Practical Laboratory Medicine 7 (2017) 1–5

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm

The significance of reporting to the thousandths place: Figuring out the laboratory limitations

Joely A. Straseski[a,b,*], Casey Whale[b], Andrew Wilson[c], Frederick G. Strathmann[a,b]

[a] Department of Pathology, University of Utah, Salt Lake City, UT, United States
[b] ARUP Laboratories, Salt Lake City, UT, United States
[c] Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, United States

ARTICLE INFO

Keywords:
Significant figures
Imprecision
Prostate cancer
Prostate specific antigen
PSA

ABSTRACT

Objectives: A request to report laboratory values to a specific number of decimal places represents a delicate balance between clinical interpretation of a true analytical change versus laboratory understanding of analytical imprecision and significant figures. Prostate specific antigen (PSA) was used as an example to determine if an immunoassay routinely reported to the hundredths decimal place based on significant figure assessment in our laboratory was capable of providing analytically meaningful results when reported to the thousandths places when requested by clinicians.

Design and methods: Results of imprecision studies of a representative PSA assay (Roche MODULAR E170) employing two methods of statistical analysis are reported. Sample pools were generated with target values of 0.01 and 0.20 μg/L PSA as determined by the E170. Intra-assay imprecision studies were conducted and the resultant data were analyzed using two independent statistical methods to evaluate reporting limits.

Results: These statistical methods indicated reporting results to the thousandths place at the two assessed concentrations was an appropriate reflection of the measurement imprecision for the representative assay. This approach used two independent statistical tests to determine the ability of an analytical system to support a desired reporting level. Importantly, data were generated during a routine intra-assay imprecision study, thus this approach does not require extra data collection by the laboratory.

Conclusions: Independent statistical analysis must be used to determine appropriate significant figure limitations for clinically relevant analytes. Establishing these limits is the responsibility of the laboratory and should be determined prior to providing clinical results.

1. Introduction

The discussion of significant figures in result reporting is given relatively little formal attention in the field of laboratory medicine. While a few well-written discussions can be found in the literature [1–3], it is clear that available guidelines or requirements are not always practiced or well known. Further complicating the topic is the futility of a discussion about significant figures when laboratory information systems are only capable of reporting in reference to a decimal place. The available literature provides several useful mechanisms for establishing significant figures for the reporting of a given assay. However, less guidance is

Abbreviations: PSA, prostate specific antigen

* Correspondence to: University of Utah, ARUP Laboratories, 500 Chipeta Way, Mail Code 115, Salt Lake City UT 84018, United States.
E-mail address: joely.a.straseski@aruplab.com (J.A. Straseski).

http://dx.doi.org/10.1016/j.plabm.2016.11.001
Received 31 October 2015; Received in revised form 2 September 2016; Accepted 7 November 2016
Available online 11 November 2016

provided on determining how to establish reporting limits in situations where decimal place consistency is more important than significant figures. For example, prostate specific antigen (PSA) may be measured by methods referred to as “ultrasensitive” with performance claims allowing for the detection of PSA below 0.10 μg/L (0.10 ng/mL). The complication comes from a claimed sensitivity of 0.010 μg/L; an indication of reporting to the hundredths decimal place, but suggestion of a potentially clinically meaningful digit in the thousandths decimal place. Further, strict adherence to the two significant figures claim would allow reporting of 0.011, 0.015 and 0.019 μg/L but not 0.111, 0.115 and 0.119 μg/L. The latter set would require reporting as 0.11, 0.12, 0.12 μg/L causing a perceived loss of resolution between results.

PSA plays a prominent role in the early detection, management, and staging of prostate cancer [4,5].”Ultrasensitive” PSA assays may be used by some clinicians to detect residual or recurrent disease in patients post-prostatectomy [6,7]. Some manufacturers offer assays which claim to have a functional sensitivity (coefficient of variation ≤20%) as low as 0.010 μg/L [8–10] or results that can be reported to two significant figures using the thousandths place. Despite the many advances in the sensitivity and precision of the PSA assay, laboratories commonly report results in this range to two decimal places since the precision of these assays has not been well studied at these low concentrations. However, it has been brought to our attention that values reported to the thousands place are believed by some to aid in patient surveillance.

The goal of this study was to investigate the analytical validity of reporting to the thousandths place regardless of significant figure protocol for PSA at concentrations typically measured with an “ultrasensitive” method. Here we report the results of imprecision studies of a PSA assay with a reported functional sensitivity of 0.030 ng/mL (Roche MODULAR E170, Indianapolis, IN) employing two unique methods of statistical analysis. While straightforward in the approach, the laboratory's assessment of the precision of high sensitivity assays may have considerable clinical implications.

2. Materials and methods

2.1. Patient samples

Residual serum samples submitted to ARUP Laboratories for PSA testing were de-identified stored frozen (-20C) for 10–14 days prior to analysis. This project and its protocols were approved by the University of Utah Institutional Review Board (IRB protocol #00007275).

2.2. Data collection

Data was obtained by analyzing twenty replicates each of a low value (target 0.01 μg/L) and a high value (target 0.20 μg/L) PSA sample pool. Selected sample values were chosen to represent clinically relevant PSA concentrations [11,12] and were within the analytical measurement range of the Roche MODULAR E170 PSA assay 0.014–100 μg/L). After preparation, sample pools were assayed to obtain an initial value and appropriately adjusted using a high value sample or a low value sample until the desired target values were obtained.

Aliquots were tested using the Roche MODULAR E170 automated chemistry analyzer. In order to reduce imprecision, all replicates were performed simultaneously and one measuring cell was inactivated to eliminate any cell-to-cell variation. Testing was performed according to manufacturer's guidelines and using Roche proprietary reagent for the total PSA assay (Catalog #04491734).

2.3. Statistical methods

Two methods were used to evaluate statistical precision and, thereby, assess the appropriateness of reporting. Method I is recommended by the National Resources Management and Environment Department [13] that involves using the within-run variation to direct significant figure reporting. Method II uses a χ^2 test to compare performance claim standard deviation (σ) to observed standard deviation (S). Both of these methods are described in detail below.

2.4. Method I

The Natural Resources Management and Environment Department guideline recommends the following procedure that uses within-run variation to direct reporting of significant figures and determination of rounding rules (n ≥20):

Calculate the upper boundary b_t of the rounding interval a using the standard deviation (s) of the unrounded results, by letting: b_t=s/2. Then choose a equal to the largest decimal unit (e.g., 0.1, 0.01, 0.001 etc.) which does not exceed the calculated b_t.

2.5. Method II

The Clinical Laboratory Standards Institute global consensus guideline [14] uses a χ^2 test to compare performance claim standard deviation (σ) to observed standard deviation (s), where s^2 is the sample variance, σ^2 is the claimed variance, and R is the total number of determinations or measurements: $\chi^2 = (s^2 \cdot R) / \sigma^2$. The calculated χ^2 result is then compared to an upper 95% critical value for R degrees of freedom and can be treated as a formal hypothesis test of the claimed variance.