



TITLE: **Rapid Hemoglobin A1c Testing for Evaluation of Glucose Control**

AUTHOR: **Jeffrey A. Tice, MD**
Assistant Adjunct Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of CA, San Francisco

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RAPID HEMOGLOBIN A1C TESTING FOR EVALUATION OF GLUCOSE CONTROL

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of rapid hemoglobin A1c (HbA1c) testing in the clinic and home settings.

BACKGROUND

Diabetes mellitus

Diabetes has been classified into type 1 diabetes mellitus, characterized by lack of insulin production, and type 2 diabetes, characterized by insulin resistance. An estimated 17 million people in the United States are known to have diabetes mellitus, of which 1.4 million have type 1 diabetes. Current management guidelines recommend target pre-prandial (pre meal) blood glucose values of 90 to 130 mg per deciliter, peak post-prandial (after meal) blood glucose values <180 mg per deciliter, and hemoglobin A1c (HbA1c) levels of $\leq 7.0\%$ (American Diabetes Association 2003).

Chronically uncontrolled hyperglycemia leads to a wide range of adverse health outcomes including retinopathy, nephropathy, neuropathy, and cardiovascular disease. These complications result in significant morbidity and mortality for patients with diabetes. Strategies to prevent or reduce the occurrence of secondary diabetic complications have been intensively studied.

Intensive management of glucose levels

Two large randomized controlled trials demonstrated that intensive management of blood glucose levels reduced the rate of diabetic complications compared with conventional management. However, intensive management was also associated with a three-fold increase in the rate of severe hypoglycemic events. Intensive management of diabetes mellitus consists of three or more daily injections of insulin, use of an insulin pump, or use of oral agents to achieve normoglycemia.



BACKGROUND, continued

The Diabetes Control and Complications Trial (DCCT).

The Diabetes Control and Complications Trial randomized 1441 patients with insulin-treated diabetes into either intensive management or conventional therapy (Diabetes Control and Complication Research Group 1993). The primary endpoint was diabetic retinopathy. Secondary outcomes included renal, neurologic, cardiovascular, and neuropsychological outcomes and adverse effects associated with the treatment regimens.

Patients in the DCCT had a mean age of 27 years and were followed for an average of 6.5 years. At baseline, the median HbA1c level was 8.9%. In the intensive treatment arm, HbA1c dropped to median of about 7% while patients in the usual care group maintained a median HbA1c of 9%.

Patients without retinopathy at baseline who received intensive glucose management had a 76% (95% CI: 62-85%) reduction in retinopathy compared to patients randomized to usual care. Among participants with retinopathy at baseline who were randomized to intensive therapy, there was a 54% (95% CI: 39-66%) reduction in progression of retinopathy. Furthermore, intensive therapy significantly reduced the risk of microalbuminuria (39%), albuminuria (54%), and clinical neuropathy (60%). The incidence of major cardiovascular and peripheral vascular events was low as expected in this young cohort (0.5 events per 100 person-years vs. 0.8 events, RR 0.59, 95% CI 0.32-1.10). Mortality was not reduced by intensive therapy. A trend towards more deaths in the intensively treated group was observed (7 deaths among those randomized to intensive therapy vs. 4 deaths in the usual care group).

Intensive therapy was associated with more than a three-fold increased risk of severe hypoglycemia defined as an episode with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and was associated with a blood glucose level < 50 mg/dl and prompt recovery after therapy for hypoglycemia. The rate of severe hypoglycemia was 62 episodes per 100 person-years in the intensive therapy group versus 19 episodes per 100 person-years in the usual care group. During 5 years of follow-up, 60% of patients in the intensive therapy group experienced at least 1 severe hypoglycemic event and 36% experienced 3 or more.



BACKGROUND, continued

The United Kingdom Prospective Diabetes Study (UKPDS).

The United Kingdom Prospective Diabetes Study (UKPDS) enrolled 3,867 patients with a new diagnosis of type 2 diabetes who had persistent elevation of fasting blood glucose (between 110 and 270 mg/dL) after 3 months of dietary treatment (UK Prospective Diabetes Study Group 1998). The study compared intensive glycemic management with medications (goal of fasting blood glucose < 108 mg/dL) to conventional management with diet therapy alone until fasting blood glucose levels were greater than 270 mg/dL. The primary outcome was the incidence of any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, myocardial infarction, angina, heart failure, stroke, peripheral vascular disease, renal failure, amputation, retinopathy, blindness or cataract extraction). Secondary outcomes included diabetes-related death and all-cause mortality.

Patients in the UKPDS had a mean age of 53 years and were followed for a median of 10 years. At baseline, the median HbA1c level was 7.1%. In the intensive treatment arm, HbA1c was maintained at about 7% during follow-up while patient in the usual care group maintained a median HbA1c of 7.9%.

Patients in the intensive management group had a 12% lower risk of any diabetes-related endpoint (95% CI: 1-21%) compared to patients randomized to conventional management. The intensive management group also had a non-significant 10% reduction in diabetes-related death ($p=0.34$) and a non-significant 6% reduction in all-cause mortality ($p=0.44$). The most significant factor was a 25% reduction in microvascular endpoints (95% CI: 7-40%).

As in the DCCT, there was a significant two to three-fold increased risk of severe hypoglycemic events. The rate of severe hypoglycemia was 1.8 episodes per 100 person-years in the intensive therapy group treated with insulin and 1.2 episodes per 100 person-years in the intensive therapy group treated with oral therapy, versus 0.7 episodes per 100 person-years in the usual care group.



BACKGROUND, continued

The United Kingdom Prospective Diabetes Study (UKPDS), continued

Post-hoc observational analyses in both the DCCT and UKPDS suggest that there is a continuous reduction in microvascular and macrovascular complications of diabetes: for every 1% lowering of HbA1c from greater than 10% down to 6%, there is a corresponding reduction in complications of between 12-43%. There was no clear threshold below which benefits stopped accruing. Observational studies including patients with and without diabetes suggest that this relationship continues for HbA1c levels below 5% (Khaw et al. 2001). Although observational studies cannot demonstrate a cause and effect relationship, they can estimate the potential dose effect.

Hypoglycemia

Severe hypoglycemic episodes were the major adverse events associated with intensive therapy in both the DCCT and the UKPDS. Untreated severe hypoglycemic episodes may result in coma, seizures, and even death. Furthermore, avoidance of hypoglycemia in children may be of particular importance because of the potential sensitivity of the developing neurological system. The authors of one study examining neuropsychiatric function of children with diabetes suggest that children with recurrent hypoglycemia may accumulate long term deficits in verbal knowledge, even if the brain is not permanently damaged (Northam *et al.* 2001).

Blood glucose monitoring

Currently, many outpatients with both type 1 and type 2 diabetes mellitus monitor their blood glucose levels one or more times each day, using fingerstick blood sampling and analysis with reagent strips and a portable glucose meter device. Test results are used to adjust insulin dosing, assess the response to exercise and meals, and prevent hypoglycemia. Performance of four or more self-monitored blood glucose (SMBG) tests per day is particularly important in type 1 diabetics receiving intensive insulin therapy. This importance is because due to the primary drawback of such intensive therapy is a several-fold increase in the occurrence of severe hypoglycemia (Diabetes Control and Complication Research Group 1993; UK Prospective Diabetes Study Group 1998).



BACKGROUND, continued

Blood Glucose Monitoring, continued

However, the finger pricks necessary to obtain the blood samples are painful and often inconvenient (Bantle *et al.* 1997). Perhaps for this reason, the long-term compliance with such monitoring has been poor (Fischer 1995). A 1993 study showed that 20% of patients with type 1 diabetes never tested their own blood glucose, and only 15% tested it at least 3 times a day (Harris *et al.* 1993). Furthermore, the precision of patients' fingerstick SMBG is weak, sometimes leading to wrong or even dangerous therapeutic decisions. Conventional SMBG recordings, even if performed multiple times per day, often may not sufficiently reflect an individual's true diurnal blood glucose profile (Bolinder *et al.* 1997).

Hemoglobin A1c

Hemoglobin A1c, also known as glycosylated hemoglobin or glycohemoglobin, is a measure of a patient's blood glucose control over the preceding 2-3 months. It is a term used to describe a series of stable minor hemoglobin components that form slowly and nonenzymatically from hemoglobin and glucose. It is formed when glucose in the blood binds irreversibly to hemoglobin to form a stable complex. Given that the lifespan of red blood cells averages about 120 days and that HbA1c is eliminated only when the red cells are replaced, HbA1c values are directly proportional to the concentration of glucose over approximately 2-3 months. HbA1c values do not reflect the hour-to-hour fluctuation of glucose, but are more heavily influenced by more recent values. Studies estimate that approximately 50% of the HbA1c value reflects the last 30 days, 25% reflects the last 60 days and 25% reflects the last 90 days (Sacks *et al.* 2002). Thus, meaningful changes in HbA1c can be detected within 60 to 90 days of a change in therapy.

The primary study documenting that knowledge of hemoglobin A1c values would result in improved metabolic control was published in 1990 (Larsen *et al.* 1990). Larsen et al randomly assigned 240 patients with type 1 diabetes to one of two groups that were comparable in age, sex, duration of diabetes, and initial hemoglobin A1c levels. The patients were followed for a year, and the hemoglobin A1c concentration was measured at three-month intervals. The hemoglobin A1c values were used in assessing glycemic control and modifying therapy in one of the two groups. In the other, caregivers were not aware of the hemoglobin A1c levels and relied on blood or urine glucose measurements to monitor treatment.



BACKGROUND, continued

Hemoglobin A1c, continued

Among the 222 patients still being followed after one year, the mean hemoglobin A1c value decreased significantly--from 10.1 to 9.5 percent (P less than 0.005)--in the group whose hemoglobin A1c level was monitored (n = 115), whereas the initial and one-year values in the control group (n = 107) were 10.0 and 10.1 percent, respectively. The proportion of patients with poor control, defined as those having a hemoglobin A1c value above 10.0 percent, decreased from 46 to 30 percent (P less than 0.01) in the group whose hemoglobin A1c level was monitored but did not change significantly (45 to 50 percent) in the control group. The patients in the group whose hemoglobin A1c level was monitored were seen and their insulin regimens changed more often, but they were hospitalized for acute care of their diabetes less often than those in the control group. A similar decrease in hemoglobin A1c values occurred in the control group in the following year, when their caregivers knew their hemoglobin A1c values. The authors concluded that regular measurements of hemoglobin A1c lead to changes in diabetes treatment and improvement of metabolic control, indicated by a lowering of hemoglobin A1c values.

The American Diabetes Association, in their 2003 consensus guidelines (American Diabetes Association 2003), recommended that A1C testing should be performed routinely in all patients with diabetes, first to document the degree of glycemic control at initial assessment and then as part of continuing care. Since the A1C test reflects mean glycemia over the preceding 2–3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has been reached and maintained within the target range. They note that glycemic control is best judged by the combination of the results of the patient's SMBG testing and the current A1C result. The A1C should be used not only to assess the patient's control over the preceding 2–3 months, but also as a check on the accuracy of the meter (or the patient's self-reported results) and the adequacy of the SMBG testing schedule. They specifically recommend that clinicians perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control) and quarterly in patients whose therapy has changed or who are not meeting glycemic goals. No reference is made to the utility of rapid HbA1c measurements.



BACKGROUND, continued

Testing HbA1c

Several different types of HbA1c assay methods are available in clinical laboratories with high-performance liquid chromatography (HPLC) still considered the reference method. The optimal use of the HbA1c requires standardization of test assays to ensure reported results between laboratories are comparable. Studies have shown the advantages and feasibility of standardizing HbA1c assays (Little *et al.* 1986; Little *et al.* 1991; Bodor *et al.* 1992; Little *et al.* 1992) and a reference method was proposed almost a decade ago. The National Glycohemoglobin Standardization Program (NGSP), sponsored by the American Diabetes Association, CDC, and NIH, was established in 1996 to standardize HbA1c tests to DCCT values. On an annual basis, manufacturers of both traditional and “rapid” HbA1c test assay methods are awarded a “certificate of traceability to the DCCT reference method” if their assay method passes rigorous testing criteria for precision and accuracy (Bland-Altman, described below). They must be calibrated to results obtained using HPLC based on ion exchange columns. Manufacturers are awarded Certificates of Traceability if the total imprecision (coefficient of variation) is $\leq 4\%$ and the 95% CI of the difference between methods falls within $\pm 1\%$. In July 2002, the precision criteria were tightened from a coefficient of variation (CV) of $<5\%$ to $CV < 4\%$. Each certificate is effective for one year from the date of certification. Certified assays are listed on the NGSP website (<http://www.ngsp.org>).

Most of the methods used to measure HbA1c are time-consuming and technically demanding, with the results of the assay not being available at the time of the patient visit. Thus, an important element in the clinical decision-making process is not available at the time of the visit. The delay in the results is inefficient, requiring the health care provider to communicate the result and any changes in therapy to the patient after the visit. The delay in feedback could lead to decreased patient compliance and delay adjustments in diabetic therapy. Companies have developed several different approaches to rapid HbA1c testing in order to address this need.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

BACKGROUND, continued

DCA 2000 Analyzer (Bayer Diagnostics)

The DCA 2000 is an integrated instrument and cartridge system that uses an immunochemical technique for measuring HbA1c. The concentration of HbA1c and total hemoglobin is measured and the ratio is reported as percent HbA1c. All the reagents are contained in the DCA 2000 hemoglobin A1c reagent cartridge. Total hemoglobin is measured using potassium ferricyanide to oxidize the hemoglobin in the sample to methemoglobin. The methemoglobin then complexes with thiocyanate to form thiocyan-methemoglobin, the colored species that is measured. The extent of color development at 531 nm is proportional to the concentration of total hemoglobin in the sample. HbA1c is measured using an inhibition of latex agglutination assay. An agglutinator (synthetic polymer containing multiple copies of the immunoreactive portion of HbA1c) causes agglutination of latex coated with HbA1c specific mouse monoclonal antibody. A monoclonal antibody reacts specifically with an amino acid sequence on the HbA1c molecule. This agglutination reaction causes increased scattering of light, which is measured as an increase in absorbency at 531 nm. HbA1c in whole blood competes for the limited number of antibody-latex binding sites causing an inhibition of agglutination and a decreased scattering of light. The decreased scattering is measured as a decrease in absorbency at 531 nm. The DCA 2000+ analyzer performs all measurements and calculations. .

Whole blood is collected by finger stick or venipuncture. A 1µl sample is drawn into a pre-calibrated capillary holder. The sample volume is standardized by completely filling the capillary and wiping excess blood from the outside of the tube prior to placing it in the cartridge which contains the reagents necessary for the assay. Loading the cartridge into the analyzer initiates an automatic calibration. After loading the cartridge, sample and reagents are allowed to mix by removing a small plastic tab. No further action is required of the operator. The results are available on the display in about 9 minutes. It is recommended that a Normal and Abnormal Quality Control test be performed every 24 hours of patient testing. The instrument requires calibration whenever a new lot number of reagent cartridges is used.

The DCA 2000 Analyzer was last certified by the National Glycohemoglobin Standardization Program to be traceable to the DCCT Reference Method and values in June 2003.



BACKGROUND, continued

A1cNow (Metrika)

The A1cNow test is a single use, disposable, battery powered device. It must be stored at 2-8° C and must be left at room temperature for at least 30 minutes before use. Once the bag containing the device is opened, it must be used within 15 minutes. The device uses MODM™ (Micro-Optical Detection Method) technology that incorporates microelectronics, optics, and dry-reagent chemistry strips within a cassette sized plastic casing. It is quantitative and does not require calibration by the user since each test unit is calibrated at the factory. It is simple to operate and requires only brief training. A 10- μ L sample of whole blood is diluted 70-fold into a dilution buffer and then applied to the device's sample port. Inside the unit are all the elements necessary to perform the test and present the results to the user. Test results (% HbA1c) are displayed as a number on the device's display within 8 minutes after sample application. The device has no switches or buttons; it turns on automatically when the sample is added. It contains two dry reagent lateral flow strips, each having an HbA1c immunoassay test zone and a total hemoglobin test zone. With the addition of the sample, blue microparticles conjugated to anti-HbA1c antibodies (sheep polyclonal antibodies) migrate along the reagent strips. The amount of blue microparticles captured on the immunoassay zone of each strip reflects the amount of HbA1c in the sample. For the total hemoglobin portion of the assay, the sample diluent, which contains ferricyanide, converts hemoglobin to met-hemoglobin, which is red-brown in color. The intensity of the color measured on the second test zone of each reagent strip is proportional to the concentration of hemoglobin in the sample. Assay results are then calculated from the reflectance of the test zones by an onboard microprocessor and are expressed as % HbA1c. The microprocessor corrects for lot-specific reagent characteristics and optical variation. It also checks electrical functioning and proper sample volume.

The A1cNow system was last certified by the National Glycohemoglobin Standardization Program to be traceable to the DCCT Reference Method and values in June 2003.



BACKGROUND, continued

DiaSTAT HbA1c Analyzer (Bio-Rad Diagnostics Group)

The DiaSTAT™ Analyzer is a fully automated low-pressure liquid chromatography (LPLC) system designed for the rapid and automated measurement of hemoglobin A 1c in a small laboratory or clinic. A1c results are available in less than 10 minutes. The one-step sample preparation accepts capillary or venous blood samples and the instrument uses simple touch screen commands for operation.

The DiaSTAT™ Analyzer was last certified by the National Glycohemoglobin Standardization Program to be traceable to the DCCT Reference Method and values in June 2003.

HemaQuant Analyzer with Glycosal cartridges (Provalis Diagnostics)

Glycosal is a rapid, point-of-care test using the established method of affinity chromatography for the quantitative determination of HbA1c. The Glycosal test cartridge integrates with HemaQuant, a compact spectrophotometric analyzer equipped with a light emitting diode (LED) photo-optic detection system. An interactive liquid crystal display (LCD) provides the operator with a guide through the test procedure with the final result being expressed as HbA1c. Glycosal has a linear working range of at least 3%-18% HbA1c, requires approximately 10 microL of whole blood and generates a result in approximately 4 minutes.

The Glycosal test in the cartridge uses boronate affinity chromatography to separate the glycosylated hemoglobin fraction from the non-glycosylated fraction. The blood is lysed to release the hemoglobin and the boronate affinity resin binds the glycosylated hemoglobin. After a short incubation step, the unbound non-glycosylated hemoglobin is measured photometrically, then the boronate affinity resin is washed and the bound glycosylated hemoglobin is eluted from the resin and measured; the HbA1c concentration is calculated by the instrument.

A pipette provided in the kit, or a calibrated pipette is used to collect 10 µL of blood, which is added to a sample tube. After inverting the sample tube to mix the contents, there is an incubation period of 60 seconds. The contents of the tube are remixed and poured into the test cartridge. After a 50-second countdown the cartridge is rotated to position 2 and the contents of a second tube are added.



BACKGROUND, continued

HemaQuant Analyzer with Glycosal cartridges (Provalis Diagnostics), continued

After a 40-second countdown the cartridge is rotated again (position 3) and the contents of a third tube are added. After a final 80-second countdown the cartridge is rotated back to the starting position and removed from the instrument. At this time the HemaQuant instrument will display the percentage HbA1c value for the sample. The HemaQuant can be connected to a serial printer and the results printed out as each measurement is completed. Past results can be printed out individually or as a print out obtained for the 400 results stored with their unique identification numbers.

The HemaQuant Analyzer with Glycosal cartridges was last certified by the National Glycohemoglobin Standardization Program to be traceable to the DCCT Reference Method and values in December 2002.

B-D A1c At-Home-Test (Becton Dickinson)

Recently, a number of at-home sampling kits have been developed that facilitate the timely availability of HbA1c results. The B-D A1c At-Home-Test combines a filter paper technique for spotting capillary blood with an immunoturbidometric assay (a variation of the Cobas Integra Hemoglobin A1c method also referred to as Roche Unimate). Patients place 1-2 drops of fingerstick blood on each of two target areas on filter paper in the test kit. The sample is left to air-dry overnight at room temperature, placed in a pre-addressed bag, and mailed to a central laboratory. Laboratory personnel elute the blood from one spot on the filter paper and perform the assay for HbA1c. The second spot is stored at -70° C for contingency purposes. Assay results are mailed to the patient and their doctor within 2 weeks. This product may add to the convenience of both patient and health care provider by making it easier for patients to obtain their HbA1c values and by having them available at their visit to the clinician.

The underlying central laboratory test (Cobas Integra) was last certified by the National Glycohemoglobin Standardization Program to be traceable to the DCCT Reference Method and values in July 2003. The authors of a paper evaluating the accuracy of the method (Parkes *et al.* 1999) report that the A1c At-Home-Test has received NGSP certification, though it is not listed on the website.



TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

DCA 2000 Analyzer (Bayer Diagnostics) received CLIA Waived status by the FDA on November 12, 1997

A1cNow (Metrika) received CLIA Waived status by the FDA on August 17, 2001. Other Metrika devices are: DRX Professional Use Hemoglobin A1c Test and A1cNow for Prescription Home Use – CLIA waived on 3/8/2002; A1cNow for Home Use – CLIA waived on November 19, 2002

DiaSTAT HbA1c Analyzer (Bio-Rad Diagnostics Group) received CLIA Waived status on December 17, 2002.

HemaQuant with Glycosal Cartridges (Provalis Diagnostics) received CLIA Waved status on November 9, 2001

B-D A1c At-Home-Test (Becton Dickinson) has received FDA approval although the exact date is was not found.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Outcomes assessed in the various clinical trials summarized below include: accuracy and precision of rapid HbA1c results compared to traditional laboratory approaches with HPLC. All four of the technologies evaluated have been certified by the National Glycohemoglobin Standardization Program, but the data supporting the certification process have not been published. Adverse effects, such as pain, irritation, or infection were rarely reported. Ideally, trials would report data on important clinical outcomes such as retinopathy, renal function, neuropathy, heart attacks and strokes. However, long-term control of hyperglycemia (HbA1c levels), avoidance of hypoglycemic episodes, and quality of life are adequate surrogate markers given the findings from the DCCT and the UKPDS. Most studies included patients with both type 1 and type 2 diabetes.



TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes (continued)

1. DCA 2000

At least 18 case-series including over 3000 participants have been published assessing the accuracy and precision of the DCA 2000 device compared to conventional measures of HbA1c. The effect of knowledge of HbA1c at the time of the clinic visit results on clinical decision making was assessed in one case series without controls (n=18), one retrospective case series with concurrent controls (n=599), two large pseudo-randomized clinical trial (n=1597), and one randomized clinical trial (n=201). The effects of immediate availability of HbA1c results on long term glycemic control at 6 to 12 months of follow-up was assessed in the 3 “randomized” clinical trials.

Level of Evidence: 1, 3, and 5

2. A1cNow

One case-series including 50 participants has been published assessing the accuracy of the A1cNow device compared to conventional measures of HbA1c. Further unpublished data on 286 samples are available from the manufacturer. No published trials on the effects of use of A1cNow on clinical outcomes were identified.

Level of Evidence: 5

3. DiaSTAT Analyzer

One case-series including 122 participants has been published assessing the accuracy of the DiaSTAT analyzer compared to conventional measures of HbA1c. The effect on clinical decision making of knowledge of HbA1c at the time of the clinic visit results was assessed in that same study and one additional retrospective trial using concurrent controls (n=115) evaluated the effects of the use of DiaSTAT analyzer on HbA1c at 1 year.



TA Criterion 2: **The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes (continued)**

Level of Evidence: 3, 5

4. HemaQuant analyzer with Glycosal cartridges

One case-series including 62 participants has been published assessing the accuracy of the DRX HbA1c device compared to conventional measures of HbA1c. No published trials on the effects of use of DRX on clinical outcomes were identified.

Level of Evidence: 5

5. A1c At-Home-Test

One case-series including 59 participants has been published assessing the accuracy of the A1c At-Home-Now test compared to conventional measures of HbA1c. No studies with clinical outcomes used this device, but one randomized clinical trial (n=140) evaluated the utility of home fructosamine (a reasonable surrogate for HbA1c) measurements, and one case series (n=380) described the effect of mailing home HbA1c tests directly to patients.

Level of Evidence: 1, 3, and 5

6. Other tests

A large pseudo-randomized trial (n=1138) that evaluated the impact of rapid HbA1c test results on clinical decision making and HbA1c levels over 7 months of follow-up was included in this review even though the device used (TinaQuant, Roche) was not marketed for in-clinic use. The results of the study are relevant when evaluating whether knowledge of HbA1c levels at the time a patient sees their doctor improves clinical outcomes for the patient.



TA Criterion 3: The technology must improve the net health outcomes.

Accuracy and Precision

A clinical measurement comparison of a new measurement technique with an established one is often needed to see whether they agree sufficiently for the new to replace the old. Such investigations are often analyzed inappropriately, notably by using correlation coefficients or regression equations (Bland *et al.* 1986). The use of correlation is misleading as it measures the strength of the association between two variables, not the agreement between them. An illustrative example is the correlation between a measurement and twice the measurement – it is 1.00, perfect, even though the values differ by 100%. Bland and Altman suggest an alternative approach, based on graphical techniques and simple calculations of the average differences between paired measurements and the standard deviation of the differences. The difference between paired measurements is plotted on the y-axis versus the average of the two measures on the x-axis. Horizontal lines are drawn for the average difference and the 95% confidence interval for the difference (see Figure 4 in Guerri 1997). This allows for an assessment of whether there is any association between measurement error and the true value. Since we do not know the true value, the mean of the two measurements is the best measure available. More recent papers in this review used the approach proposed by Bland and Altman, though many authors simply report the correlation coefficients or calculate the regression line coefficients.

For tests that give a numerical value, precision is usually measured using the coefficient of variation (CV). The CV is defined as the mean divided by the standard deviation and is usually expressed as a percent. It has the advantage of being unit-less, and thus can be compared across different types of assays. It is a useful measure of the relative spread in data and standardizes the variation so that sensible comparisons can be made. For laboratory tests, pooled or standardized blood (or other test material) is used as a reference standard. The reproducibility of a test is determined by repeating the test many times (often 10-20 times) on the same sample. The mean and standard deviation (SD) of each test is then calculated and used to find the CV for that reference standard. Usually the CV is calculated for several standards at different levels because tests often have greater variability at higher levels. In the case of HbA1c, it is important to test the precision at levels ranging from below 6% to above 9%.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Accuracy and Precision, continued

For many tests, a CV < 10% is acceptable. For NGSP certification, a method to test HbA1c must have a CV < 4%. Laboratory tests frequently report both intra-assay (within batch) and inter-assay (between batch) CV. To calculate the intra-assay CV, a sample is tested multiple times using the same batch of reagents on the same day. The mean and SD of the set of measurements is calculated and used to compute the CV. To calculate the inter-assay CV, a sample is tested multiple times using the different reagents on the different days. The mean and SD of the set of these measurements is calculated and used to compute the CV.

1. DCA 2000

Guthrie et al (1992) evaluated the clinical performance of the DCA 2000 in physicians' office laboratories. Three physicians' offices participated in the evaluations. The clinicians routinely use HbA1c test results to monitor their patients' long-term blood glucose control. Precision and interlaboratory variability were assessed using three levels of lyophilized controls. Correlation of the method's results to currently available laboratory methods was made. Comparison of finger-stick (capillary) results to venous EDTA whole blood results was made on 134 patients. Physician and laboratory personnel input was evaluated with regard to the clinical utility of the system. The intra-assay CV and inter-assay CV were a maximum of 4.5 and 4.4% for the immunoassay system on three levels of control materials at the three sites. Interlaboratory variability among the control means was found to be 4.9-5.4, 8.0-8.3, and 11.7-12.0% HbA1c. Correlation coefficients (r) ranged from 0.95 to 0.99. There was a positive bias by the DCA 2000 compared with the in-house method at site 1. Minimal negative biases were seen by the DCA 2000 with comparative methods used at sites 2 and 3. Median percentage differences with the comparative methods were 12, -1.4, and -5.6%. Comparison of capillary to venous sample results, from the DCA 2000, showed no clinically significant differences. The authors concluded that precision was acceptable and interlaboratory variability was low. The immunological method correlated well with manual ion exchange and automated HPLC methods. The small amount of blood required and the good comparison between capillary and venous sample results make fingerstick sampling acceptable.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Marrero et al (1992) compared the performance of the DCA 2000 with two standard laboratory methods in both nondiabetic and diabetic pediatric patients. Two hundred seven pediatric subjects (103 nondiabetic, 104 with insulin-dependent diabetes mellitus) had HbA1c measured with the DCA 2000 and laboratory measures using the same whole-blood capillary aliquot. Glucose values were also obtained from the same blood samples. Correlation and regression analyses show excellent correspondence between the three assays. The correlation between the two laboratory methods was 0.98 (P less than 0.001); between the DCA 2000 and AC methods was 0.99 (P less than 0.001) and between the DCA 2000 and CE methods was 0.97 (P less than 0.001). The intra-assay CV for the DCA 2000 ranged from 1.7 to 3.5% and inter-assay CV 2.7 to 4.1%. The study results suggest that the DCA 2000 method gives extremely accurate and reliable values over the clinical range of interest.

Pope et al (1993) evaluated the DCA 2000 using 48 patient samples and a separate within-clinic prospective study of 59 diabetic patients. Individuals were recruited from general (48 patients), pediatric (19 patients), obstetric (24 patients), and general practice (15 patients) diabetic clinics. Agreement was evaluated between HbA1c results obtained using the DCA 2000 and an established laboratory assay (DIAMAT HPLC system). The Bland-Altman approach was used to assess accuracy. The mean differences between the two results (AMES DCA 2000-DIAMAT) (95% confidence intervals) were: laboratory -0.69% (-1.42 to 0.04%), pediatric clinic -0.93% (-1.93 to 0.07%), obstetric clinic -0.29% (-1.09 to 0.51%), and general practice clinic -0.77% (-1.3 to -0.24%). For the DCA 2000, the inter-assay CV for HbA1c of 5.2% was 1.6% and for HbA1c of 13%, 2.4%. Four different operators used this instrument without difficulty after 15 minutes of training. Intra-assay coefficient of variation for each operator was < 3.4%. No equipment failures occurred during the 3-month study period. The results using the DCA 2000 were consistently lower than those obtained using HPLC. The authors suggest that one test should be used consistently for individual patients.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Rumley et al (1993) assessed the accuracy of the Ames DCA 2000 in 78 patients with Type 1 diabetes at the outpatient clinic. Significant correlations were noted with both the Corning Glytrac total HbA1 assay ($r = 0.89$) and the Novoclone assay for HbA1c ($r = 0.95$). No Bland-Altman assessment was reported. Mean intra-assay CV was 1.6% and 3.0% at HbA1c of 5.4% and 13.0%, respectively, while inter-assay CVs were 4.2% and 3.8%. These results were better than the routine laboratory method based on the Corning HbA1 assay. The authors concluded that the DCA 2000 was simple to use in the clinic and correlated well with existing assays.

John et al (1994) evaluated the analytical quality of the DCA 2000 clinical analyzer for the measurement of hemoglobin A1c. The analyzer demonstrated good intra-assay (1.9-3.1% CV) and inter-assay (2.2% CV) precision, and was not affected by hemoglobin concentration. The analyzer was linear throughout the analytical range, and was found to correlate well with other methods to measure HbA1c, including agar electroendosmosis ($r = 0.93$), affinity chromatography ($r = 0.97$), HPLC ($r = 0.90$), and EIA ($r = 0.98$). The authors concluded that the DCA 2000 gave reliable analytical results and was easy to use. They did not report the Bland-Altman statistics for evaluation of the accuracy of the new method.

Mortensen et al (1994) evaluated the accuracy, precision and feasibility of the DCA 2000 used in a diabetes clinic by a technical assistant and in a general practice clinic by non-lab staff. The results were compared with a high performance liquid chromatographic method (AUTO A1C, Kyoto Daiichi Kagaku Co., Kyoto, Japan), which was their current laboratory method. Blood samples were drawn after informed consent from 118 patients during a period of two months at the outpatient pediatric clinic of Glostrup Hospital ($n = 67$) and at a general practice clinic ($n = 51$). Each sample was analyzed twice by each method on two consecutive days. In the HbA1c range from four to 14% ($n = 67$), the average intra-assay precision for the HPLC method was 0.13% and 0.23% for the DCA 2000 method. The intra-assay precision was low and acceptable and it was independent of the current HbA1c concentration. For the DCA 2000, precision was similar when carried out by a technical assistant (SD: 0.20%) and by non-lab staff (SD: 0.25%). Inter-assay variations were low.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Le Marois et al (1996) compared HbA1c values measured by the DCA 2000 to a reference HPLC HbA1c method and home blood glucose monitoring. One hundred three blood samples and the corresponding mean capillary glucose values (4.4 +/- 1.2 tests/day) of the preceding 2 months were collected from 34 insulin-dependent diabetic adults. They measured accuracy using correlation coefficients; the residual plots method (Bland-Altman), and regression equations. A highly significant correlation ($r^2 = 0.85$, $P < 0.001$) and an acceptable agreement (97% of values within 2 SD of the mean difference of 0.9% +/- 0.4%) were found between DCA and HPLC values. A significant correlation ($r^2 = 0.40$, $P < 0.01$) was also found between the DCA 2000 and capillary glucose values. The authors concluded that the three methods of assessment of diabetes control were highly correlated and had acceptable precision for the clinical setting.

Carter et al (1996) tested whether the DCA 2000 analyzer provides valid and reliable HbA1c results when used under field conditions and operated by non-medical personnel. This study was part of a community diabetes education program, the Native American Diabetes Project, in which HbA1c was measured as an indicator of average glycemic control. Two study samples were taken, the first in the spring of 1994, and the second in the spring of 1995. Seven community members in 1994 and six new community members in 1995 were trained over 2 days, using standard protocol, to operate the DCA 2000 HbA1c analyzer and to collect two capillary blood samples from participants in the Native American Diabetes Project. Duplicate DCA 2000 HbA1c measurements performed by the community workers were compared with measurements from a high-performance liquid chromatography (HPLC) system. Of the participants, 43 were studied in 1994 and 14 in 1995. Comparison of the mean DCA 2000 results with those of HPLC showed high validity, with the absolute relative difference (Bland-Altman) between the mean DCA 2000 and the external reference of HPLC being 4.0 and 2.0% for 1994 and 1995, respectively. The Pearson correlation coefficients (r) between these two measures were 0.968 and 0.996 for 1994 and 1995, respectively. While the 1994 data appeared to have less validity for values >10%, they included only one value with a 60-min warm-up of the DCA analyzer. The 1995 data, all collected after a 60-min warm-up, had good correlation throughout the range of values.



TA Criterion 3: The technology must improve the net health outcomes
(continued)

1. DCA 2000, continued

The intra-assay CV for these measures was 3.0% in 1994 and 2.8% in 1995. Both validity and reliability were improved by changing the warm-up period of the DCA 2000 analyzer from 5 to 60 min. All correlation coefficients were statistically significant ($P < 0.0001$). The authors conclude that the DCA 2000 gave valid and reliable HbA1c results when operated in a community setting by non-medical personnel. They note that extending the warm-up period of the device to 60 min slightly improved the validity and reliability of the test.

McGlone et al (1997) compared the DCA 2000 with their established laboratory method (Dako HbA1c system) in 58 children routinely attending a diabetic outpatient clinic. Results showed that DCA 2000 and laboratory estimations of HbA1c were closely correlated throughout the range of values ($R = 0.95$). The mean difference between values was 1.83% with a 95% range of agreement of 0.23-3.4%. In this study, the DCA 2000 tended to overestimate HbA1c slightly as compared to HPLC. The authors concluded that the DCA 2000 could be used to provide a rapid estimate of HbA1c upon which treatment changes could be based at diabetic clinics.

Eaton et al (1997) compared the performance of the DCA 2000 system with that of two automated high-performance liquid chromatography systems (Diamat and Glycomat) heterozygotes for sickle cell disease ($n=39$) or Hemoglobin C ($n=8$). Heterozygotes for these hemoglobin variants may not have clinically apparent disease and the use of immunoassay measures of hemoglobin A1c may give falsely low values. Results were presented using Bland-Altman plots. For hemoglobin S heterozygotes, the DCA 2000 showed a small positive bias of 0.10% (95% CI $-0.1-0.3\%$) compared with the Diamat HPLC and a small negative bias of -0.09% (95% CI $-0.33-0.15\%$) compared with the Glycomat HPLC. For hemoglobin C heterozygotes, the DCA 2000 showed a positive bias of 0.60% (95% CI $-0.16-1.36\%$) compared with the Diamat HPLC and a positive bias of 1.12% (95% CI $0.55-1.69\%$) compared with the Glycomat HPLC.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

The authors conclude that DCA 2000 has good concordance with established laboratory methods for patients heterozygous for hemoglobin S, but that their sample size was too small for making any conclusions about patients heterozygous for hemoglobin C. A similar study (Roberts *et al.* 2000) evaluated 5 different HbA1c assays in 40 patients with 9 other hemoglobin variants. The DCA 2000 was the only test to give unbiased results for all 9 hemoglobin variants and had good accuracy compared with the reference boronate affinity assay (chosen as the reference because it is unaffected by hemoglobin variants).

The largest study designed to assess the accuracy of the DCA 2000 was performed by Guerci *et al.* (1997) at 5 diabetes clinics in France. They compared the performance of the DCA 2000 system with that of high-performance liquid chromatography (HPLC). A total of 1,016 insulin-dependent and non-insulin-dependent diabetic patients from 5 outpatient clinics took part. The correlation coefficients between DCA 2000 and HPLC data ranged between 0.94 and 0.98. The Bland-Altman mean variations and 95% confidence intervals for the differences between the results for each sample were: site A -0.172 (-1.186 to 1.53), site B -0.275 (-1.317 to 0.767), site C -0.146 (-0.868 to 0.576), site D -0.088 (-0.864 to 0.688), and site E -0.251 (-1.099 to 0.597). For pooled results, the correlation coefficient assayed by the two methods was 0.95 ($p < 0.00001$) and the mean difference between the two methods was -0.116 (95% CI -1.2 to 1.0). The authors concluded that the DCA 2000 slightly underestimated HbA1c compared to HPLC, but that the precision and accuracy of the results was sufficient for routine use in diabetes clinics.

Fonfrede and Grimaldi (Fonfrede *et al.* 1998), in response to Guerci *et al.* (1997), reported their experience with two DCA 2000 systems in outpatient diabetes clinics in France. They compared the DCA 2000 results with HPLC in 300 samples. Using a HbA1c cutoff of 7% for clinical decision, they found that 23% of the readings using the DCA 2000 would have resulted in incorrect classification. They advocated an inter-assay CV of less than 2% for acceptable precision. In their analysis, the inter-assay CV for the DCA 2000 machines were 2.5% and 2.8% at HbA1c of 5.6% and 3.5% and 4.6% at HbA1c of 9.7%. For the HPLC analyzer, the between run CV was 1.6% at HbA1c of 5.6% and 1.9% at HbA1c of 9.7%.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

They express concern about the accuracy of the DCA 2000 and suggest that only methods certified by the NGSP be used to measure HbA1c.

Papoz and Delcourt (Papoz *et al.* 1998) responded to Fonfrede and Grimaldi by questioning the methods used in their letter (Fonfrede *et al.* 1998). They note that the subjects in the study are inadequately described and that no statistics were presented. The correlation coefficients were not presented, nor were the Bland-Altman plots. They also note that HPLC is not free from analytical error and that there is no established gold standard for the measurement of HbA1c. They argue that the results of Guerci *et al.* (1997) are valid and that the DCA 2000 is sufficiently accurate to be used for both clinical practice and epidemiological studies.

Matteucci *et al.* (1998) compared the DCA 2000 to the HPLC (Diamat, Bio-Rad) reference method used in a routine hospital laboratory in 161 patients. The DCA 2000 showed intra- and inter-assay coefficients of variation of 1.1% and 2.3% with normal HbA1c levels, 1.0% and 4.2% with elevated HbA1c; HPLC yielded CVs of 1.3% and 7.0%, 1.3% and 5.7%, respectively. The HPLC method exhibited significant variability over time. Intra- and inter-assay CVs of HPLC were 0.6% and 2.5% (normal standard serum), 0.3% and 1.9% (high standard serum), but after 6 months of routine laboratory use, they became 3.1% and 3.2%, 1% and 12.3%, respectively. The main sources of error were inaccurate auto-dilution, unsuitable parameter settings, and disregard of the maintenance schedule. The tendency to overlook major critical aspects in the routine use of HPLC is detrimental to the quality of HbA1C determination and implies the loss of HbA1C value in clinical practice. Carefully supervising laboratory quality is essential for any assay methodology.

As part of their clinical trials of rapid HbA1c testing, Grieve *et al.* (1999) assessed the accuracy and precision of the DCA 2000. Precision was good; the intra-assay CV for the DCA 2000 ranged from 3.3 to 4.7% on 2 different machines with 33 samples of normal HbA1c and 33 samples of high HbA1c. The intra-assay CV for the central laboratory method on the same samples ranged from 2.1 to 3.6%. They concluded that the accuracy and precision was acceptable for routine use of the test in the clinic.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Cagliero et al assessed the accuracy of the DCA 2000 (Cagliero *et al.* 1999) as part of a randomized clinical trial of the device. They compared the performance of the DCA 2000 system with that of HPLC in 264 patients at the diabetes clinic of Massachusetts General Hospital. The correlation coefficient between the DCA 2000 and HPLC results was 0.924 ($p < 0.001$) and the mean difference between the two methods was -0.071 (95% CI -0.511 to 0.653). The intra-assay CV for the DCA 2000 was 2.1% and the inter-assay CV was 2.0%. They concluded that the DCA 2000 provided a reliable and accurate measure of HbA1c.

Jermendy et al (1999) assessed the accuracy and precision of the DCA 2000. They reported that reproducibility was acceptable (intra-assay CVs were 3.48% and 4.80%) and that there was a close, linear correlation ($r = 0.974$; $p < 0.001$; $n = 106$) between HbA1c-values measured simultaneously by DCA 2000 and DIAMAT (Bio-Rad high pressure liquid chromatography).

Arsie et al (2000) assessed the accuracy of the DCA 2000 for rapid assessment of HbA1c. They evaluated 171 subjects including 22 healthy volunteers, 78 type 2 diabetic patients with different degrees of metabolic control, 11 women affected by gestational diabetes mellitus (GDM), 6 patients with hyperlipidemia, 38 patients with chronic renal failure, 13 diabetic patients with chronic renal failure, and 3 patients with hemoglobinopathies. The DCA 2000 model was compared with the Diamat HPLC system. Data from intra-assay studies showed excellent precision, for both DCA 2000 (CV 3-4%) and the HPLC system (CV 2-3%). The correlation between the two different systems was good ($y = 0.911x + 0.462$, $r = 0.923$). Results from the control group and diabetic patients were used to compare the two methods. The mean difference (Bland-Altman test) was -0.83 (95% CI -1.8-0.13). They conclude that the DCA 2000 gives reliable results with good precision and good agreement with the HPLC reference system.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Hawkins et al (2003) assessed four commercially available point-of-care HbA1c analytical systems for accuracy compared with the central laboratory HbA1c method (TinaQuant, Roche) and precision. Analytical accuracy was assessed by analysis of 110 patient samples on all five analytical platforms (Biorad Diastat, Drew DS5, Bayer DCA 2000, Nycomed Nycocard and Roche Tinaquant). Analytical precision was assessed by analysis of two levels of patient sample four times daily for six days, as well as analysis of two levels of commercial control. Deming linear regression for agreement: Diastat= $0.98 \times \text{Tinaquant} + 0.36$; DS5= $1.23 \times \text{Tinaquant} - 0.65$; DCA2000= $0.95 \times \text{Tinaquant} + 0.63$; Nycocard= $0.94 \times \text{Tinaquant} + 0.92$. Analytical coefficients of variation (CVs) at Tinaquant HbA1c levels of 6.2-10.8% were: Tinaquant 0.8-1.1%, Diastat 1.6-6.6%, DCA2000 2.6-7.2%, DS5 5.1-11.7%, Nycocard 8.5-15.3%. Two HbE samples gave elevated HbA1c results with the DS5 method. The authors conclude that the Diastat and DCA2000 systems gave the best performance with acceptable precision and good agreement with both the central lab and each other. The DS5 was less precise with a significant positive bias compared to the other methods and interference from HbE, while the Nycocard system showed the poorest precision in the evaluation. The authors concluded that the Diastat and DCA2000 systems were satisfactory analytical alternatives to both central laboratory testing and each other.

2. A1cNow

Stivers et al (2000) evaluated the accuracy of A1cNow (or DRx in the reference) for rapid quantitative testing at the point of care. For testing accuracy, subjects with and without diabetes were recruited in order to obtain samples with a wide range of HbA1c values. Whole blood samples were analyzed using both A1cNow units and an HPLC laboratory method (Bio-Rad DiaSTAT). A1cNow testing was performed by laboratory personnel and by subjects who received brief training. Repeatability, linearity, sample volume tolerance, diluted sample stability and hematocrit tolerance of the A1cNow test were assessed by trained laboratory personnel. The linear %HbA1c range of the assay extended from approximately 3% to 15%.



TA Criterion 3: The technology must improve the net health outcomes (continued)

2. A1cNow

A1cNow clinical sample test results (n = 50) correlated linearly to the Bio-Rad DiaSTAT method (r = 0.935) with slope and intercept values of 0.994 and 0.003, respectively. The CVs ranged from 5-9%. The authors concluded that DRx HbA1c performance is closely equivalent to that of existing tests.

Since that time improvements have been made in the technology and the device has obtained NGSP certification, which requires a CV < 4%. Unpublished data supporting that application were based on 286 blood samples certified by the NGSP. The correlation coefficient was 0.93 with a CV of 4.0% at HbA1c level of 6% and 3.9 at HbA1c level of 9%. On average, the A1cNow measurements were 1% higher than the NGSP reference levels. For example, for the reference level 6.0%, the A1cNow gave a reading of 6.1% (1.7% high) and for the reference level 11%, the A1cNow reading was 11.04 (0.3% high). Using the Bland-Altman method, the 95% CI of the mean difference ranged from -0.8 to 0.6.

3. DiaSTAT Analyzer

Rumley et al (1990) assessed the performance of the Diamat HPLC analyzer (Bio Rad Instruments) in 122 patients with diabetes. The intra-assay CV for HbA1 at concentrations of 8.3 and 13.4% was 3.8 and 0.4%, respectively, with inter-assay CV of 5.0 and 3.0%.

4. HemaQuant analyzer with Glycosal cartridges

Stevenson (1999) evaluated the accuracy of Glycosal, a rapid, point-of-care test using the established method of affinity chromatography for the quantitative determination of hemoglobin A1c (HbA1c). Glycosal was evaluated in the clinical environment compared to two routine HbA1c autoanalyzer methods used in the Clinical Chemistry Department of the Malmo University Hospital, Sweden. The Variant (BioRad) and the Mono-S (Pharmacia) systems are both cation exchange high-performance liquid chromatography (HPLC) systems specifically measuring HbA1c. Fresh (< 2 days) EDTA anticoagulated blood samples were randomly selected from the routine diabetic clinic (n = 54) along with nondiabetic samples from consenting volunteers (n = 8).



TA Criterion 3: The technology must improve the net health outcomes
(continued)

4. HemaQuant analyzer with Glycosal cartridges, continued

The Variant and Mono-S HPLC methods showed excellent agreement compared to each other (correlation coefficient $[r] > 0.99$). The agreement between Glycosal and Variant ($r = 0.98$) and Glycosal and Mono-S ($r > 0.98$) HPLC methods were almost as high. A further final evaluation of a 10 sample series (4%-10% HbA1c) of the hospital's HbA1c reference materials by Glycosal produced very strong agreement ($r > 0.99$) against the Mono-S HPLC. Glycosal had a mean coefficient of variation of less than 5% across its linear range. The authors conclude that the Glycosal rapid test was comparable to two high-precision cation exchange HPLC autoanalyzers.

5. A1c At-Home-Test

Parkes et al (1999) assessed the accuracy, precision, and reproducibility of the B-D A1c At-Home-Test. The B-D A1c At-Home test kit was evaluated using 1625 dried blood spot samples from 59 subjects diagnosed with type 1 or type 2 diabetes collected in an in-clinic setting. Data for replicate samples were compared against those from the standard Cobas Integra Hemoglobin A1c assay and from the BioRad Variant HPLC assay. The effect of subjecting the dried spotted blood samples to prolonged elevated temperatures was evaluated in a separate laboratory analysis. The B-D A1c At-Home results were highly correlated with the standard Cobas Integra Hemoglobin A1c assay, ($r^2 = 94.7\%$). The intra-assay CV was 2.7% and the inter-assay CV was 3.9%. There were no clinically significant differences (i.e. < 0.3 units) in samples aged 3 to 10 days, between venous or capillary blood samples, or from freezing and thawing or prolonged exposure of B-D A1c At-Home dried blood samples to elevated temperatures before assay. The authors conclude that the B-D A1c At-Home kit combined the accuracy, precision, and reproducibility of a clinical laboratory test with the convenience of at-home sample collection.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Clinical benefits

1. DCA 2000

Pope et al (1993) evaluated both the accuracy (described above) and clinical effects of the DCA 2000. A random sample of 18 patients from the 39 attending the obstetric and general practice clinics was used to assess the clinical utility of the DCA 2000. In 9/18 (50%) patients, knowledge of the HbA1c results at the time of consultation lead to a change in treatment. Treatment changes included initiation of insulin therapy in patients with gestational diabetes whose HbA1c levels were rising and increased doses of oral hypoglycemic agents in diabetics with elevated HbA1c. The authors suggest that the device may be particularly effective for pediatric and obstetric patients in whom rapid deterioration in diabetic control may be prevented.

Grieve et al (1999) reported a complex clinical trial of the clinical effects of the availability of rapid HbA1c results (near patient testing [NPT]) compared with conventional testing. The primary outcomes were the effect of the testing method on the process of care, the accuracy of testing, patient satisfaction, and clinician attitudes. A secondary aim was to assess the effect of the testing on clinical outcomes. Three alternative strategies were considered: (1) Conventional testing in which doctors had the option of requesting at test. The results were sent for processing at a central laboratory with a delay of 5-7 days before results were returned; (2) laboratory NPT in which laboratory personnel operated a testing service next to the diabetes clinic. Test results of glucose, HbA1c, lipids, and creatinine were available prior to the patient's appointment with the doctor; and (3) nurse NPT in which samples were analyzed by a nurse using desktop analyzers in the clinic. Again, the test results were available prior to the patient's appointment with the doctor. The DCA 2000 was used for NPT. A controlled trial compared the effect of the testing method on the process of care. Five hundred ninety-nine patients were alternately allocated to either nurse NPT or conventional testing. Patients were more likely to have a change in management related to their glycemic control if they were in the NPT rather than the conventional testing group (OR 1.52, 95% CI 1.02-2.26).



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Subgroup analyses showed that patients with poor glycemic control were more likely to have management changes in the NPT group than in the conventional group (OR 1.72, 95% CI 1.12-2.76). For patients with good control, the number of management changes did not differ between the groups. Thus, processes of care may be improved by the availability of HbA1c results prior to the clinic visit. No changes in process of care were found for the provision of lipid and creatinine results.

Patients for both NPT strategies were significantly more satisfied with the test information provided than those who were conventionally tested (laboratory NPT versus conventional, $p=0.004$; nurse NPT versus conventional, $p<0.001$). A higher proportion of users of the NPT services recalled being told the results of their HbA1c test (64%) compared with those who used the conventional testing service (19%). A sample of doctors interviewed stated that immediate access to HbA1c results meant that they could make more informed decisions about what changes in management should be implemented. They also said that without immediate access to test results, changes in patient management might be sub-optimal. Again, conventional testing was considered adequate for lipid and creatinine results.

The authors also reported on a retrospective cohort study (Grieve *et al.* 1999) which compared mean HbA1c levels between patients using conventional testing ($n=500$) and laboratory NPT ($n=500$). After controlling for case-mix variables, mean HbA1c level was significantly lower for the NPT cohort compared with the conventional testing cohort (7.8 versus 8.7, $p<0.001$). The authors note that the potential for confounding due to the non-randomized design of the study means that a prospective randomized controlled trial is needed to confirm the validity of these findings. They also note that users of the NPT service made fewer hospital visits per year than those of the conventional service and that this finding should also be investigated with a randomized trial.

TA Criterion 3: The technology must improve the net health outcomes
(continued)

1. DCA 2000, continued

Cagliero et al (1999) tested the hypothesis that immediately available HbA1c results could improve glycemic control by changing physician or patient behavior or both. They conducted a randomized controlled trial in 201 consecutive type 1 and insulin-treated type 2 diabetic patients attending an academic diabetes clinic. Over 90% of eligible patients participated in the study. Patients were randomized to either an immediate assay group (DCA 2000 used to provide HbA1c results during the visit) or a control group (HbA1c levels measured by the diabetes laboratory as per usual clinical practice). Treating physicians were aware of the nature of the study, but were blinded to the specific outcomes. HbA1c levels, changes in insulin therapy, and use of health care resources were assessed during a 12-month follow-up period. At baseline, the patients were on average 49 years old, 53% were male, and 56% had type 1 diabetes. The average HbA1c level was 8.6%. There were 37 patients who did not complete the study: 14 in the immediate assay group and 23 in the control group (p=NS). Of these 37 patients, 3 died, 6 switched care to other physicians, 7 were lost to follow-up, and 20 did not have any HbA1c measurements within 6 months of the study completion. The patients who did not complete the study had higher baseline HbA1c levels than those who completed the study (9.20 vs. 8.40, p=0.012), but otherwise had similar baseline characteristics. HbA1c levels decreased significantly at 6 and 12 months in the immediate assay group (-0.57 +/- 1.44 and -0.40 +/- 1.65%, respectively; P < 0.01) but did not change in the control group (-0.11 +/- 0.79 and -0.19 +/- 1.16%, respectively; NS). The between group differences in HbA1c levels were significant at 6 months (p=0.022, intention to treat analysis), but not at 12 months (p=0.346). The changes were similar for both type 1 and type 2 diabetic patients. There were no differences in the rates of hypoglycemic events (1.14/year in immediate assay group versus 1.42/year in control group, p NS) or use of health care resources. Patients in the immediate assay group changed insulin regimens less frequently than patients in the control group, suggesting that immediate feedback of HbA1c results led to clinically appropriate adjustments of insulin regimens. The authors concluded that immediate feedback of HbA1c results at the time of the patient visit resulted in a significant improvement of glycemic control at 6-month follow-up that persisted for the 12-month study period.



TA Criterion 3: The technology must improve the net health outcomes (continued)

1. DCA 2000, continued

Miller et al (2003) assessed whether rapid-turnaround A1c availability would improve intensification of diabetes therapy and reduce A1c levels in patients with type 2 diabetes. In this prospective controlled trial, HbA1c was determined on capillary glucose samples and made available to providers, either during ("rapid") or after ("routine") the patient visit. Patients whose baseline visits fell on an even numbered day of the month were assigned to the "rapid" group and those whose baseline visits fell on an odd numbered day of the month were assigned to the "routine" group. The primary outcomes were frequency of intensification of pharmacological diabetes therapy in inadequately controlled patients and change in HbA1c levels from baseline to follow-up. They recruited 597 participants who were predominantly female (79%) and African American (96%). They had mean age of 61 years and their baseline HbA1c level was 8.5%. The rapid and routine groups had similar clinical demographics. Rapid A1c availability resulted in more frequent intensification of therapy when A1c was $\geq 7.0\%$ at the baseline visit (51 vs. 32% of patients, $P = 0.01$). In 275 patients with two follow-up visits (mean 188 days from baseline to second visit), A1c fell significantly in the rapid group (from 8.4 to 8.1%, $P = 0.04$) but not in the routine group (from 8.1 to 8.0%, $P = 0.31$). Between-group comparisons were not reported in the paper and there were no data on incident hypoglycemic events. The authors concluded that the availability of rapid A1c measurements increased the frequency of appropriate intensification of therapy and lowered A1c levels in patients with type 2 diabetes.

2. A1cNow

The literature search did not find any published studies evaluating clinical outcomes using the A1cNow system.



TA Criterion 3: The technology must improve the net health outcomes
(continued)

3. DiaSTAT Analyzer

Rumley et al (1990) assessed the effect of this on-site HbA1c assay on the therapeutic decisions made at the diabetic clinic. On a single day 122 HbA1c tests on consecutive patients were performed at the clinic. In 43 insulin-treated patients and 79 non-insulin-treated diabetic patients the HbA1 result changed the management decision in 25 and 18% of patients, respectively. The relationship between HbA1 and self-blood glucose monitoring (SBGM) results in the previous 6-week period were also evaluated. In 41% of patients with insulin-treated diabetes who produced SBGM diaries there was a discrepancy between categories of blood glucose control, all of these patients having better SBGM than HbA1 values. This study highlights the feasibility and value of a within-clinic HbA1 assay for clinical decision-making and its usefulness in identifying problems of agreement with self-monitored tests.

Ferenczi et al (2001) assessed the effect of an immediately available hemoglobin A1c (HbA1c) result on glycemic control and physician decisions about pharmacologic therapy in an office practice. In a 1-year retrospective review of medical records, HbA1c results were analyzed in 115 patients beyond the age of 65 years, who had type 2 diabetes and were referred for the first time to a private endocrinology practice between April 1, 1997, and March 31, 1998. These patients were classified into two groups: group A (N = 93, insured by standard Medicare) had immediate HbA1c results (during the patient encounter) and group B (N = 22, insured by Medicare health maintenance organization) had commercial laboratory HbA1c results available within 2 to 3 days. The changes in HbA1c levels during the 12-month period and the presence or absence of a change in therapy at each visit were assessed. HbA1c levels were measured by ion-exchange low-pressure liquid chromatography in group A and by one of three capitated commercial laboratories in group B. At the end of the 12 months, the mean HbA1c decrease was 1.03 +/- 0.33% in group A and 0.33 +/- 0.83% in group B. During the first visit, 52% of the patients in group A had pharmacologic treatment interventions, whereas only 27% in group B had such interventions. The authors conclude that the availability of the HbA1c results during the clinical encounter improves the ability of the physician to make appropriate therapeutic decisions and results in improved glycemic control.



TA Criterion 3: The technology must improve the net health outcomes
(continued)

4. HemaQuant analyzer with Glycosal cartridges

The literature search did not find any published studies evaluating clinical outcomes using the HemaQuant analyzer with Glycosal cartridges.

5. A1c At-Home-Test

Rector et al (2001) evaluated the effect of free home HbA1c kits provided to members of two health plans. A sample of members from each health plan were sent HbA1c self-test kits in January 2000 and participated in a follow-up telephone interview. To understand why members did or did not use self-test kits sent by their health plans, the survey focused on perceived ease of use, outcomes, and normative beliefs. In the group of 380 members who were interviewed, 170 (45%) used the kit. HbA1c values were > 8 mg/dl in 43%. Among the 170 who used the kit, 160 said that they would use the kit. Their most common reason for using the kit was to find out how well their blood glucose was being controlled (48%). Convenience (12%) was the next most frequent reason for using the kit. Among the 210 members who did not use the kit, 81 members said that they would not or were not sure if they would when interviewed. Their most frequent reason for not using the kit was duplication of tests done by physicians (34%). Others were too busy (12%), wanted to talk with their physician (11%), or had difficulty using the kit (11%). Because the majority of health plan members did not use the kit and the majority who did use the kit had HbA1c levels < 8 mg/dl, sending home test kits to members did not result in a high yield of members with elevated HbA1c levels. No other clinical outcomes were assessed.

Petitti et al (2001) conducted a randomized clinical trial of home measurement of fructosamine. One hundred forty adult patients with HbA1c values of 8% or greater were recruited to the trial through referral from physicians and a direct mailing to potentially eligible persons. Participants were randomized to weekly home fructosamine monitoring in addition to daily glucose monitoring or daily glucose monitoring alone. Both groups of patients were contacted regularly by telephone and were given the same instructions on diet and exercise. The primary outcome was glycemic control 3 and 6 months after randomization.



TA Criterion 3: The technology must improve the net health outcomes (continued)

5. A1c At-Home-Test, continued

No significant difference was found between the two groups in the mean absolute decrease of HbA1c levels at 3 months (0.5% in the fructosamine group vs. 0.8% in the control group; $P > 0.2$), and the difference favored the control group at 6 months (0.7% fructosamine vs. 1.2% control; $P = 0.04$). Both groups had a statistically significant improvement in glycemic control. The addition of home fructosamine monitoring to routine glucose monitoring appeared to worsen overall glycemic control. Since fructosamine is another glycohemoglobin measure like HbA1c, this study suggests that home HbA1c monitoring is unlikely to lead to improved clinical outcomes for patients.

6. Other systems

Thaler et al (1999) assessed the impact of rapid-turnaround HbA1c results on providers' clinical decision-making and on follow-up HbA1c levels. They performed a large, pseudo-randomized clinical trial in which rapid HbA1c results were made available to providers on even days of the month (rapid, $n = 575$), but delayed by 24 hours on odd days (conventional, $n = 563$). The same NGSP-certified method for measuring HbA1c levels was used for both groups (TinaQuant, Boehringer-Mannheim/Roche). The population was predominantly African American (92%) and female (68%) with a mean age of 58 years. All participants had type 2 diabetes. Glycemic control was good at baseline (mean HbA1c level 7.6%). Adjustment of therapy for patients with type 2 diabetes was considered appropriate if therapy was intensified for HbA1c values $>7\%$ or not intensified for HbA1c values $\leq 7\%$. A post-hoc analysis was also performed using patients ($n = 574/1138$, 50%) who returned for follow-up 2-7 months later (mean 3.8 months) to ascertain the effect of rapid HbA1c availability on subsequent glycemic control. Rapid HbA1c availability resulted in more appropriate management compared with conventional HbA1c availability (79 vs. 71%, $P = 0.003$). This difference was due mainly to less frequent intensification when HbA1c levels were $\leq 7\%$ (10 vs. 22%, $P < 0.0001$) versus more frequent intensification for patients with HbA1c values $>7\%$ (67 vs. 63%, $P = 0.33$). Over 2-7 months of follow-up, HbA1c rose more in patients with conventional HbA1c results compared with rapid results (0.8 vs. 0.4%, $P = 0.02$).



TA Criterion 3: The technology must improve the net health outcomes
(continued)

6. Other systems

In patients with initial HbA1c >7%, rapid HbA1c results had a favorable impact on follow-up HbA1c independent of the decision to intensify therapy (P = 0.03). The authors concluded that the availability of rapid HbA1c determinations facilitated diabetes management and improved HbA1c levels.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

1. Rapid HbA1c testing

The established alternative to rapid HbA1c measurement is for the physician to send the patient to a laboratory to have blood drawn and HbA1c measured by a central laboratory. Test results are available to the physician several days later, usually after the patient's visit with the physician. The key question is whether the availability of the test results at the time of the patient visit (rapid HbA1c test) is at least as effective as standard measurement in improving long-term glycemic control. A potential harm that could arise due to rapid HbA1c testing is an increase in hypoglycemic events due to more frequent intensification of therapy.

The specific technology used to assess HbA1c level is immaterial, as long as it meets accepted standards of accuracy and precision (NGSP certification). The various technologies described above will be considered together in the assessment of clinical outcomes compared with the current standard.

The literature search found two case series that evaluated changes in processes of care, two cohort studies using concurrent controls that evaluated both processes of care and changes in HbA1c, three large pseudo-randomized clinical trials, and one good quality randomized clinical trial which evaluated HbA1c levels over one year. For the process of care outcomes, care was usually considered more appropriate if therapy was intensified for patients with HbA1c levels greater than 7.0% and not intensified for patients with HbA1c levels less than 7.0%.



TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

1. Rapid HbA1c testing, continued

The primary clinical outcome evaluated was the change in HbA1c level after six to twelve months of follow-up. One study reported on the incidence of major hypoglycemic events.

The first case series (Rumley *et al.* 1990) reported that knowledge of the HbA1c test result during the clinic visit resulted in a change in therapeutic recommendations for 25% of patients treated with insulin (n=43) and 18% of the other patients with diabetes (n=79). A major reason for the changes in therapy was that HbA1c levels indicated that glycemic control was worse than what was reflected in the patients' logs of self-blood glucose monitoring. The second case series that assessed the effect of rapid HbA1c testing reported that in half of the patients (n=9/18), knowledge of the test result changed therapy (Pope *et al.* 1993). Both were small studies with no follow-up, so it is unclear whether the changes in process of care led to improved outcomes.

A large case-series with concurrent controls assessed the effects of rapid HbA1c testing in two hospital-based clinics in England (Grieve *et al.* 1999). The study compared HbA1c levels in 500 patients treated at a clinic that used rapid HbA1c testing to HbA1c levels in 500 patients treated at a second clinic that rarely used HbA1c testing. The analysis adjusted for age, gender, ethnicity, socio-economic status, body mass index, duration of diabetes, and type of diabetes treatment in order to control for differences in case-mix between the two clinics. HbA1c levels were significantly lower in patients treated at the clinic using rapid HbA1c testing (7.8 versus 8.7, adjusted $p < 0.001$). Patients at the clinic with rapid HbA1c testing also made fewer hospital visits per year than those treated at the clinic using conventional HbA1c testing. The authors acknowledge the possibility of other unmeasured confounders that might explain the differences in clinical outcomes. Certainly, there may be other differences in the processes of care at the two clinics, which may be responsible for the significantly better glycemic control.



TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

1. Rapid HbA1c testing, continued

The second case-series with concurrent controls (Ferenczi *et al.* 2001) reviewed therapeutic decisions and glycemic control in an office practice. Patients with standard Medicare (n=93) had rapid HbA1c results available during office visits while patients with HMO Medicare had commercial HbA1c results available within 3 days of the office visit. During the first visit, 52% of patients in the rapid test group had a change in therapy compared to 27% of patients in the conventional group. After 12 months of follow-up HbA1c levels decreased by 1.0% in the rapid HbA1c testing group and 0.33% if the conventional testing group ($p<0.001$). As in the prior study, the results support the hypothesis that rapid availability of HbA1c results improves HbA1c levels, but these findings could be confounded by other differences in patient care due to the differences in their insurance status. Only randomized clinical trials can control for unmeasured confounders and prove causality.

Three large clinical trials (n>500 in each) used a pseudo-randomized design (Grieve *et al.* 1999; Thaler *et al.* 1999; Miller *et al.* 2003). Two of the studies assigned patients to the rapid HbA1c testing group every other day and the third study assigned every other person to rapid HbA1c testing. These design decisions were made to streamline clinic operations, but can introduce subtle selection bias. Patients expected to do better may be preferentially scheduled for clinic visits on days when rapid testing is available. Similarly, the order in which patients are seen in the clinic can be unconsciously shifted by clinic staff if they are aware that patients given even numbered visits will be assessed with rapid HbA1c testing and those with odd numbered visits will receive conventional testing. In general, this systematic sampling design is not recommended for clinical trials because it is susceptible to errors caused by natural periodicities in the population and it allows the investigator to predict and perhaps manipulate those who will be in each group (Hulley 2001).

TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

1. Rapid HbA1c testing, continued

The first of the pseudo-randomized trials (Grieve *et al.* 1999) alternately assigned 599 patients to either rapid HbA1c testing or conventional testing. Patient characteristics include age, gender, HbA1c level, and diabetic complications were similar in the two groups. Patients in the rapid HbA1c testing group were 50% more likely to have a change in therapy during the visit compared to patients in the conventional group (OR 1.52, 95% CI 1.02-2.26). This effect was particularly evident (OR 1.72, 95% CI 1.12-2.76) in patients with poor glycemic control (HbA1c > 7.5%) were particularly likely to have changes in therapy.

The second pseudo-randomized trial (Thaler *et al.* 1999) provided rapid HbA1c test results during the clinic visit on even days of the month (n=575) and the day after the visit for patients seen on odd days of the month (n=563). The same test technology (TinaQuant, Roche) was used to measure HbA1c in both groups. The study was primarily designed to assess the appropriateness of changes in therapy in patients with good glycemic control (mean HbA1c 7.6%). Therapeutic management was assessed as appropriate more frequently in the group assigned to rapid HbA1c testing (79% versus 71%, p<0.0001). A post-hoc analysis found that the increase in HbA1c levels 2-7 months after the clinic visit was less in those with rapid HbA1c testing compared with conventional testing (0.4% versus 0.8%, p=0.02). The increase in overall HbA1c levels probably reflects the remarkably low baseline HbA1c levels in the group studied.

The most recent pseudo-randomized trial (Miller *et al.* 2003) provided rapid HbA1c test results during the clinic visit on even days of the month and the day after the visit for patients seen on odd days of the month at an urban, community clinic in Atlanta. Of the 597 patients recruited for the study, 275 had at least two follow-up visits with an average of 6 months of follow-up. During the initial visit, therapy was intensified more often in patients with HbA1c > 7% if they were assigned to the rapid HbA1c group (51% versus 32%, p=0.01). After 6 months of follow-up, there was a significant decrease in HbA1c for patients in the rapid HbA1c group (8.4% to 8.1%, p=0.04), but not in the conventional testing group (8.1% to 8.0%, p=0.31). No between-group comparison was presented. The fact that baseline HbA1c levels were higher in the rapid HbA1c group may partially explain the larger improvement in that group.



TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

1. Rapid HbA1c testing, continued

Finally, there is one randomized clinical trial of 201 patients seen at an academic diabetes clinic and followed for one year after randomization. The average HbA1c at randomization was 8.6%. Follow-up was complete for 82% of the patients with loss to follow-up equivalent in the two study groups. HbA1c levels decreased significantly at 6 and 12 months in the rapid test group (-0.6 and -0.4 respectively, $p < 0.01$), but not in the control group (-0.1 and -0.2 respectively, p NS). The between-group difference in HbA1c level was significant at six months, but not at one year. There was a trend towards fewer hypoglycemic events in the rapid test group (1.14/year versus 1.42/year, p NS). This randomized clinical trial confirmed the prior studies' consistent finding of better glycemic control in patients randomized to rapid HbA1c tests without any evidence of an increase in hypoglycemic events. The difference at twelve months was not significant, but the trend was towards better, not worse glycemic control.

2. Home monitoring of HbA1c

The established alternative is laboratory testing of HbA1c and home monitoring of blood glucose. There were no clinical trials evaluating the clinical outcomes of home HbA1c testing, but there was one study evaluating patient utilization of free testing kits provided by researchers and one randomized clinical trial evaluating home fructosamine testing (a comparable test that correlates well with HbA1c). Only 170/380 (45%) of patients who were mailed home HbA1c kits used the kit (Rector *et al.* 2001). Those who used the kit, primarily reported that they used it to see how well their diabetes was controlled (48%) which might reflect poor communication about HbA1c levels from their doctor. Among the 210 members who did not use the kit, the most frequent reasons for not using the kit was duplication of tests done by physicians (34%), being too busy (12%), wanted to talk with their physician (11%), or had difficulty using the kit (11%). This study suggests that there was poor acceptance of the test among patients with diabetes.



TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

2. Home monitoring of HbA1c, continued

The clinical trial of home measurement of fructosamine (Petitti *et al.* 2001) randomized 140 adult patients with HbA1c values of 8% or greater to weekly home fructosamine monitoring in addition to daily glucose monitoring or daily glucose monitoring alone. No significant difference was found between the two groups in the mean absolute decrease of HbA1c levels at 3 months (0.5% in the fructosamine group vs. 0.8% in the control group; $P > 0.2$), and the decrease favored the control group at 6 months (0.7% fructosamine vs. 1.2% control; $P = 0.04$). As fructosamine is another glycohemoglobin measure like HbA1c, this randomized clinical trial suggests that home HbA1c monitoring is unlikely to lead to improved clinical outcomes for patients and may be harmful.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

1. Rapid HbA1c testing

All of the assays for HbA1c require careful adherence to the assay protocols and regular quality control checks to maintain both accuracy and precision. Laboratory assays are not immune to problems arising from lax quality control (Matteucci *et al.* 1998), but laboratory personnel are more accustomed to implementing regular quality control of assay systems than office staff. On the other hand, for these rapid HbA1c tests, the manufacturer performs most of the quality control.

The DCA 2000 has been extensively studied in both academic and non-academic settings. For example, the device has been used in urban, community clinics (Miller *et al.* 2003) in rural community outreach projects (Carter *et al.* 1996), and in a number of epidemiological studies (Costa *et al.* 1999; Kaufman *et al.* 1999; Stolarczyk *et al.* 1999). It is simple to use and has minimal requirements for maintaining rigorous quality control.



TA Criterion 5: The improvement must be attainable outside the investigational settings (continued)

1. Rapid HbA1c testing, continued

The other devices have been less extensively studied, but have been designed to provide high quality results with minimal operator training. Given that the instructions for use and maintenance of the devices are followed, accurate and reliable HbA1c test results would be available at the time of the patient's visit to the clinic. It is the real-time availability of HbA1c levels that improves the processes of care and longer-term clinical outcomes.

2. Home monitoring of HbA1c

There is no evidence that home HbA1c testing improves clinical outcomes inside or outside of the investigational setting.



OPINIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

Neither the BCBSA Technology Evaluation Center Medical Advisory Panel or the Medical Policy Panel has reviewed this technology at this time.

Centers for Medicare and Medicaid Services (CMS)

CMS indicates the following on their website:

NCD (National Coverage Decision) for Glycated Hemoglobin/Glycated Protein
Indications and Limitations of Coverage

“Indications:

Glycated hemoglobin/protein testing is widely accepted as medically necessary for the management and control of diabetes. It is also valuable to assess hyperglycemia, a history of hyperglycemia or dangerous hypoglycemia. Glycated protein testing may be used in place of glycated hemoglobin in the management of diabetic patients, and is particularly useful in patients who have abnormalities of erythrocytes such as hemolytic anemia or hemoglobinopathies.

Limitations:

It is not considered reasonable and necessary to perform glycated hemoglobin tests more often than every three months on a controlled diabetic patient to determine whether the patient’s metabolic control has been on average within the target range. It is not considered reasonable and necessary for these tests to be performed more frequently than once a month for diabetic pregnant women.....”

CMS does not specify the setting in which testing should be performed.

American Diabetes Association (ADA)

The ADA recommendations are referenced in the third paragraph under Background, Hemoglobin A1c of this review. The ADA has been asked to provide representation at the meeting.



OPINIONS OF OTHERS, continued

American Society of Clinical Endocrinologists (ASCE)

The ASCE has been asked to provide a position statement and will have representation at the meeting.

CONCLUSION

1. Rapid HbA1c testing

HbA1c level has become the standard measure of diabetes control and lower HbA1c levels have been shown to translate into improved clinical outcomes in patients with type 1 (Diabetes Control and Complication Research Group 1993) and type 2 diabetes (UK Prospective Diabetes Study Group 1998). Many different HbA1c assays are available. The optimal use of the HbA1c requires standardization of test assays to ensure reported results between laboratories are comparable. The National Glycohemoglobin Standardization Program (NGSP) was established to standardize HbA1c tests. On an annual basis, manufacturers of both traditional and “rapid” HbA1c test assay methods are awarded a “certificate of traceability to the DCCT reference method” if their assay method passes rigorous testing criteria for precision and accuracy. They must be calibrated to results obtained using HPLC based on ion exchange columns. Manufacturers are awarded Certificates of Traceability if the total imprecision (coefficient of variation) is $\leq 4\%$ and the 95% CI of the difference between methods falls within $\pm 1\%$. Each certificate is effective for one year from the date of certification. Certified assays are listed on the NGSP website (<http://www.ngsp.org>). All of the rapid HbA1c tests evaluated in this review have received NGSP certification within the past twelve months. Any test that receives NGSP has sufficient accuracy and precision to be used for routine management of patients with diabetes. There can be slight differences in the results given by different methods, so it is recommended that the same assay methodology be used to monitor patients’ response to treatment over time.



CONCLUSION, continued

1. Rapid HbA1c testing, continued

Most of the traditional methods used to measure HbA1c are time-consuming and technically demanding, with the results of the assay not being available at the time of the patient visit. Thus, an important element in the clinical decision-making process is not available at the time of the visit. The rapid HbA1c tests were developed to address this need, but it was not clear that this translated into improved patient outcomes. Several large retrospective and prospective clinical trials with concurrent controls demonstrated that the availability of HbA1c results at the time of the patient's visit with the physician resulted in more appropriate decision-making about changes in therapy. For example, a recent clinical trial of 597 diabetic patients in a general medicine clinic in Atlanta (Miller *et al.* 2003) found that therapy was intensified in over half of patients allocated to the rapid HbA1c result group, but in less than one third of patients allocated to usual care. The one study that evaluated hypoglycemic episodes found a trend towards fewer hypoglycemic episodes in patients randomized to rapid HbA1c testing (Cagliero *et al.* 1999). The four clinical trials with concurrent controls and one randomized clinical trial consistently reported lower HbA1c levels in the group allocated receive rapid HbA1c testing when compared with the established alternative of laboratory HbA1c measurement.

Thus TA criteria 1-5 are met for all rapid HbA1c assay systems that have current NGSP certification.

2. Home monitoring of HbA1c

There is a paucity of data on home monitoring of HbA1c. One study (Rector *et al.* 2001) mailed free HbA1c kits to patients with diabetes reported that less than half of the patients used the kits. The main reasons given for not performing the tests were that their physicians had already done the test or that they were too busy. A randomized clinical trial (Petitti *et al.* 2001) of 140 patients with diabetes found that patients randomized to home fructosamine monitoring (another glycoprotein that correlates well with HbA1c) had higher levels of HbA1c after 3 and 6 months of follow-up. Thus, the current evidence suggests worse outcomes, rather than better outcomes, with home monitoring of glycoproteins.



CONCLUSION, continued

2. Home monitoring of HbA1c

Day to day clinical decisions about diabetes therapy are based on daily glucose testing, not HbA1c. HbA1c levels are usually used to make long-term changes in care in consultation between the patient and their doctor. It is unlikely that home HbA1c testing will improve clinical outcomes for patients with diabetes.

TA criteria 2-5 are not met for home monitoring of HbA1c.



RECOMMENDATION

It is recommended that rapid HbA1c testing in the office/clinic setting meets California Technology Assessment Forum technology assessment criteria.

It is recommended that rapid HbA1c testing in the home does not meet California Technology Assessment Forum technology assessment criteria.

October 8, 2003

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