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White Paper

Quantitative Measurement of Hemoglobin A1c on the DCA Vantage Point-of-Care Analyzer as a Diagnostic Test for Diabetes: An Internal Validation Study

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Summary

The use of Hemoglobin A1c (HbA1c) testing as an aid in the diagnosis of Type 2 diabetes and detection of pre-diabetes is endorsed by multiple advisory healthcare associations. The American Diabetes Association (ADA) states that testing should be performed with a method that is NGSP-certified and is standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference test.[1]

The DCA® Vantage analyzer from Siemens Healthcare Diagnostics is a point-of-care device that quantitatively measures percent HbA1c in blood. This internal validation study assessed the precision, agreement, and bias of the DCA HbA1c test against an NGSP-certified laboratory HPLC method. The study results demonstrated equivalent test performance when compared to the reference method. Results support the use of the DCA HbA1c test as a reliable aid in the diagnosis of diabetes and identification of patients at risk of developing diabetes.

Introduction

Diabetes: A Global, and Growing, Health Problem

Diabetes mellitus is one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most high-income countries, and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries.[2]

Diabetes is undoubtedly one of the most challenging health problems in the 21st century. The International Diabetes Federation (IDF) estimates that 371 million people are living with diabetes, and of these, 185 million are undiagnosed.[2] New cases are increasing by 8.3% worldwide, and as many as 470 million people will be at risk with pre-diabetes by 2033.[3]

Table 1. HbA1c test result criteria for the diagnosis of diabetes and indication of pre-diabetes (American Diabetes Association).

HbA1c Test Result	Clinical Guideline
≥ 6.5% (≥ 48 mmol/mol)	Indicates diabetes
5.7% – 6.4% (39 – 46 mmol/mol)	May indicate pre-diabetes

Diagnosing Type 2 Diabetes: Clinical Practice Guidelines Recommend the HbA1c Test

For decades, the diagnosis of diabetes was based primarily on plasma glucose criteria. Diagnosis of a person with diabetes was limited to the measurement of fasting plasma glucose (FPG), or an oral glucose tolerance test (OGTT). The scope of diagnostic methodology was extended in 2009, when an International Expert Committee that included representatives from the American Diabetes Association (ADA), the IDF, and the European Association for the Study of Diabetes (EASD) formally recommended the use of the HbA1c test to diagnose diabetes.[4] In 2010, the ADA officially endorsed this recommendation.[5] Previously, the measurement of HbA1c had only been permitted for the monitoring of long-term glycemic control of individuals with diabetes. In 2011, the World Health Organization (WHO) concluded that HbA1c could be used as a diagnostic test for diabetes in accordance with strict quality assurance and test standardization.[6]

Accepted ADA HbA1c test result criteria[7] for the diagnosis of diabetes, and the potential indication of a pre-diabetic state, are given in Table 1. The diagnostic test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference test.[1]

Fighting Diabetes on the Front Line: The Utility of HbA1c Testing

Point-of-care HbA1c tests that can demonstrate analytical performance concordant with that of central laboratory methods represent tools of increasing utility in the fight against diabetes. Their convenience (for both patients and practitioners), speed, simplicity of use, greater practicality, and potential for wider uptake in primary care and in-office settings may assist in:

- Reaching the undiagnosed diabetic sooner. The ADA has observed that HbA1c testing 'may actually increase the number of diagnoses made'[1]
- The identification of pre-diabetes to lower the risk of disease progression. Patients identified as being at risk can stop or reverse disease progression through lifestyle adjustments and/or pharmacological treatment
- Driving and monitoring glycemic control to help mitigate potential complications

Table 2 compares HbA1c testing on the DCA Vantage analyzer to traditional test methods for Type 2 diabetes and pre-diabetes detection.

Study Purpose

Recent clinical practice guidelines advise that the HbA1c test can be used to diagnose diabetes and identify at-risk patients.

Siemens' DCA HbA1c test is standardized to both NGSP and IFCC reference methods. The purpose of this study was to validate use of the DCA HbA1c test as a diagnostic aid for diabetes, and in the identification of a pre-diabetic state. The study investigated:

- Precision of the DCA HbA1c test at the specific (ADA-defined) HbA1c concentrations recommended for diagnosing diabetes and pre-diabetes
- Test agreement and bias versus an NGSP reference method used for HbA1c test standardization

Table 2. Traditional diabetes diagnostic methodology versus HbA1c testing on the DCA Vantage point-of-care analyzer.

Test	Indicates Diabetes	May Indicate Pre- Diabetes	Procedural Advantages and Disadvantages
Fasting Plasma Glucose Test (FPG)	Yes	Yes	– Requires phlebotomy – High day-to-day variation – Sample integrity requires, and relies upon, patient compliance with fasting/dietary change – Results may not be available during the patient visit, which can necessitate a follow-up call and/or consultation
Oral Glucose Tolerance Test (OGTT)	Yes	Yes	– Requires ingestion of a glucose beverage, and 3 serial blood draws – Test process takes up to 3 hours – Considered more sensitive than FPG, but less convenient[8] – May be ordered if FPG test is normal
Random Plasma Glucose (Casual Glucose) Test	Yes	No	– Requires phlebotomy – No patient fasting or glucose beverage ingestion required – May not be as reliable as the FPG test – Can only be used for diagnosing diabetes if >11.1 mmol/L
DCA Vantage Analyzer HbA1c Test	Yes	Yes	– No phlebotomy – only a small (1 µL) finger stick blood sample is needed – Low day-to-day variation – No patient fasting or glucose beverage ingestion required – No sample or reagent preparation – Simple, 4-step test process – The same test kit* is used to assist in both the diagnosis and management of diabetic patients – Actionable results are available in just 6 minutes, at the time of visit – no waiting for lab results, or delays to the doctor/patient consultation and resulting plan of treatment

*Not all product offerings are available in all countries. Not available for sale in the U.S. Kit #10698915.

Methods

Precision Study

Precision of the DCA HbA1c test was evaluated at HbA1c concentrations of 31 mmol/mol (5.0%), 48 mmol/mol (6.5%), 64 mmol/mol (8.0%), and 108 mmol/mol (12.0%) in clinical samples across three instruments and three reagent lots. Clinical samples with these HbA1c concentrations were obtained from the University of Missouri School of Medicine (the location of the Central Primary Reference Laboratory for the NGSP). HbA1c concentrations in each supplied sample were measured using the Tosoh G7 HPLC method (Tosoh Bioscience) in a Secondary Reference Laboratory of the NGSP network located at the site. Clinical samples with the desired HbA1c concentrations were pooled on site, mixed thoroughly, and then frozen. Samples were shipped to Siemens frozen, and upon receipt were stored at temperatures ≤ -70°C until testing. Upon receipt, samples were inspected thoroughly. No compromised samples were found.

The precision evaluation was designed in accordance with the CLSI document EP5-A2.[9] For each HbA1c level, the evaluation was conducted over twenty days. Two runs were performed each day, and two replicates of each sample were tested during every run. Normal and abnormal controls were tested on each lot for each run. Sample order was altered for each run throughout the testing period. Total (within laboratory) precision was calculated for each HbA1c concentration over the entire study period.

Agreement and Bias Study

Method comparison between the DCA HbA1c test and an NGSP-certified laboratory HPLC technique was used to determine agreement and bias in HbA1c measurement. Method comparison evaluation was designed in accordance with the CLSI document EP9-2A.[10]

HbA1c levels in 127 clinical samples were determined in a Reference Laboratory at the University of Missouri School of Medicine using a Tosoh G7 HPLC analyzer (Tosoh Bioscience). Cold (5°C) samples were shipped to Siemens and then tested within 14 days of receipt.

Samples were run twice per day across three DCA Vantage analyzers and one reagent lot over a period of 10 days, with a minimum of five samples tested per day. Normal and abnormal controls were tested on each run. In each second run, the clinical sample order was tested in reverse. Approximately 50% of the samples tested had HbA1c levels in the clinically significant 42-53 mmol/mol (6.0-7.0%) range.

Results from both analytical methods were used to perform a Deming regression. The slope (95% CI), intercept (95% CI), correlation coefficient (R), and coefficient of determination (R^2) were calculated. Bias and percent bias of the DCA HbA1c test were calculated across the measurement range 26-108 mmol/mol (4.5%–12.0% HbA1c).

Results

Precision Study

DCA HbA1c test precision at concentrations of 31 mmol/mol (5.0%), 48 mmol/mol (6.5%), 64 mmol/mol (8.0%), and 108 mmol/mol (12.0%) is shown in Table 3.

Table 3. DCA HbA1c test precision.

HbA1c (mmol/mol)	HbA1c (%)	% CV	SD
31	5.0	1.8	0.09
48	6.5	1.7	0.11
64	8.0	2.0	0.16
108	12.0	3.6	0.43

The results show that at HbA1c concentrations of 31 mmol/mol (5.0%), 48 mmol/mol (6.5%), and 64 mmol/mol (8.0%) the DCA HbA1c test demonstrated tight precision, with CVs of 2.0% or less in the important clinical ranges for diagnosing and monitoring. These results exceed the acceptance criteria for precision as specified in the CLSI guidelines.

Agreement and Bias Study

Figure 1 shows a plot of the Deming regression performed on HbA1c results from DCA Vantage analyzers compared to the Tosoh G7 reference HPLC method. Table 4 presents method comparison statistics. Table 5 details bias and % bias HbA1c values calculated from the regression equation y = 0.9721X + 0.2169.

Figure 1. Plot of Deming regression.

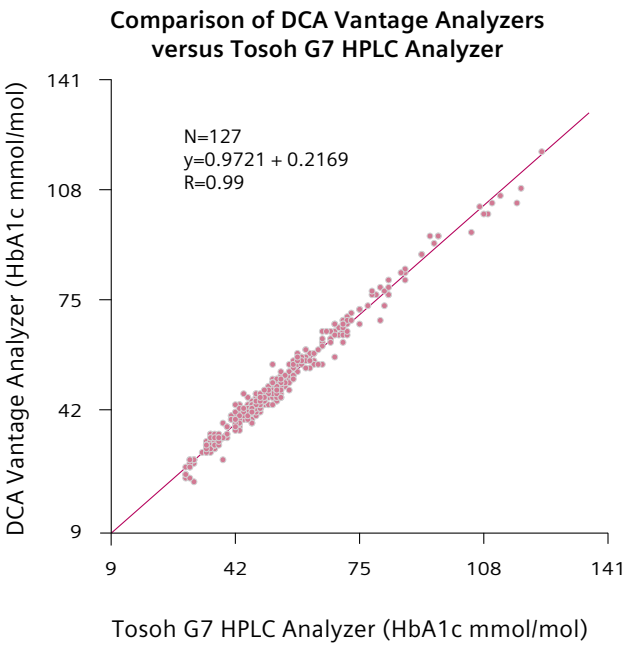

Table 4. DCA Vantage analyzer versus Tosoh G7 HPLC method comparison statistics.

Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient (R)	Coefficient of Determination (R^2)
0.9491 to 0.9951	0.05349 to 0.3803	0.9912	0.9825

Table 5. Calculated % HbA1c difference and % bias to reference method.

HbA1c (mmol/mol)	HbA1c (%)	Y (from regression equation)	% HbA1c Difference	% Bias
26	4.5	4.59	-0.09	-2.0
31	5.0	5.08	-0.08	-1.5
37	5.5	5.56	-0.06	-1.2
42	6.0	6.05	-0.05	-0.8
48	6.5	6.54	-0.04	-0.5
53	7.0	7.02	-0.02	-0.3
59	7.5	7.51	-0.01	-0.1
64	8.0	7.99	0.01	0.1
108	12.0	11.88	0.12	1.0

This study demonstrated excellent correlation (R=0.99) of the DCA HbA1c test with the NGSP-certified Tosoh G7 central laboratory HbA1c method.

The study also showed the low bias of the test compared with Tosoh G7 laboratory HPLC. At the diagnostically indicative HbA1c concentrations of 42 mmol/mol (6.0%), 48 mmol/mol (6.5%), and 53 mmol/mol (7.0%), percent bias was less than ± 1.0%, meeting the NGSP acceptance criterion defined as not to exceed ± 2.0%. The percent bias throughout the wider HbA1c measurement range was ≤ ± 2.0%.

Discussion and Conclusions

Siemens DCA systems have consistently achieved annual IFCC and NGSP certifications for more than a decade. With robust technology highlighted in more than 140 clinical articles, Siemens DCA systems are used by three out of four physicians who perform HbA1c testing in the office.[11] The DCA Vantage analyzer used in this validation study is one of just two point-of-care HbA1c analyzers that meet NGSP performance criteria.[12] To enhance patient counselling, the DCA Vantage analyzer provides HbA1c trend graphs to track progress.

The College of American Pathologists (CAP) is a leading organization of board-certified pathologists, serving patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. CAP proficiency survey results are published bi-annually at www.ngsp.org. In the December 2012 report on HbA1c assays, precision CVs ranged between 2.6–2.8% across all target HbA1c levels tested, based on results reported by more than 300 Siemens DCA system users. This study reported DCA HbA1c test CVs of 2.0% or less in serial testing of HbA1c levels. The demonstrated precision of the DCA HbA1c test provides confidence that fluctuations in reported results are most likely due to changes in patient status, as opposed to test method variation. Results of this study demonstrated the tight test precision necessary when tracking a patient's HbA1c status and making clinical treatment decisions over time.

The DCA HbA1c test and NGSP-certified reference HPLC method showed outstanding agreement, with a correlation coefficient (R) of 0.99. Test bias was notably low within the diagnostically significant 42-53 mmol/mol (6.0-7.0%) HbA1c range. The study showed that 48 mmol/mol (6.5%) HbA1c results on the Tosoh G7 would read only -0.04 lower at 47 mmol/mol (6.46%) on the DCA Vantage analyzer.

Taken collectively, the study results validated that the DCA HbA1c test has similar, if not equal, performance to the Tosoh G7 NGSP reference method. A recent, independent study similarly found DCA Vantage analyzer performance to have comparable analytical quality to laboratory methods, meeting the analytical specifications required to diagnose diabetes.[13] Trained healthcare practitioners can use the DCA HbA1c test at the point of care to assist in the monitoring of glycemic control, diagnosis of diabetes, and the identification of at-risk, pre-diabetic individuals. Early detection and tight glycemic control can help mitigate the serious conditions that accompany diabetes: heart and kidney disease, limb neuropathy, retinopathy, and stroke.

The reliable, lab-quality analytical performance of the DCA HbA1c test is complemented by its speed, simplicity, convenience, and overall practicality in point-of-care environments. The advantages of HbA1c testing when compared to traditional methods of blood glucose level measurement[14] can only but help to improve patient management and outcomes in the fight against the growing worldwide epidemic of diabetes.

Exclusions to Test Usage

The DCA HbA1c test should not replace glucose testing for Type 1 diabetes, pediatrics, and pregnant women. It is not intended for use as an aid in the diagnosis of patients with:

- A hemoglobinopathy, but normal red cell turnover (for example, a sickle cell trait)
- Abnormal red cell turnover (for example, anemias from hemolysis and iron deficiency)
- Iron deficiency and hemolytic anemia, various hemoglobinopathies, thalassemias, hereditary spherocytosis, malignancies, and severe chronic hepatic and renal diseases

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