ESTABLISHING AND REPORTING ACCEPTABLE RISK

THROUGH MEASUREMENT OF ANALYTICAL ERROR IN A1c TESTING

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1. Describe how to prioritize between Risk, Quality, and Utility when interpreting A1c test results 2. Recognize underlying analytical limitations in A1c testing 3. Explain how measuring and reporting analytical error in A1c testing can mitigate risk

SITUATION

Care of patients with type II diabetes requires balancing long-term benefits of glycemic control against short term risks for hypoglycemia.[1] Hemoglobin A1c [**A1c**] test results are critical in establishing the risk for, diagnosis of, and management of diabetes. **Integrated Systems Management** dictates that ***Risk*** is the critical issue. In this case, **Systematic Analytical Error [SAE]** can introduce a significant shift of test results leading to **Systematic Diagnostic Error [SDE]** and inappropriate therapy without the clinician being aware they are incurring this ***Risk***.

PROBLEM

How can we reduce the impact of **Systematic Analytical Error** on the balance between:

⇨ Short term ***Risk*** of hypoglycemia against
⇨ Long term ***Risk*** of persistent hyperglycemia

So as to lay the ground work for establishing:

Acceptable Risk?[2]

SOLUTION

An efficient, cost effective means of helping clinicians to establish ***Acceptable Risk*** is to utilize readily available Quality Control Data [**QCD**] to estimate test reliability; then create a clear and concise report that effectively communicates the ***Risks*** incurred in utilizing only one or two **A1c** test results.[3] In essence,

Quality Control is really Risk Control

The goal is to use the reporting of this information to lead the clinician to be more judicious in how a diagnosis is rendered and treatment considered to the benefit of the patient.[4]

IMPLEMENTATION

Implementation of reliability [also know as uncertainty] measurement can be achieved through a two stage approach:

⇨ Methodology validation prior to implementation.
⇨ Publication of collated Quality Control Data as:

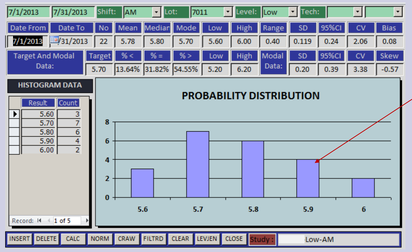
Bias, Imprecision, Skewing, and Significance of Two Results

This provides an estimate of the probability a single test result is clinically significant and that two are significantly different.[5]

MEASURE	SYMBOL	CALCULATED ON AT LEAST 3 MONTHS QC DATA
BIAS	X - u	$\Sigma x/n$ – Vendor Target Value
BIAS BAR	-	Percent QC Results below, at, and above Target Value
IMPRECISION	SD	$(\Sigma(x - X)^2/(n-1))^{1/2}$
IMPRECISION	95% CI	1.96 x SD
IMPRECISION	CV	(SD/X) x 100
SIGNIFICANCE	P(A1c – A1c2) > 95%	P(Two A1c results lie outside a 5% overlap of distributions)

EXAMPLE RELIABILITY MEASUREMENTS FOR A1C WITH CV = 2.0%[6]

Example Collated Data Analysis of One Month's QC Highlighting Skewing of Results

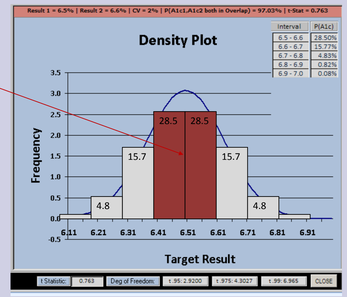


NOTE: Skewness can further affect the reliability of A1c testing by causing an asymmetrical distribution of patient results.

Example Density Plot Cumulative Probabilities for Each 0.1% Interval Within 3 Standard Deviations

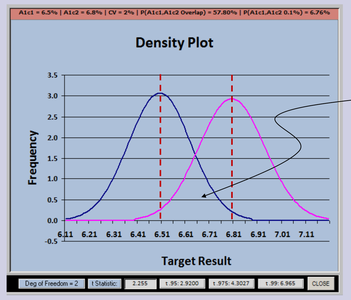
NOTE: Reported A1c is within 0.1% of Actual Patient A1c only 57% of the time.

Skewness will further distort the test results.



Example Effect of CV on Potential Significance of Two A1c Results That are Close Together

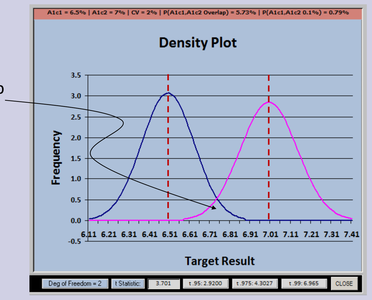
Two A1c Results 0.3% Apart



Probability both A1c results in Overlap = 57.80%
Probability both A1c results within 0.1% = 6.76%

Overlap Zone

Two A1c Results 0.5% Apart



Probability both A1c results in Overlap = 5.73%
Probability both A1c results within 0.1% < 1%

REFERENCES – SELECTED:

1. Pogach, L., Aron, D.; **Know Your A1c Number or Your A1c Range? The Need to Implement Glycemic Numeracy into Policy and Practice**; Journal of Diabetes, Vol 2, 2010 Pages 67 – 70.
2. Nichols, JH.; EP23: **Laboratory Quality Control Based on Risk Management**; Clinical Laboratory Standards Institute 1st Ed 2011
3. Wiebe, DA., Westgard, JO.; **Cholesterol – a Model System to Relate medical needs with Analytical Performance**; Clinical Chemistry, Vol 39, No 7, 1993 Pages 1504 – 1513.
4. Hielborne, L.; **The Pathologist-Clinician Interaction**: *A Key to Achieving Desired Patient Outcomes*; Pathology Patterns Supplement to the AJCP, Vol. 103, No. 4, S1, April 1995, pages S1-2
5. Pogach, L., Gusack, MD.; **Measuring Reliability of hemoglobin A1c and Communicating Results to Clinicians**; Presentation to NGSP Oversight Board 23 June 2013 Chicago, Il
6. Gusack, MD.; **An Automated System to Estimate Reliability of Analytical Laboratory Tests Using MS Access and VBA**; Alpha 20130815.

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COST BENEFIT ANALYSIS

Measuring and publishing reliability information can help direct the clinician to moderate a propensity to diagnose and/or treat on a few, potentially misleading test results; guiding them to depend more on trending multiple **A1c** test results as well as to integrate available clinical information. Automation offers the capacity to achieve this with low administrative overhead.[6]

Systematic Diagnostic Errors leading to mismanagement of diabetes will be reduced helping optimize long term glycemic control while reducing potentially dangerous hypoglycemic events.

EXAMPLE RELIABILITY REPORT FOR CV = 2.0%

HEMOGLOBIN A1C – A GUIDE TO SAFE USE IN DIAGNOSIS AND MANAGEMENT OF YOUR PATIENTS

==========TECHNICAL CONSIDERATIONS WHEN INTERPRETING YOUR PATIENT'S A1C==========

Based on our Quality Control data the following should be considered before acting:

- **TOTAL VARIABILITY:** Your patient's actual A1c falls within **-0.4% and +0.2%** of the A1c reported in CPRS.
- **TWO A1C RESULTS**: A difference < 0.5% between any two A1c test results is probably not clinically significant.
- **SKEWING**: Your patient's actual A1c will often lie below and rarely above the reported value as shown.

AS MUCH AS 0.4% BELOW REPORTED A1C	SAME AS REPORTED A1C	AS MUCH AS 0.2% ABOVE REPORTED A1C
55% OF THE TIME	31% OF THE TIME	14% OF THE TIME

TEST LIMITATIONS

- Your patient's actual A1c will often lie significantly away from the reported value reducing reliability of single results.
- A1c is an average of the patient's glycemic state over periods greater than 2 – 3 months.
- A1c does not measure wide swings in glycemia over this time period nor can it fully predict risk for hypoglycemia.

WARNINGS

- Aggressive treatment of a single A1c result near a Target A1c level may result in an increase in clinically significant hypoglycemic events.
- Use caution when considering modifying treatment where two A1c results that are < 0.4% apart.

RECOMMENDATIONS

- A1c testing is best suited to long term trending of at least two test results over a 3 to 12 month period.
- A1c predictive value for microvascular complications of chronic hyperglycemia improves at higher values.
- A1c is best used in combination with collated glucose meter test results, clinical status, and patient goals.

==========BIOLOGIC CONSIDERATIONS WHEN INTERPRETING YOUR PATIENT'S A1C==========

Biologic variation specific to each patient can affect A1c test results. This is especially true of anemias which can reduce A1c levels and lead to chronic under treatment of their glycemia. Therefore, if your patient has a low hemoglobin and/or elevated reticulocyte count at the time of A1c testing, you should consider modifying treatment at lower A1c levels.

CONCLUSION

Readily available **Quality Control [QC] Data** is really ***Risk Control*** **[RC]** ***Data*** that can be used to report useful statistical information to clinicians. This provides a critical part of the information needed to establish

Acceptable Risk

Other critical issues include but are not limited to determining the most important adverse outcomes, their **Frequency**, **Severity**, and **Perception** of cost, combined with knowledge of maximum sensitivity and specificity of the specific methods used in clinical decision making.