standards Institute report provided guidelines for COQ measurement but did not address analytical errors [2]. We were only able to identify 2 studies that had attempted to measure COQ in clinical laboratories [1,15]. One study, performed in Morocco, found that COQ accounted for 30% of the direct laboratory expenses [15]. The majority (83%) of COQ was attributed to conformance costs (prevention, appraisal). Another study, performed in the US, found that the cost of conformance accounted for 93% of the total cost of failure [1]. That study found that the total annual COQ was about $18,000 per month. Neither of these studies accounted for measurement error or run failure. Our study found that the cost of analytical error was about $4727 per year for just 12 tests. This suggests that the costs of analytical error may be greater than recognized. However, the impact of analytical error depends on the selection of a cost function which is difficult to select, as described below.

We found that selecting the cost function was the most challenging aspect of estimating COQ. Selecting the cost function involves 2 steps: 1) selecting the functional form of the cost function, and 2) calibrating the cost function. There are many possible choices for the functional form of the cost function. We selected the goal-post cost function because it is easy to apply, and we believe it is an accurate representation of the way in which most laboratories view costs; that is, a cost is incurred only if there is a non-conformance. The goal-post cost function has several problems. First, errors with significantly different magnitudes incur the same cost (e.g., points 1 and 2, top panel, Fig. 2) or errors with similar magnitude have incur very different costs (e.g., points 2 and 3, top panel, Fig. 2). Some quality experts believe that any deviation from the target should be assigned cost and recommend assigning a cost that is proportional to the magnitude of the error (middle and bottom panels, Fig. 2). For example, Taguchi recommends using a quadratic cost function to reflect the fact that larger errors incur greater costs [16]. Although such cost functions have some advantages, simple cost models (Eq. (11) and ((12))) assume a constant cost and cannot be used to estimate the cost of errors when more complex cost functions are used.

Calibrating the cost function is also challenging (i.e., ensuring that the cost function accurately reflects true costs). In our model, the cost of an error was constant, and we assumed that the cost of an error was equal to the direct cost of the test. We reasoned that, in theory, an unacceptable result should be repeated so that the direct cost is a reasonable starting point. From a laboratory perspective, unacceptable results errors increase the risk of proficiency testing failures, increase administrative costs (e.g., changing results and notifying clinicians), and increase operating costs. Many of the costs associated with errors are hidden. Many quality experts refer to COQ as a “cost iceberg,” in which the visible costs account for a relatively small proportion of the overall costs [17]. The appropriate cost also depends on perspective. From a societal perspective, inaccurate results contribute to additional tests and inappropriate care in addition to the laboratory costs. Thus, the true cost of an unacceptable result may be greater than the direct cost. On the other hand, many, if not most, measurement errors go undetected and, from that perspective, do not represent a real cost. Even if it is not detected, any inaccurate result increases risk of incurring costs, so we believe that any inaccurate result should be assigned a cost; however, it is challenging to determine the correct cost to assign.

Given the challenges in selecting a cost function (functional form, calibration), our COQ estimates are approximations of the true cost. We have found that the estimates are useful, despite the fact that they are approximations. In many cases, COQ estimates are used to evaluate relative costs rather than absolute costs, for example, to determine whether a quality improvement effort has been effective or to prioritize quality improvement projects. A rough estimate may be sufficient for these purposes. In our simple model, the cost function assigned a fixed cost to any error greater than the specification limit. Other models might assign costs to any deviation from a target. For example, one might assign a cost proportional to the size of the deviation (i.e., $c(x) = a(x - x_0)$) or some other function of the deviation (e.g., $c(x) = (x - x_0)^2$). In general, the costs estimated by models based on deviations will exceed the costs of the simple model if the cost of the simple model equals the cost of the deviation model at the specification limit.

Capability calculations are dependent on the method used to estimate the SD [18]. We believe the SD should reflect the actual day-to-day between-run variation. Thus, for this purpose, the long-term SD provides a good estimate of the variation [9,10]. The short-term SD can be used to estimate the potential SD that might be achieved after quality improvement efforts.

The run failure rate (both current and future) depends on the specific set of QC rules. The run failure rate for a simple 1_{3S} rule will be less than the full set of Westgard rules. Our method is applicable to any rule set and to a variety of monitoring methods (e.g. exponentially weighted moving average or cumulative sum charts). We used the full set of Westgard rules to estimate run failure rates.

We provided 2 methods for estimating COQ: absolute and relative. The absolute method compares current COQ to a future state in which errors are eliminated. The relative method compares current COQ to COQ in a future state in which errors are reduced but not eliminated. Both estimates have their uses, but we believe the relative method is more practical because it can be used to guide investment in quality initiatives. These decisions should be guided by savings that can be reasonably achieved rather than a theoretical estimate based on a future state that is unlikely to be achieved.

Our general model can be applied to any process with variable output for which one can assign costs to deviations from the target. Thus, the general model can be applied to a wide range of processes. The simple model is also general but can only be applied to processes which have specification limits (costs are only incurred if the output exceeds the specification limit). Neither the general or simple model is limited with respect to assay, platforms, or operational considerations (e.g. batch vs random access).

Our model has a number of limitations. We assumed that run failures and measurement errors are independent. Our model for the cost of measurement errors assumed a stable process. In fact, the rate of measurement errors depends on the underlying stability of the process. An unstable process will increase the rate measurement errors. Thus, our model most likely underestimates the rate of measurement errors. However, our model provides a good approximation for a reasonably stable process. Our model also assumes that the error in QC measurements is a good indicator of the error in patient results; that is, we assume that the bias and imprecision in QC results reflects the bias and imprecision in patient results. While this assumption is not necessarily true, all QC monitoring rests on this assumption. The simplified model requires a number of assumptions but we believe it provides a reasonable approximation for routine use. The simplified model is particularly useful for measuring relative performance, for example, to measure reduction in COQ over time or to compare the COQ of 2 assays. For these purposes, the change in cost is more important than the absolute value of COQ.

Despite these limitations, the models provide a way to estimate COQ associated with analytical error, which have not been previously incorporated into clinical laboratory standards or published literature. Laboratories with limited resources may select the simplified model for estimating the cost of analytical errors and use the goal post function for cost of errors. Retrospective QC data can be used for estimating the cost of run failures. Estimating COQ and using those data to prioritize improvement efforts can be challenging for laboratories but are important for value-driven patient care. We are currently implementing these COQ metrics at our laboratory and are beginning to use them to

prioritize improvement projects.

Appendix A. Calculations for general model for cost of quality

The expected cost of the error associated with an observed result is given by

$$\overline{C}_{e,i}(x_0) = \int_0^\infty c_{e,i}(x \mid x_0) f_i(x \mid x_0) dx \tag{A1}$$

This model is entirely general and requires no assumptions about the cost function or distribution of observed values. The model is flexible because it allows for the cost and distribution of observed values to vary with x_0, the underlying true value. The subscript i indicates that the probability distribution and cost function may vary by assay.

Eq. (A1) determines the cost of the error associated with a single result. A laboratory produces many results which are distributed according to a distribution, $g(x_0)$. At any given level, x_0, the expected cost is given by the expected cost of error at that level, $\overline{C}_{e,i}(x_0)$, times the probability of obtaining a result at that level, $g(x_0)$. The total expected cost of error is obtained by summing up this quantity over all levels:

$$\overline{C}_{e,i}^{tot,abs} = V_i \int_0^\infty \overline{C}_{e,i}(x_0) g(x_0) dx_0 = V_i \int_0^\infty \int_0^\infty c_{e,i}(x \mid x_0) f(x \mid x_0) g(x_0) dx dx_0 \tag{A2}$$

where V_i is the annual volume of the assay and $g(x_0)$ is the distribution of true patient results. $g(x_0)$ and V_i can be estimated from historical patient results. The superscript *abs* indicates that this is an estimate of the absolute cost of error relative to a state in which all errors are eliminated. While the absolute cost may be an interesting benchmark, it is unrealistic to expect that all errors will be eliminated. Thus, it may be more useful to calculate the cost of avoidable errors which we call the relative cost of errors. Avoidable errors are defined as the difference in the current error rate and the error rate that could be reasonably achieved from a quality improvement program. A quality improvement program would change the distribution of measurement errors, $f(x|x_0)$. For example, bias and imprecision may be reduced as a result of improvement efforts (Fig. 4). In general, we can estimate that there will be 2 distributions, $f_f(x|x_0)$ and $f_c(x|x_0)$, where the subscripts c and f designate the current and future state of the assay. The future distribution of measurement errors, $f_f(x|x_0)$, can be estimated from the short term variation [9,10]. The relative cost of errors is defined as follows:

$$\overline{C}_{e,i}^{tot,rel} = \alpha(\overline{C}_{e,i,c}^{tot,abs} - \overline{C}_{e,i,f}^{tot,abs}) < \overline{C}_{e,i,c}^{tot,abs} - \overline{C}_{e,i,f}^{tot,abs} = C_{e,i}^{*} \tag{A3}$$

The subscripts f and c indicate that Eq. (A2) is evaluated using the current and future measurement error distributions. $C_{e,i}^{*}$ indicates the total improvement opportunity—the savings that would be obtained if measurement errors were reduced to a hypothetical minimum. In reality, a quality improvement program would not achieve all of this opportunity. The parameter α indicates the proportion of the total improvement opportunity that is attainable. In general, α would depend on technological factors related to a particular assay and the ability of the quality improvement team to reduce bias and imprecision. We include α because management may believe that the organization will only be able to achieve a portion of the improvement opportunity. Incorporating α provides a way to scale the savings opportunity so that investments in improvement projects are allocated correctly.

Our model (Eqs. A2 and A3) is general. It requires no assumptions and can be adapted to almost any situation by specifying the inputs. We have described how the inputs $c_{e,i}(x|x_0)$, V_i, $f_i(x|x_0)$, and $g(x_0)$ can be estimated. Eqs. (A1) and (A2) can be estimated using numerical integration which can be performed using Microsoft Excel or any programming language. (A spreadsheet for performing these calculations is provided in the Supplementary Material.)

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