

Available online on 15.04.2024 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2024 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Research Article

## Application of Sigma Metrics for Evaluating Analytical Performance of HbA1C Testing on D10- HbA1C Analyzer

Bibek Pun Magar \*<sup>1</sup>, Amit Thapa <sup>2</sup>, Shreeman Acharya <sup>3</sup>, Narayan Ghimire <sup>4</sup>, Sanjiv Kumar Pandey <sup>5</sup>, Rabindra Kumar Rokaya <sup>6</sup>, Suman Lamichhane <sup>7</sup>

<sup>1</sup> Department of Biochemistry, Karnali Academy of Health Sciences, Jumla, Nepal

<sup>2</sup> Province Public Health Laboratory, Karnali Province Surkhet, Nepal

<sup>3</sup> Rapti Academy of Health Sciences, Ghorahi, Dang, Nepal

<sup>4</sup> School of Health and Allied Sciences, Pokhara University, Pokhara, Nepal

<sup>5</sup> Nepal Pharmacy Council, Kathmandu, Nepal

<sup>6</sup> School of Pharmacy, Karnali Academy of Health Sciences, Jumla, Nepal

<sup>7</sup> Shree Medical and Technical College, Bharatpur, Nepal (Purvanchal University, Nepal)

### Article Info:



#### Article History:

Received 31 Jan 2024

Reviewed 24 February 2024

Accepted 04 March 2024

Published 15 April 2024

#### Cite this article as:

Magar BP, Thapa A, Acharya S, Ghimire N, Pandey SK, Rokaya RK, Lamichhane S, Application of Sigma Metrics for Evaluating Analytical Performance of HbA1C Testing on D10- HbA1C Analyzer, Journal of Drug Delivery and Therapeutics. 2024; 14(4):27-32

DOI: <http://dx.doi.org/10.22270/jddt.v14i4.6424>

#### \*Address for Correspondence:

Bibek Pun Magar, Department of Biochemistry, Karnali Academy of Health Sciences, Jumla, Nepal

### Abstract

In this study, analyzed HbA1C over a period of 6 months. Six Sigma improves the quality of process outputs by analyzing and eliminating the source of defects and reducing variability in manufacturing and business practices. In terms of clinical laboratory, the identification of test with low Sigma values ( $< 3\sigma$ ) indicate that actions should be taken to improve analytic quality or the laboratory should use alternate methods and reagents. Our study showed methodologies for HbA1C is of world class performance achieving Sigma value  $>6$ , to maintain and improve this frequency of QC should be run as rule as per the westgard QC rule. Sigma metrics helps to assess analytical methodologies and augment laboratory performance. It acts as a guide for planning quality control strategy. It can be a self-assessment tool regarding the functioning of clinical laboratory. Using Six Sigma techniques, able to identify problem areas as well as recurring issues that affect the overall quality expectation of laboratory result.

**Keywords:** HbA1C, Six Sigma, Six Sigma values

### INTRODUCTION:

Six Sigma is characterized as latest management fad to repack old quality management principle, technique and tools<sup>1</sup>. Sigma is the mathematical term(symbol) for the standard deviation (SD) Six sigma gives a more quantitative frame work for evaluating process performance with evidence of process improvement and describes how many Sigma fit within the tolerance limits<sup>2</sup>. Sigma methodology can be applied where an outcome of a process can be measured. A bad outcome is count as defect or error, where it is quantified as DPM (defect per million)<sup>3</sup>. The analytical quality of laboratories is evaluated by analysis of data such as internal quality control which check the precision of the method, external quality control which check the accuracy of the analytical method, patents result. they are graphically represented by statistical charts <sup>4</sup> Six Sigma methodology composed of five steps define, measure, analysis, improve, control (DMAIC). These steps are universal and can be applied in business, industry and medicine. The performance of analytical process evaluated according to the Six Sigma methodology in clinical laboratory and is expressed in single

number which is defined as "process Sigma level". High Sigma level that means the analytical errors are low and the test result can be acceptable. Low Sigma level is accepted as error<sup>5</sup>. To make improvements and increase quality in management of reagents Six Sigma methodology can be used. Six Sigma method can improve the effectiveness and efficiency of laboratory reagents management. The lean management tools focus on the speed and efficacy of a process, where as those of Six Sigma focus on its precision and accuracy. Lean Six Sigma is dedicated to increase quality, reduce variability and remove any waste from the healthcare Centre <sup>6</sup>, methods help to reduce variation/ errors in Laboratory processes, thus reducing cost of laboratory services, increases customer's satisfaction and increase quality of laboratory results.<sup>7</sup>

#### Glycated hemoglobin:

Glycated or glycosylated hemoglobin refers to the glucose derived products of normal adult hemoglobin (HbA). Glycation is a post-translational, non-enzymatic addition of sugar residue to amino acids of proteins. Among the glycated hemoglobin, the most abundant form is HbA1c. Diabetes affects about 2-3% of the population and is a major cause of

blindness, renal failure, heart attack and stroke.

The hormone insulin has been implicated in the development of diabetes. Diabetic ketoacidosis is frequently encountered in severe uncontrolled diabetics. The management includes administration of insulin, fluids and potassium. The hypoglycemic drugs commonly used in diabetic patients include tolbutamide, Glibenclamide and acetohexamide. Measurement of glycated hemoglobin (HbA1c) serves as a marker for diabetic control. HbA1c is produced by the condensation of glucose with N-terminal valine of each E-chain of HbA. Diagnostic importance of HbA1c: The rate of synthesis of HbA1c is directly related to the exposure of RBC to glucose. Thus, the concentration of HbA1c serves as an indication of the blood glucose concentration over a period, approximating to the half-life of RBC (hemoglobin) i.e. 6–8 weeks. A close correlation between blood glucose and HbA1c concentrations has been observed when simultaneously monitored for several months. Normally, HbA1c concentration is about 3–5% of the total hemoglobin. In diabetic patients, HbA1c is elevated (to as high as 15%). Determination of HbA1c is used for monitoring of diabetes control. HbA1c reflects the mean blood glucose level over 2 months period prior to its measurement. In the routine clinical practice, if the HbA1c concentration is less than 7%, the diabetic patient is considered to be in good control. Estimated average glucose (eAG) : eAG is a new term (introduced by American Diabetic Association) used in diabetic management. It is a laboratory tool to understand the approximate relationship between HbA1c and glucose concentrations<sup>8</sup>. Hemoglobin is a protein that present in the red blood cell and help to carry the oxygen. After the synthesis of hemoglobin is formed by post translations and hemoglobin A1c(HbA1c) most frequently seen<sup>9,10</sup>. The HbA1c test is a biomarker to evaluate the long-term outcome of diabetes and therefore it plays important role in management of diabetes. There are more than 70 methods are available for the analysis of around the world<sup>11</sup>. Hemoglobin A1c (HbA1c) measurements give the information about the level of glucose in the last 3 months<sup>12,13</sup>. HbA1c is a most frequent test in the laboratory, the principle is based on reverse-phase cation exchange “high performance liquid chromatography”<sup>4</sup>. The methods of detection used in clinical laboratories such as, HPLC (high performance liquid chromatography) systems and electrophoresis, are mainly based on different electric charges or glycosylation molecules present on the HbA1c<sup>13,14</sup>. HbA1c is a common method for long-term glycemia monitoring and efficacy of drugs evaluation. According to current American Diabetes Association (ADA) recommended that HbA1c > 6.5 % was important criteria for the diagnosis of diabetes. Lowering the HbA1c value, 7% could reduce the risk of microvascular complication in diabetes, hence evaluation of HbA1c level is important role in diagnosis and treatment of diabetes<sup>15</sup>. High quality of the HbA1c test can be achieved by HPLC systems and monitoring their performance by QC programs with appropriate materials that will increase the confidence of operators in their performance<sup>16,17</sup>.

## MATERIALS AND METHODS

**Study design:** Retrospective study

This study was conducted in the clinical biochemistry laboratory of Padmashree diagnostic center Vijayanagara, Bangalore. This is a NABL accredited diagnostic center, which provide all kind of laboratory services (hematology, biochemistry, microbiology, histopathology, serology, clinical pathology, etc) they offer services other than lab includes

radiology and imagine service, neurology, cardiology, ophthalmology, etc. Aim of our study was to analyze Sigma metrics of Glycated hemoglobin (HbA1C) so as to assess the functioning of D-10 HbA1C analyzer that works on the principle of reverse phase cation exchange (high performance liquid chromatography). Internal quality control data of HbA1C were analyzed retrospectively over a period of 6 months in 2020 with D-10 HbA1C analyzer that measure glycated hemoglobin based on the principle of reverse phase cation exchange “High Performance Liquid Chromatography” - HPLC.

**Total Allowable Error:** TEa is a model that combines both imprecision and bias (Trueness) of a method to calculate the impact on a test result. Analytical Quality Requirements are defined by Clinical Laboratory Improvement Amendment (CLIA) -88 Proficiency Testing Criteria in terms of total allowable error “TEa” (or more correctly “total allowable variation”) for acceptable performance for each analyte. The most recent and extensive listing of biologic goals has been provided by Ricos et al, which is taken as reference value. These values are in accordance with CLIA guidelines.<sup>(30,31)</sup>

**Bias:** The difference between the average value and the true value is the bias, which is expressed numerically and so is inversely related to the trueness. Bias was taken from % of Deviation of the peer group data from results returned from RIQAS;

Bias (%) = (mean of all laboratories using same instrument and method - our mean) / mean of all laboratories using same instrument and method) X 100

**Coefficient of Variance:** The degree of precision is usually expressed on the basis of statistical measures of imprecision, CV%. CV was determined from the calculated laboratory mean and calculated standard deviation procured from the internal QC data over the 3 months:

CV (%) = (Standard deviation / Laboratory mean) X 100

### Sigma metric calculation

Sigma (s) value was used in order to determine the analytical performance characteristics of Sigma value tests by using CV (obtained from IQC data), Bias% and TEa values. Sigma value calculated using the standard equation:

Sigma metric (s) = (%TEa - %Bias) / CV%

## RESULT AND DISCUSSION

Sigma values were used to determine the analytical performance characteristics of the test. A Sigma level <3 is an indication of a poor performance procedure, whilst a good performance is indicated by a Sigma level >3. Above Six Sigma level is a world class performance.<sup>(32)</sup> The present study was carried out to evaluate the analytical performance of d-10 HbA1C analyzer. The six-month data for CV%, from internal quality program) and Bias%, from external quality control program were collected from Padmashree Diagnostics, clinical biochemistry department Vijayanagar.

### Use of Sigma metrics for the evaluation of analyte performance

To understand the performance of HbA1C on D-10 HbA1C analyzer in Padmashree diagnostic Vijayanagara, Bangalore, the Sigma metrics of analyte as the QC materials levels 1 and level 2 were calculated and are summarized in table no.1.

According to Sigma metrics, the performance of the analytes is divided in to six different grades. They are.

Table 1: Sigma metrics of analyte

$\text{Sigma} \geq 6$	world class
$5 \leq \text{Sigma} < 6$	excellent
$4 \leq \text{Sigma} < 5$	good
$3 \leq \text{Sigma} < 4$	marginal
$2 \leq \text{Sigma} < 3$	poor
$\text{Sigma} \leq 2$	unacceptable

Table 2: Bias, TEa%, CV% and Sigma value for quality control 1 and 2 :

Month	Parameter	TEa%	Bias %	Level 1		Level 2	
				CV%	Sigma	CV%	Sigma
April	HbA1c	6	0.15	0.94	6.22	0.90	6.50
May	HbA1c	6	0.1	1.33	4.44	0.60	9.83
June	HbA1c	6	0.1	0.94	6.27	0.70	8.43
July	HbA1c	6	0.03	1.53	3.90	1.00	5.97
August	HbA1c	6	0.8	1.53	3.34	0.63	8.25
September	HbA1c	6	0.2	1.53	3.79	0.63	9.20

The Process Sigma level were determined according to IQC1 QC2 and EQC results by month as April (6.22-6.50-0.15), May (4.44-9.83-0.1), June (6.27-8.43-0.1), July (3.90- 5.97-0.03), August (3.34-8.25-0.8), September (3.79-9.20-0.2) respectively. The Sigma values from month of July to

September for level-1 QC is showing gradual decreasing compared to previous months so here, root cause analysis for this declining Sigma value has to be done and necessary corrective action for this issue should be taken to maintain the accurate and précised HbA1C report.

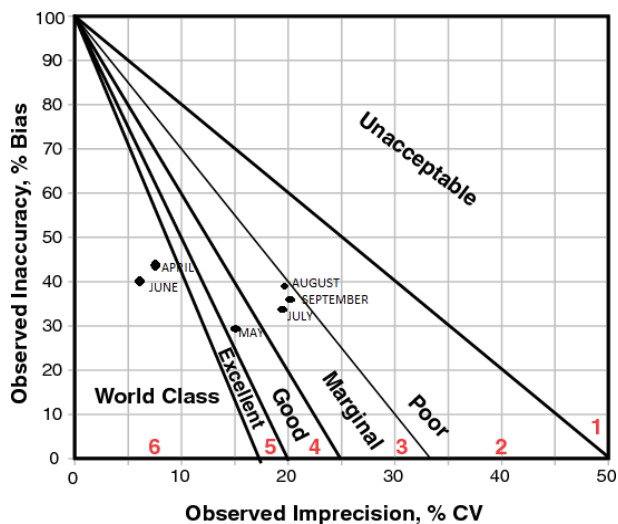


Figure1: Sigma matrix chart for HbA1c level 1 QC

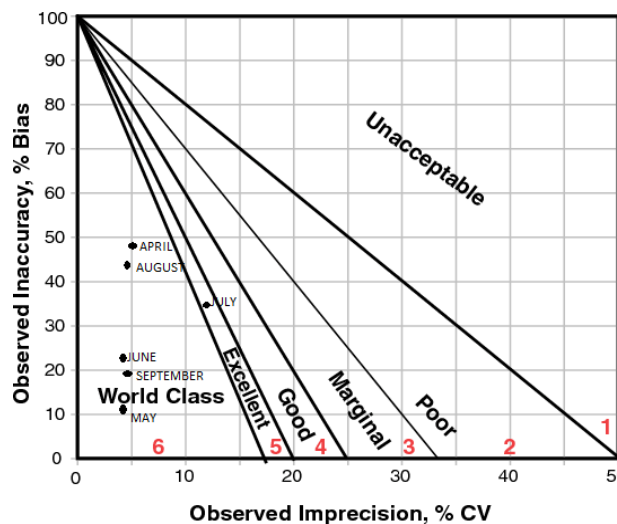


Figure2: Sigma matrix chart for HbA1c level 2 QC

In this study, analyzed HbA1C over a period of 6 months. Six Sigma improves the quality of process outputs by analyzing and eliminating the source of defects and reducing variability in manufacturing and business practices. In terms of clinical laboratory, the identification of test with low Sigma values ( $< 3\sigma$ ) indicate that actions should be taken to improve analytic quality or the laboratory should use alternate methods and reagents.

To calculate Sigma, have calculated mean, standard deviation (SD), coefficient of variation (CV) and bias. SD quantifies the closeness of numerical values in relation to each other. Since SD increases as the concentration of analyte increases, CV can

be regarded as statistical analyzer. Since CV is the ratio of two, it cancels that effect. CV is therefore standardization of the SD that allows comparison of variability estimates regardless of analytes concentration. CV is dimensionless and does not vary with changes in measurement units have obtained lower CV for HbA1C, as CV is correlated to precision. Lesser the CV, better is the precision. This suggests that precision is high for HbA1C. Bias is the difference between the measured value and actual value. It is used to describe the inaccuracy of the method. Lower the bias more is the accuracy. In this study obtained low bias values. This suggests that the methods for measurement of HbA1C is accurate. The Six Sigma scale ranges

from zero to six, but a process can actually exceed Six Sigma, if variability is sufficiently low as to decrease the defect rate. In laboratory 3 Sigma is considered to be the minimal acceptable performance for a process. When performance falls below 3 Sigma, the process is considered to be essentially unstable and unacceptable. I have got Sigma values >Six Sigma. It implies that procedures for HbA1C is of world class standard. The Six Sigma idea asserts an association between the numbers of product defects, wasted operating costs and levels of customer satisfaction. It can be inferred that as Sigma increases, the consistency and steadiness of the test improves, thereby reducing the operating costs. As Sigma increases, the consistency, reliability, steadiness and overall performance of the test improves, thereby decreasing the operating costs.<sup>34</sup> Consider testing specimens in duplicate. Total quality management works on plan, do, check and act rules whereas Sigma metrics works on define, measure, analyze, improve, control. When process performance is validated against Westgard rules or any other quality criteria for acceptability of control data, probability for rejection and probability of error detection are of paramount importance.<sup>35</sup> In analytical process; test methods, analyzers, internal and external quality control, calibration rise to prominence and in this process the control of the variables is possible<sup>17</sup> in order to prove the

performances, Six Sigma methodology is an effective tool<sup>36</sup> To provide a holistic perspective, pre-analytical and post-analytical processes must be evaluated with the analytical process. HbA1c is a globally accepted analyte in its utility for monitoring the complications of diabetes<sup>37</sup> The HbA1c unit established by international scientific circles is mmol/mol but there is a continuing discussion on units. In the USA percentage (%), HbA1c (recommended by NGSP) unit is accepted, however IFCC accepts both units, but IFCC recommends using mmol HbA1c/mol<sup>38,39</sup>. In our laboratory, % HbA1c unit which is recommended by NGSP is used and this unit was also used during the evaluation with Six Sigma methodology<sup>4</sup>. To achieve Six Sigma is considered as the gold standard for defining world class measure of quality. In clinical laboratory, Six Sigma methodology give attention on regulating a process within 6 standard deviations which represents 3.4 defects per million opportunities<sup>40</sup> Process performance at the 3-Sigma level is considered as the minimum acceptable level of quality. The Sigma metrics represent the correlation among numbers of product defects, wasted operating costs and customer satisfaction. Therefore, as Sigma increases, the consistency, reliability, steadiness and overall performance of the test improves, thereby decreasing the operating costs<sup>41</sup>.

Table 3: Sigma metric tools for QC design and frequency.

Sigma metric	Control rule	QC frequency
Six sigma	1 <sub>3s</sub> , n=2	1 per 1000 patient samples
Five sigma	1 <sub>3s</sub> /2 2s/ r 4s, n=2	1 per 450 patient samples
Four sigma	1 <sub>3s</sub> /2 2s/ r 4s/4 1s, n=4	1 per 200 sample samples
Three sigma	all "Westgard Rules" n=6	1 per 45 patient samples
Two sigma and below	max "Westgard Rules" n=6	1 per 10 patients samples

When the method quality goals are set at Six Sigma, stringent internal QC rules are mandatory. However, false rejections rate should also be kept in mind which can be minimized by relaxing control limits up to 3 SD. On other hand, if method is performing at Sigma level below 3, it will require to implement a newer and better method because quality of the test cannot be assured even after multiple QC cycles.<sup>42</sup> Application of Six Sigma in clinical laboratory involves calculating the performance of the test method using standard QC procedures and also specifying the quality requirements for the test in term of total allowable error (TEa). It also requires continuous scrutiny of the data, computing a Six Sigma value (Sigma ( $\sigma$ ) = [TEa - bias]/CV), improvisation of process based on the data analysis and long term follow up<sup>43</sup> Analytical reproducibility in HbA1c measurement is important for monitoring diabetic patients. Changes in results between two HbA1c test results should reflect responses to treatment, and an optimal imprecision goal for HbA1c of 2.1% has been proposed<sup>44,45</sup> This criterion is very strict, however, and difficult to meet, with an imprecision of 3% CV being a more

realistic target<sup>46</sup>. On the month from April to June Six Sigma was fine and afterwards till September Sigma value has come down. Root cause analyst suspected that it may be due to contamination and decontamination has corrected the issue.

## CONCLUSION:

HbA1C is an important indicator of long term glycemic control with the ability to reflect the cumulative glycemic history of the preceding 2-3 months. It is not only providing a reliable measure of chronic hyperglycemia but also correlates well with the risk of long- term diabetes complications, thus accurate and précised report for testing is mandatory. Six Sigma technique are able to identify problem areas as well as recurring issues that affect the overall quality of laboratory results hence, implementation Sigma methodology is important to maintain and improve quality result. Our study showed methodologies for HbA1C is of world class performance achieving Sigma value >6 ,to maintain and improve this frequency of QC should be run as rule as per the westgard QC rule. Sigma metrics helps to assess analytical methodologies and augment laboratory performance. It acts as

a guide for planning quality control strategy. It can be a self-assessment tool regarding the functioning of clinical laboratory. Using Six Sigma techniques, able to identify problem areas as well as recurring issues that affect the overall quality expectation of laboratory result.

## REFERENCES:

- Schroeder RG, Linderman K, Liedtke C, Choo AS, Six Sigma: Definition and underlying theory *Journal of Operations Management*. 2008; 26: 536-554. <https://doi.org/10.1016/j.jom.2007.06.007>
- Nevalainen D, Berte L, Kraft C, Leigh E, Picaso L, Morgan T. Evaluating laboratory performance on quality indicators with Six Sigma scale. *Arch Pathol Lab Med*. 2000;124(4): 516-9. 5 <https://doi.org/10.5858/2000-124-0516-ELPOQI> PMID:10747306
- Coskun A. Six Sigma and calculated laboratory tests. *Clin Chem*. 2006;52:770-1 <https://doi.org/10.1373/clinchem.2005.064311> PMID:16595831
- Aslan D, Demir S. Laboratuvar Tıbbında Altı Sigma Kalite Yönetimi. *Türk J Biochem* 2005;30:272-278.
- Hens K, Berth M, Armbruster D, Westgard S. Sigma metrics used to assess analytical quality of clinical chemistry assays: importance of the allowable total error (TEa) target. *Clin Chem Lab Med* 2014;52:973- 980. <https://doi.org/10.1515/cclm-2013-1090> PMID:24615486
- Syahputri, K., R. M. Sari, Anizar, I. R. Tarigan, and I. Siregar. 2018. "Application of Lean Six Sigma to Waste Minimization in Cigarette Paper Industry." *IOP Conference Series: Materials Science and Engineering*. 2018; 309(012027). <https://doi.org/10.1088/1757-899X/309/1/012027>
- Sirajuddin, T. Yuri Zagloel, and S. Rauf. 2016. "Improving Indonesian Logistics Performance with Using Six Sigma, DMAIC and Integration Process." Pp. 2857-58 in Vols. 8-10 March. Department of Industrial Engineering, Engineering Faculty, Indonesia University, Kampus UI Depok 16424, Indonesia: IEOM Society
- Dr. U. Satyanarayana, Dr. U. Chakrapani: *Biochemistry*; 4th edition; 2013
- Radin MS. Pitfalls in Hemoglobin A1c Measurement: When Results may be Misleading. *J Gen Intern Med* 2014;29:388-394. <https://doi.org/10.1007/s11606-013-2595-x> PMID:24002631 PMID:PMC3912281
- Tekce BK, Tekce H, Aktaş G, Tosun M. Comparing the HbA1c Assay Results of Architect C 8000 and MQ-2000PT. *Jarem* 2015;5:52-55. <https://doi.org/10.5152/jarem.2015.684>
- Goodall I, Colman PG, Schneider HG, McLean M, Barker G. Desirable performance standards for HbA1c analysis - precision, accuracy and standardisation: consensus statement of the Australasian Association of Clinical Biochemists (AACB), the Australian Diabetes Society (ADS), the Royal College of Pathologists of Australasia (RCPA), Endocrine Society of Australia (ESA), and the Australian Diabetes Educators Association (ADEA). *Clin Chem Lab Med* 2007;45:1083-1097 <https://doi.org/10.1515/CCLM.2007.158> PMID:17579563
- Sacks DB. Measurement of hemoglobin A1c: a new twist on the path to harmony. *Diabetes Care* 2012;35:2674-2680 <https://doi.org/10.2337/dc12-1348> PMID:23173136 PMID:PMC3507560
- Sandberg S, Fraser CG, Horvath AR, et al. Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem Lab Med*. 2015;53: 833-835. <https://doi.org/10.1515/cclm-2015-0067> PMID:25719329
- Njoroge SW, Nichols JH. Risk management in the clinical laboratory. *Ann Lab Med*. 2014;34:274-278. <https://doi.org/10.3343/alm.2014.34.4.274> PMID:24982831 PMID:PMC4071183
- Njoroge SW, Nichols JH. Risk management in the clinical laboratory. *Ann Lab Med* 2014;34:274-8. <http://dx.doi.org/10.3343/alm.2014.34.4.274> PMID:24982831 PMID:PMC4071183
- Sandberg S, Fraser CG, Horvath AR, Jansen R, Jones G, Oosterhuis W, et al. Defining analytical performance specifications: Consensus statement from the 1st strategic conference of the European Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem Lab Med* 2015;53:833-5. <http://dx.doi.org/10.1515/cclm-2015-0067> . <https://doi.org/10.1515/cclm-2015-0067>
- Njoroge SW, Nichols JH. Risk management in the clinical laboratory. *Ann Lab Med* 2014;34:274-8. <http://dx.doi.org/10.3343/alm.2014.34.4.274> PMID:24982831 PMID:PMC4071183
- Nevalainen D, Berte L, Kraft C, Leigh E, Picaso L, Morgan T. Evaluating laboratory performance on quality indicators with Six Sigma scale. *Arch Pathol Lab Med*. 2000;124(4):516-9. <https://doi.org/10.5858/2000-124-0516-ELPOQI> PMID:10747306
- Westgard JO. *Six Sigma quality design and control*, 2nd ed. Madison WI: Westgard QC Inc., 2006;338.
- Brussee W. *Statistics for Six Sigma made easy*. New York: McGraw-Hill 2004;229.
- James O. Westgard, Sten A. Westgard. *The Quality of Laboratory Testing Today: An Assessment of Sigma Metrics for Analytic Quality Using Performance Data From Proficiency Testing Surveys and the CLIA Criteria for Acceptable Performance*. *Am J Clin Pathol*. 2006;125:343-354. <https://doi.org/10.1309/V50H4FRVWVWX12C79>
- Westgard JO: 2006, Quality control. How labs can apply Six Sigma principles to quality control planning. *Clin Lab News* 32:10-12.
- Coskun A, Inal T, Unsal I, et al. Six Sigma as a quality management tool: evaluation of performance in laboratory medicine. *Quality Management and Six Sigma* 2010. ISBN: 978-953-307-130-5. <https://doi.org/10.5772/9928>
- Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of Sigma metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. *Am J Clin Pathol* 2006;125(3):343-54. <https://doi.org/10.1309/V50H4FRVWVWX12C79> PMID:16613337
- Little RR, Rohlfing CL, Sacks DB. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. *Clin Chem* 2011; 57: 205-14. <https://doi.org/10.1373/clinchem.2010.148841> PMID:21148304
- Weykamp C. HbA1c: a review of analytical and clinical aspects. *Ann Lab Med* 2013; 33: 393-400 <https://doi.org/10.3343/alm.2013.33.6.393> PMID:24205486 PMID:PMC3819436
- Woodworth A, Korpi-Steiner N, Miller JJ, Rao LV, Yundt Pacheco J, Kuchipudi L, et al. Utilization of assay performance characteristics to estimate hemoglobin A1c result reliability. *Clin Chem* 2014; 60: 1073-9. <https://doi.org/10.1373/clinchem.2013.220772> PMID:24815907
- Westgard JO, Westgard SA. Assessing quality on the Sigma scale from proficiency testing and external quality assessment surveys. *Clin Chem Lab Med* 2015; 53: 1531-5. <https://doi.org/10.1515/cclm-2014-1241>
- Weykamp C, John G, Gillery P, English E, Ji L, Lenters Westra E, et al. Investigation of 2 models to set and evaluate quality targets for HbA1c: biological variation and Sigma-metrics. *Clin Chem* 2015; 61: 752-9. <https://doi.org/10.1373/clinchem.2014.235333> PMID:25737535 PMID:PMC4946649
- Farr AJ, Freeman KP. Quality control validation, application of Sigma metrics, and performance comparison between two biochemistry analysers in a commercial veterinary laboratory. *J*

- Vet Diagn Invest 2008;20(5):536-44.  
<https://doi.org/10.1177/104063870802000502> PMID:18776084
31. Ricos C, Alvarez V, Cava F, et al. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest 1999;59(7):491-500. This database was most recently updated in 2014 <https://doi.org/10.1080/00365519950185229> PMID:10667686
32. Westgard JO, Westgard SA. Quality control review: implementing a scientifically based quality control system. Ann Clin Biochem 2016;53:32-50. <https://doi.org/10.1177/0004563215597248> PMID:26150675
33. Westgard JO. Six Sigma quality design and control. Westgard QC, Inc, Madison.
34. Tetrault G. Evaluating laboratory performance with the Six Sigma scale. Arch Pathol Lab Med 2000; 124(12):1748-9. <https://doi.org/10.5858/2000-124-1748c-ELPWTS> PMID:11100045
35. Westgard JO. Internal quality control: planning and implementation strategies. Ann Clin Biochem 2003; 40:593-611. <https://doi.org/10.1258/000456303770367199> PMID:14629798
36. Berte ML. Laboratory Quality Management: A Road Map. Clin Lab Med 2007;27:771-790. <https://doi.org/10.1016/j.cll.2007.07.008> PMID:17950897
37. Coskun A, editor. Quality Management and Six Sigma. Rijeka, Croatia; 2010. [www.sciyo.com](http://www.sciyo.com) <https://doi.org/10.5772/271>
38. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial revisited. Diabetes 2008;57:995-1001. <https://doi.org/10.2337/db07-1618> PMID:18223010
39. Little RR, Rothliff CL, Wiedmeyer H-M, Myers GL, Sacks DB, Goldstein DE. The National Glycohemoglobin Standardization Program (NGSP): A five-year progress report. Clin Chem 2001;47:1985-1992
40. Mosca A, Goodall I, Hoshino T, et al. Global standardization of glycosylated hemoglobin measurement: the position of the IFCC Working Group. Clin Chem Lab Med 2007;45:1077-1080. <https://doi.org/10.1515/CCLM.2007.246> PMID:17867998
41. Revere L, Black K. Integrating Six Sigma with total quality management: a case example for measuring medication errors. J Healthc Manag. 2003;48:377-91. <https://doi.org/10.1097/00115514-200311000-00007> PMID:14671947
42. Tetrault G. Evaluating laboratory performance with the Six Sigma scale. Arch Pathol Lab Med. 2000;124(12):1748-9. <https://doi.org/10.5858/2000-124-1748c-ELPWTS> PMID:11100045
43. Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of  $\sigma$  metrics for analytic quality using performance data from proficiency testing surveys and the CLIA Criteria for Acceptable Performance. J Clin Pathol. 2006;125: 343-54. <https://doi.org/10.1309/V50H4FRVWVX12C79>
44. Westgard JO. Quality control. How labs can apply Six Sigma principles to quality control planning. Clin Lab News. 2006;32:10-2.
45. Braga F, Dolci A, Montagnana M, Pagani F, Paleari GC, Guidi GC et al. Reevaluation of biological variability of glycosylated haemoglobin using an accurately designed protocol and assay traceable to the IFCC reference system. Clin Chim Acta 2011;412:1412-16. <https://doi.org/10.1016/j.cca.2011.04.014> PMID:21524644
46. Goodall I, Colman PG, Schneider HG, McLean M, Barker G. Desirable performance standards for HbA1c analysis-precision, accuracy and standardization: Consensus statement of the Australian Association of Clinical Biochemists (AACB), the Australian Diabetes Society (ADS), the Royal College of Pathologists of Australia (RCPA), Endocrine Society of Australia (ESA), and the Australian Diabetes Educators Association (ADEA). Clin Chem Lab Med 2007;45:1083-97. <https://doi.org/10.1515/CCLM.2007.158>