Error Grid Analysis (EGA) of Glycated Hemoglobin A1c

Jesse A. Canchola, Roche Molecular Systems, Pleasanton, California USA

Abstract

Error Grid Analysis (EGA) uses graphical error grids for performance evaluations of medical devices, for example, a new device as compared to a predicate or currently accepted or gold-standard device or for comparing candidate and comparative measurement methodologies, for example, a new blood collection method as compared to a current standard.

Although not as widely used, EGA is an instructive and visually appealing performance evaluation methodology that shows the measurement of a new or improved test on the y-axis with a paired measurement of the reference test on the x-axis overlaid on a colorful grid of clinical regions (as established by experienced clinicians by consensus or through findings in the literature). Although error grids for glucose (mg/dL and mmol/l), hematocrit (%) and hemoglobin (g/dL) have been proposed, a reasonable EGA for glycated hemoglobin A1c (HbA1c or, simply, A1c), in percent units, has not been widely adopted at this time. We propose an EGA methodology for glycated hemoglobin A1c (%).

Introduction

Error Grid Analysis was originally developed by Clarke and colleagues (1987; Clarke, et al.) for *clinical performance evaluation* of blood glucose values as obtained from a blood glucose meter and compared to a reference value as the gold standard − as opposed to the traditional *statistically-based methods comparison* approaches such as Ordinary Least Squares (OLS) Regression, Deming regression or Passing-Bablok regression. Subsequently, the phrase, "Clarke Error Grid" was coined to describe this type of analysis for glucose and, eventually, non-glucose analyte comparisons of this kind were simply called, Error Grid Analysis or EGA.

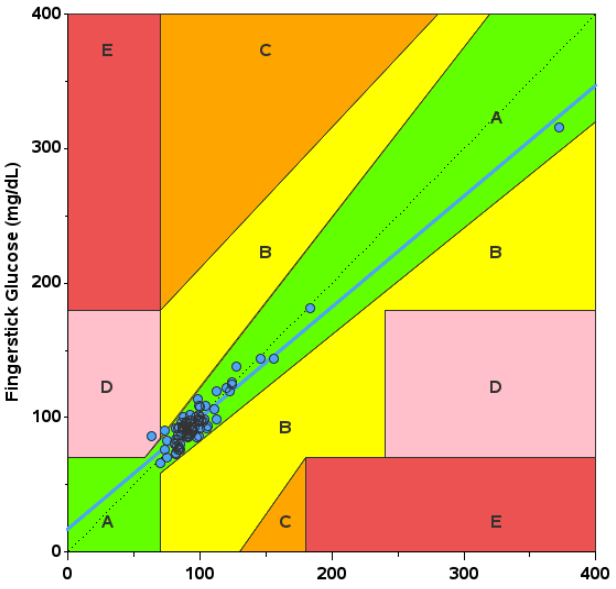

Figure 1. Clarke Error Grid for Venous vs. Fingerstick Glucose (mg/dl)

It is useful to note that there are at least two methods that can be used to develop an EGA graph (CLSI EP27-A). In one method, clinicians (or experts) decide by consensus (and currently acceptable practice) the meaning of the graphical grid areas. This is accomplished mainly through survey administration. In the second, the researcher establishes the grid regions using the literature. In our current exposition, the latter is used.

Typically, EGA consists of a pre-defined grid of color-coded regions that indicate whether the measured test as compared to reference data paired observations are within clinically acceptable boundaries. As an example, Figure 1 shows a typical five-region Clarke Error Grid of glucose measurements (mg/dL) for diagnosis and treatment of hypo- and hyper-glycemia from a blood sample drawn by fingerstick as compared to the reference sample from a venous draw. The five regions are coded so that:

(1) Region A (light green) should contain values that are considered, "clinically accurate";
(2) Region B (yellow) should contain values that are greater than the reference value but would "not lead to inappropriate treatment";
(3) Region C (orange) should contain values that would "lead to unnecessary treatment";
(4) Region D (pink) should contain values that would indicate a "potentially dangerous failure to detect hypo- or hyper-glycemia";
(5) Region E (red) should contain values that would confuse treatment of hypoglycemia for hyperglycemia and vice-versa.

A proposed EGA solution for glycated hemoglobin A1c in percent units is presented in the following section.

Motivation

The primary motivation for developing an HbA1c Error Grid comes from using HbA1c as a method for monitoring the degree of glucose metabolism or regulation. First, the term HbA1c refers to what is called “glycated hemoglobin”. It develops when hemoglobin, a protein within red blood cells that carries oxygen throughout the body, joins with glucose in the blood, becoming, ‘glycated’. By measuring glycated hemoglobin, clinicians are able to get an overall picture of what our average blood sugar levels have been over a period of two to three months. For people ***without*** Type II diabetes, knowing their A1c becomes an important motivator for lifestyle changes to prevent the onset of Type II diabetes. For people ***with*** Type II diabetes, this is important since the higher the HbA1c, the greater the risk of developing diabetes-related complications.

Table 1 shows the American Diabetes Association's (ADA) classification of glucose regulation by HbA1c for patients with "normal glucose regulation, "prediabetes", and "diabetes".

	Normal Glucose Regulation	**Prediabetes**	**Diabetes**
HbA1c (%)	< 5.7 %	5.7 % to < 6.5%	≥ 6.5 %

Table 1. Classification of glucose regulation using HbA1c (ADA, 2013)

Development

From this classification along with analogues to the Clarke Error Grid methodology (Morey et al., 2011), it is straightforward to develop a simple grid with three categories as follows:
(i) Region A (light green) will contain values that are considered, "clinically accurate";

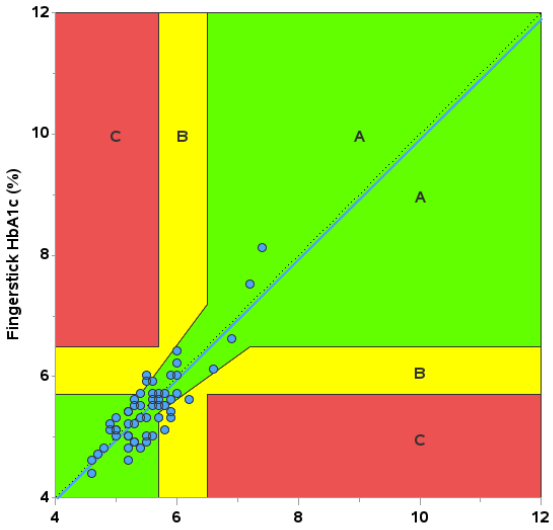

Figure 2. Error Grid for Venous vs. Fingerstick HbA1c (%)

(ii) Region B (yellow) will contain values that are greater than the reference value but would "not lead to inappropriate treatment";
(iii) Region C (red) contains values that would confuse treatment decision for diabetes.

Figure 2 shows the results of applying the literature-based cut points for creating the three regions using The SAS® System v9.3. The sample observations shown are the Venous versus Fingerstick data pairs (shown as blue dots) with an OLS regression line in solid blue following the one-to-one dotted unity line.

Conclusion

The authors exhibited the standard EGA methodology ala the Clarke Error Grid (CEG) logic. They presented a unique EGA method for hemoglobin A1c as a percent. The error grid regions were determined using ADA guidelines and created using The SAS® System v9.3, with actual sample data overlaid as an example. Future work involves production of an equivalent Parkes Error Grid (PEG) using the PEGs methodology from CLSI EP27-A.

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Contact Information

Your comments and questions are valued and encouraged. To obtain the SAS program code used in this paper or SAS program code that recreates the Parkes Error Grid of Pfützner et al. 2013, please contact the first author at:

Jesse A. Canchola
Roche Molecular Systems
6300 Hacienda Drive
Pleasanton, CA 945588
E-mail: Jesse.Canchola@Roche.Com

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