

Clinical Evaluation of a Rapid A1C Test (A1cNow) for Home Use

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Introduction: A1C can be measured by portable point-of-care methods that might offer advantages compared with conventional sampling of venous blood for eventual laboratory testing.

Methods: In a 2-part study, we compared the performance and ease of use of A1C measurement with a single-use, disposable A1C test (A1cNow) and a venous sample measured by a reference laboratory. Part 1: At 3 sites, 297 untrained subjects self-tested with an A1cNow. Trained medical professionals performed a second A1cNow test on each subject. Venous blood was sent to a National Glycohemoglobin Standardization Program Secondary Reference Laboratory for A1C testing. Untrained and professional A1cNow test results were compared with the reference results and with each other. A quiz and questionnaire evaluated, respectively, subject comprehension of A1cNow's product labeling and opinions on ease of use. Part 2: At a fourth site, trained medical professionals performed an A1cNow test on 30 subjects. Venous blood was sent to the same reference laboratory. Professional A1cNow test results were compared with reference results. The professionals recorded the amounts of time needed for A1cNow testing and reference laboratory testing.

Results: Part 1: For untrained A1cNow versus reference, the slope and y intercept were 0.988 and 0.168, respectively, with $r = 0.93$ (paired Student t test, $P = 0.50$). For professional A1cNow versus reference, the slope and y intercept were 0.965 and 0.400, respectively, with $r = 0.94$ (paired Student t test, $P = 0.21$). For untrained versus professional A1cNow, with Deming regression, the slope and y intercept were 0.972 and 0.269, respectively, with $r = 0.88$ (paired Student t test, $P = 0.58$). Overwhelmingly, subjects responded correctly to quiz questions and favorably to opinion questions about the product's ease of use. Part 2: For professional A1cNow versus reference, the slope and intercept were 0.9504 and +0.28, respectively, with $r = 0.95$ (paired Student t test, $P = 0.85$).

Conclusions: Untrained users can operate the A1cNow test with good performance equivalent to that obtained by trained medical professional users.

Key Words: A1C, glycated hemoglobin, home-use, point of care (*Point of Care* 2006;5:116–120)

High levels of blood glucose result in excess glycation of proteins throughout the body, including hemoglobin. Hemoglobin A undergoes a slow glycation with glucose that is dependent on the time-average concentration of glucose over the 120-day life span of red blood cells. The most prevalent and well-characterized species of glycated hemoglobin A is A1C, comprising approximately 3% to 6% of total hemoglobin in healthy individuals.¹ The correlation of A1C to mean blood glucose levels renders it as a useful method of monitoring long-term blood glucose levels in people with diabetes.²

A1C can be measured by a variety of techniques, including point-of-care (POC) assays that are used in physicians' offices and clinics. Immediate feedback of A1C results can better enable disease management, leading to improved A1C levels.^{3–7} Point-of-care assays can also be well suited for the home environment if they are easy to perform, require no laboratory equipment, and provide results with a rapid turnaround time from sampling to result.^{8,9}

The A1cNow A1C test (A1cNow; Metrika, Inc, Sunnyvale, Calif) is a POC test intended for home use with or without a prescription. The device is a handheld, fully integrated, single-use monitor for measuring percentage of A1C (%A1C) in capillary (finger stick) whole blood. Other POC A1C tests are either not approved for home use (Bayer DCA 2000 and Axis-Shield Nyco-Card) or are approved for prescription home use but generally not sold for patient use (Provalis Glycosal, Cholestech GDX, and BioRad MicroMat II).¹⁰

Studies designed to assess the performance of professional use and physician-directed (prescription) home use have demonstrated that both laboratory/medical office personnel and lay users who had undergone minimal training could successfully perform the test.¹¹ The 2-part present study was intended to determine whether lay users with no training (part 1) and medical care professionals with training (part 2) can successfully perform the A1cNow test with good accuracy, and whether a survey of patients and health care professionals would indicate benefits from using this product.

The primary objective of this study was to evaluate the accuracy of A1cNow in the hands of both untrained subjects with diabetes and trained health care professionals. The study's secondary objective was to ascertain the untrained user's comprehension of the product labeling for A1cNow and to

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document in a real-world setting the amounts of time needed for A1cNow testing and reference laboratory testing of A1C.

METHODS

The A1cNow monitor is a single-use, disposable, 4-channel reflectance photometer immunoassay device integrated with dry reagent chemistry strips and contained within a sealed plastic case. Each A1cNow home use test kit consists of (1) a foil pouch containing the monitor; (2) a foil pouch containing a sample dilution kit consisting of 1 vial of sample dilution buffer, 1 capillary pipette, 1 transfer pipette, and 1 tube holder; (3) a lancet; and (4) a package insert.

To measure A1C with the A1cNow, first, the finger is lanced to obtain a drop of blood. A 10 μ L capillary blood sample is collected and added to the sample dilution buffer. The diluted sample is mixed and added to the monitor using the transfer pipette. Once the sample is applied, the monitor "wakes up" and begins the analyses. Digital results are displayed in the display window after 8 minutes. In the event of a gross procedural error or a monitor error, an error code will appear in the window. The device has been designed so that a minor procedural error, such as a slight underfill of the transfer pipette or slight overfill of the capillary, does not affect the result.¹¹

The study was performed under institutional review board-approved status that included informed consent. The subjects were recruited at each site by local site personnel. Two sites in California and 2 sites in the US Midwest were selected to demographically diversify the subject population. The protocol consisted of 2 parts, which were referred to as part 1 and part 2.

Part 1

Part 1 was conducted at 3 locations (Mills-Peninsula Diabetes Research Institute, San Mateo, Calif; International Diabetes Center, Minneapolis, Minn; and Center for Clinical Studies, St. Louis, Mo). Two hundred ninety-seven subjects (282 with diabetes and 15 without diabetes) were studied. The nondiabetic subjects were included to evaluate %A1C values at the lower end of the assay's dynamic range.

Subjects arrived at the study sites at predetermined time intervals and provided informed consent. Subjects were told to imagine they had purchased A1cNow at their local pharmacies. They were asked to read the product labeling. Subjects then performed 1 A1cNow (self) test on themselves and recorded their results. After the self-test, the study staff performed a second A1cNow (professional) test on the subjects using the same lot of monitors. Finally, venous blood was collected for reference A1C testing by a National Glycohemoglobin Standardization Program Secondary Reference laboratory (NGSP, SRL #5) in Columbia, Mo, using a Tosoh 2.2 Plus. After the 3 blood samples were collected, the subjects were asked first to answer a quiz assessing their comprehension of product labeling and second to complete a questionnaire soliciting their opinions of the A1cNow system.

Blood samples from the venous collections were stored at 2 to 8°C and transported to the reference laboratory by express delivery. Samples were batch-analyzed by the NGSP

method, and these results were considered the "true" reference results. Statistical measures of product performance (linear regression, bias, and paired Student *t* test) were calculated for the following pairs of results: (1) A1cNow-untrained versus NGSP; (2) A1cNow-professional versus NGSP; and (3) A1cNow-untrained versus A1cNow-professional.

Part 2

Part 2 was conducted at a fourth site (Monteagle Medical Center, San Francisco, Calif), with 30 subjects, all of whom had diabetes. The office nurse performed an A1cNow test on each subject during an otherwise regular clinical visit for routine medical follow-up. Venous blood was drawn and sent to the same NGSP reference laboratory that was used in part 1.

The nurse then filled out a questionnaire for each subject that recorded the amount of "hands-on time" necessary to discuss the A1cNow result with each subject and whether the A1cNow result was used for management of diabetes during the visit.

RESULTS

In part 1, of the 297 subjects enrolled in the study, 11 subjects' results were excluded from data analyses because of either the presence of a variant hemoglobin (8 results identified by the NGSP laboratory), a %A1C result above the linear range of A1cNow (2 results, >13.0%A1C), or a quality control error displayed by the monitor (1 result), leaving 286 sets of A1cNow (self) versus NGSP comparative results. Ten professionals' results were excluded from data analyses because of either the presence of a variant hemoglobin (8 results), a %A1C result above the linear range of A1cNow (1 result, >13.0%A1C), or a quality control error displayed by the monitor (1 result), leaving 287 sets of A1cNow (professional) versus NGSP comparative results.

The subjects were asked to provide demographic information that included age, sex, ethnic background, education, occupation, and diabetes status (type 1, type 2, or without diabetes). The subject population was 44% male; had a mean age of 54.7 years (youngest, 13 years; oldest, 84 years); was 20% nonwhite ethnicity; had 67% with education below the baccalaureate level; and had a distribution of diabetes categories of 24% type 1, 71% type 2, and 5% without diabetes. Responses to the occupation question included administrative, manufacturing, professional, sales or service, retired, and student. No differences in results due to different demographic factors were seen.

Least-squares linear (or Deming for self A1cNow vs. professional A1cNow) regression statistics, combined for all sites, are summarized below for the comparison of results: (1) A1cNow-untrained versus NGSP; (2) A1cNow-professional versus NGSP; and (3) A1cNow-untrained versus A1cNow-professional.

The regression analyses generated slopes, *y* intercepts, and correlation coefficients; and the regression equations were used to calculate A1cNow biases at %A1C levels of 6%, 7%, 8%, and 11%, respectively. Deming regression was used for the comparison of self A1cNow and

professional A1cNow to allow for the approximately comparable imprecision in both sets of data. All samples were tested once by each method. Results from NGSP are presented on the x axis for the first 2 regression analyses, and A1cNow-professional results are presented on the x axis for the third analysis. Student *t* test was performed for each pair of data set.

A1cNow-self Versus NGSP

The least-squares linear regression statistics, combined for all 3 sites, were as follows. For all 286 results, the slope was 0.988 with a y intercept of 0.168 and $r = 0.93$. The slope and y intercept were used to calculate the expected biases at %A1C levels of 6%, 7%, 8%, and 11%, yielding biases, on average, of +1.7%, +1.1%, +0.9%, and +0.3%, respectively. Thus, on average, a true 6% A1C would report 6.1% A1C, rounded to 1 decimal place. Similarly, a true 7% A1C would report 7.1% A1C, a true 8% A1C would report 8.1% A1C, and a true 11% A1C would report 11.0% A1C, each rounded to 1 decimal place. A graphic representation of the combined regression analysis of these data is shown in Figure 1. Paired Student *t* test yielded a *P* value of 0.50, showing no statistically significant difference between the data sets.

The data were also analyzed by the use of a bias plot, similar to NGSP convention. The 95% confidence limits for A1cNow (self) were -0.90% to +1.06% A1C. These data are plotted in Figure 2.

A1cNow-professional Versus NGSP

The least-squares linear regression statistics, combined for all sites, are as follows. For $n = 287$ results, the slope was 0.965 with a y intercept of 0.400 and $r = 0.94$. As in the previous instance, the slope and y intercept were used to calculate the expected biases at %A1C levels of 6%, 7%, 8%, and 11%. These calculations demonstrated biases of +3.2%, +2.3%, +1.5%, and +0.1%, respectively. Thus, on average, a true 6% A1C would report 6.2% A1C, rounded to 1 decimal place; a true 7% A1C would report 7.2% A1C; a true 8% A1C

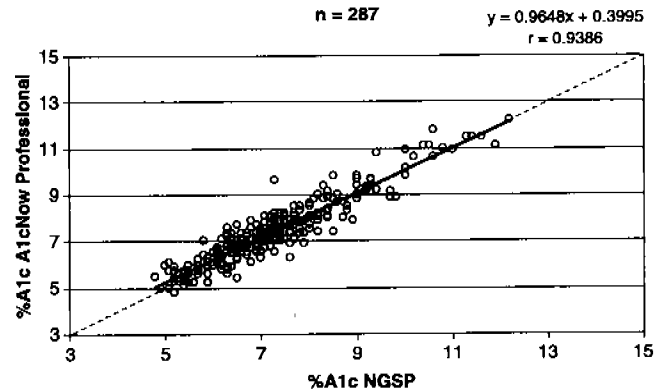


FIGURE 2. Percentage of A1C A1cNow professional testing versus percentage of A1C NGSP Tosoh 2.2 Plus (NGSP SRL method).

would report 8.1% A1C; and a true 11% A1C would report 11.0% A1C, each rounded to 1 decimal place. A graphic representation of the combined data is shown in Figure 2. The 95% confidence limits for A1cNow (professional) were calculated to be -0.81% to +1.10% A1C. Paired Student *t* test yielded a *P* value of 0.21.

A1cNow-self Versus A1cNow-professional

Deming regression, an analytical procedure that is more appropriate than linear regression when the 2 data sets being compared have comparable variability, was performed on the data from all 3 sites, combined (Fig. 3). For all 285 results, the slope was 0.972 with a y intercept of 0.269 ($r = 0.88$). Biases were again calculated at %A1C levels of 6%, 7%, 8%, and 11%; and these calculations generated biases of +1.7%, +1.0%, +0.5%, and -0.4%, respectively. Thus, on average, a true 6% A1C would report 6.1% A1C, rounded to 1 decimal point; a true 7% A1C would report 7.1% A1C, a true 8% A1C would report 8.0% A1C, and a true 11% would report 11.0% A1C. For these results, the professional results were

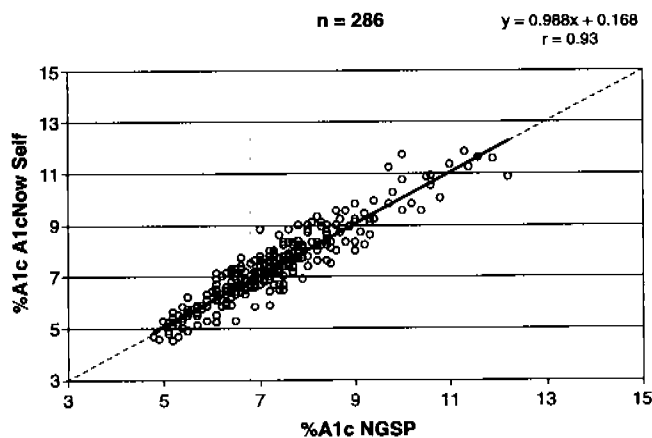


FIGURE 1. Percentage of A1C A1cNow self testing versus percentage of A1C NGSP Tosoh 2.2 Plus (NGSP SRL method).

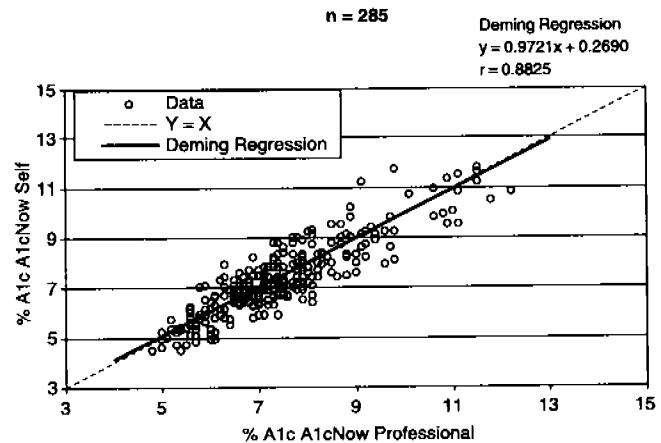


FIGURE 3. Percentage of A1C A1cNow self testing versus percentage of A1C A1cNow professional testing.

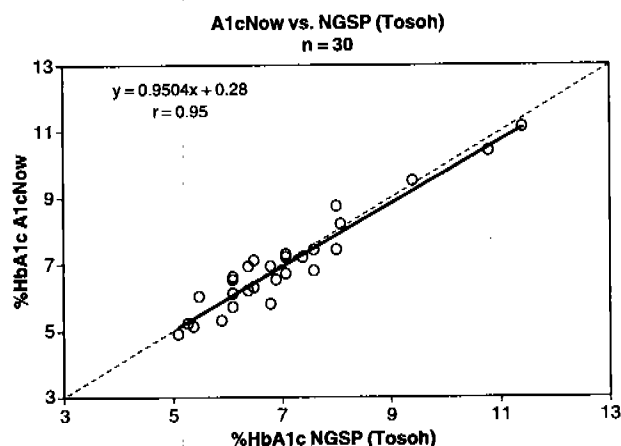


FIGURE 4. Linear regression graph A1cNow (finger stick capillary) versus NGSP SRL Tosoh (venous EDTA whole blood).

considered the true results. Paired Student *t* test yielded a *P* value of 0.58 for this data set. A graphic representation of the data is shown in Figure 4.

These analyses indicate that there are no statistically significant differences between A1cNow results obtained from untrained users (patients) and A1cNow results obtained from trained users (medical professionals).

Consumer Comprehension (Quiz Results)

The subjects were asked to complete a 15-question quiz at the end of the study to assess their comprehension of the A1cNow system and its product labeling. Quiz questions dealt with subjects such as storage requirements, procedure, disposability, and what to do with the results once obtained.

The quiz responses revealed that an overwhelming proportion of subjects had a high level of comprehension of both the product concept and the test procedure. The subjects scored approximately 90% to 99% correct responses for each question. This indicates that the product labeling is appropriate for home use.

Consumer Feedback (Questionnaire Results)

The subjects were asked to complete 5 multiple-choice, user-opinion questions at the end of the quiz. The questions solicited opinions concerning (1) the ease of the test directions, (2) the ease of getting enough blood, (3) the ease of adding sample to the test, (4) the ease of reading the result, and (5) the overall ease of performing the test. Result options ranged from *a* to *d*, with *a* being the "easiest" response and *d* being the "most difficult" response. The subjects overwhelmingly responded that A1cNow was "easy" or "somewhat easy" to operate. Approximately 96% of all subjects answered *a* or *b* to all 5 questions.

In part 2, 30 adult subjects were studied and the composition of the group was 50% male. Of the subjects, 50% had type 1 diabetes and 50% had type 2 diabetes, with an age range of 28 to 87 years.

A1cNow-professional Versus NGSP

Least-squares linear regression analysis was performed on the A1C results obtained from the A1cNow test and the NGSP laboratory (NGSP, *x* axis; Fig. 4). The slope and intercept values were 0.9504 and +0.28, respectively, with a correlation coefficient of 0.95. Average bias between the 2 data sets was -0.07% A1C, and the 95% confidence interval was -0.78% to $+0.92\%$ A1C. Paired Student *t* test was also performed to analyze the difference between the 2 data sets, with a resulting *P* value of 0.85 (no significant difference). Only 63% of subjects had obtained prior laboratory results and these results were not compared.

Duration of Tasks

The professional user recorded hands-on time to perform A1cNow testing and noted other observations on the case report forms. The average time to obtain an A1C result was 9 minutes with A1cNow and 2 days with conventional laboratory testing. The mean time spent discussing an A1C result with a patient was 1.7 minutes; and in all 30 cases, an A1C result was useful for patient management.

CONCLUSIONS

The A1cNow home use data had estimated biases of less than 2% across low, intermediate, and high levels of A1C (6%, 7%, 8%, and 11% A1C, respectively) as compared with the NGSP method. These small biases indicate a high level of product performance of the A1cNow test in the hands of the untrained user. From the bias plot analyses, the 95% confidence limits ranged from -0.9% to $+1.1\%$ A1C. The 95% confidence limits for A1cNow in the hands of the trained medical professional were quite similar, -0.8% to $+1.1\%$ A1C in part 1 and -0.78% to $+0.92\%$ A1C in part 2. This indicates equivalent performance of A1cNow regardless of the level of user training.

The A1cNow test is certified by the NGSP, whose certification requires a bias within $\pm 1\%$ of reference A1C with a 95% confidence interval and a coefficient of variation of no more than 4%.¹² College of American Pathology proficiency testing data for A1cNow indicate minimal bias and satisfactory precision in the hands of multiple medical professional users.¹³

Recent studies that measured testing frequency and outcomes indicate that there is currently a general lack of sufficient A1C testing and less than optimal A1C levels.¹⁴⁻¹⁶ Studies have shown that POC A1C testing intensifies diabetes management and improves glycemic control.³⁻⁶ In a series of patients with type 2 diabetes, when A1C results are not available at the time of an office visit and reviewed by the health care provider several days after the office visit, in 10% of the patients, a decision or implementation of the decision was deferred.¹⁷

The primary risk of using the A1cNow system (as with any testing system) is that of obtaining an inaccurate result. To mitigate this risk, A1cNow has been designed to report an error code in the event of a hardware/software malfunction or a gross procedural error. Laboratory and clinical studies have

shown that a minor procedural inconsistency in performing the test (eg, slight underfilling or overfilling of the capillary pipette with blood or slightly underfilling the transfer pipette with diluted sample) has no effect on the final test result.¹¹ A secondary risk may be the loss of data, as the monitor is a single-use, disposable unit. The monitors are programmed for the result to remain on the screen for 1 week, and the patient is instructed to record the result on the provided result card.

Product labeling addresses limitations, warnings, and precautions for those circumstances where A1cNow testing may not be appropriate (eg, a variant hemoglobin or hemophilia). Product labeling also advises users to consult with their health care professionals before changing their diabetes management. This encourages users not to misinterpret their results.

We believe that the A1cNow POC test is sufficiently simple to be operated by untrained patient users who can obtain performance equivalent to that obtained by trained medical professional users. The observed performance of A1cNow in the hands of either the untrained patient or the trained medical professional indicates to us that A1cNow can be an effective tool in the management of outpatients with diabetes.

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