Technology Assessment

Technology Assessment Program

Point of Care Testing of Hemoglobin A1c

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FINAL REPORT

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1.0 Overview

Point of care laboratory testing is the most rapidly growing segment of the clinical laboratory market, with a projected increase in sales from $4.2 billion to $6.2 billion between 2002 and 2007, representing an 8.1% increase.[1] The rising prevalence of this technology will present the Centers for Medicare and Medicaid Services (CMS) with a variety of issues surrounding the quality of care and cost effectiveness for Medicare beneficiaries. CMS has requested objective data in the form of technology assessments to better inform coverage and payment decisions that CMS will need to make in the future.

1.1 Salience of a Technology Assessment of Point of Care Hemoglobin A1c Testing Devices

This report represents the first phase of this project – an assessment of the use of hemoglobin A1c (HbA1c) in the point of care environment. A review of this topic is particularly salient for three reasons. First, diabetes induces major health and economic burdens, particularly in the Medicare population. Diabetes is a chronic disease that affects an estimated 18.2 million people in the United States, is associated with protean manifestations such as heart disease, blindness, kidney failure, and limb loss. Diabetes is estimated to cost in excess of $132 billion per year in medical treatment and productivity loss.[2] Over half of these medical costs are incurred by individuals over age 65 years.[3]

A second reason a review of point of care HbA1c devices is especially appropriate is that HbA1c measurement has been shown to influence clinical management and health outcomes for individuals with diabetes. HbA1c is the most prevalent of several chemically distinct species of glycated hemoglobins resulting from the non-enzymatic reaction between glucose and the free

amino groups of hemoglobin.[4] This reaction is irreversible and the proportion of hemoglobin in the red blood cells in the form of HbA1c depends on glucose concentration over time.[5] HbA1c has become the "gold standard" for assessing metabolic control.[6] The value of HbA1c testing in the management of individuals with diabetes can be inferred from trials of aggressive glucose control, in particular the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS).[7,8] Based on these and other studies, it appears that more successful management of glucose as measured by HbA1c level is directly related to reduction in diabetic complications.[9]

Third, assessment of HbA1c point of care devices is salient because of increasing number of devices on the market, especially devices that satisfy emerging standards for accuracy and precision. Of diagnostic tests approved for point of care use by the Food and Drug Administration (FDA), devices for measurement of HbA1c are amongst the most common.[10] Further, several manufacturers have demonstrated compliance with the Certification Protocol disseminated by the National Glycohemoglobin Standardization Program (NGSP).[11] FDA-approved HbA1c test point of care devices that also satisfy NGSP standards are listed in Table 1. The NGSP Certification Protocol is provided in Appendix A.

1.2 Questions Posed by CMS Regarding Point of Care HbA1c Testing Devices

The present evaluation of point of care HbA1c testing devices was designed to respond to four specific questions posed by CMS:

1. *What is the evidence on the performance of the tests measuring hemoglobin A1c in the point of care setting and the laboratory setting?*

2. *Is there evidence that performing hemoglobin A1c at the point of care influences patient management decisions compared to performing the test in the laboratory setting?*
3. *Is there direct evidence (from clinical studies) or indirect evidence (e.g., from clinical studies integrated using a model) that performing hemoglobin A1c at the point of care results in better clinical outcomes for Medicare beneficiaries, such as reduced length of stay, decreased morbidity and mortality, and improved quality of life, compared to performing the test in a laboratory setting?*
4. *Is there evidence quantifying the impact on health care expenditures?*

In the following section, we describe the general methods of this assessment.

2.0 Methods

2.1 Search Strategy

We identified relevant articles from citations in a recent systematic review.[12] These included six clinical studies comparing point of care glycated hemoglobin testing with standard laboratory testing[13-18] and four studies comparing the accuracy of point of care glycated hemoglobin and standard laboratory tests for hemoglobin A1c.[19-22]

Medical Subject Heading (MeSH) coding of these articles was examined for relevant terms; however, there was little consistency in terms used for the point of care testing concept. Preliminary searches designed using various combinations of the following MeSH terms did not attain reasonable specificity (Diabetes Mellitus, Hemoglobin A, Glycosylated) or sensitivity (Point of Care Systems).

We used these seed articles to identify additional relevant citations using two strategies: 1) articles that cited any of the seed articles using the Web of Science citation index database; and 2) articles identified using the "Relevant Citations" search feature from the PubMed citation of each seed article. These searches were updated to April 2005.

In addition we queried several experts in the field and evaluated citations of included studies, and reviewed publicly available FDA documentation on relevant devices.

Findings are presented by question, focusing on study characteristics that relate to the potential for biased inference (e.g., categorizing the study as a randomized controlled trial, a prospective cohort study, or an observational study), and quantitative study results. Note that we did not attempt formal extrapolations beyond the published evidence, such as a new decision, a cost effectiveness model, or a business case analysis.

3.0 Results

3.1 Question 1: What is the evidence on the performance of the tests measuring hemoglobin A1c in the point of care setting and the laboratory setting?

Since the earliest field tests[23], it has been recognized that it would generally be useful to have reference standards to support the development of effective point of care testing devices for HbA1c. As noted above, the NGSP has developed standards that, through annual recertification, serve to assure that a specific device will measure HbA1c accurately, and with precision. These are standards that apply equally to

conventional laboratory devices and point of care devices. Thus, for purposes of this report, devices that satisfy NGSP standards will be considered equivalent to devices used in a conventional laboratory and to each other.

Two caveats apply here. First, while conventional laboratories may be certified (i.e., awarded a Certificate of Traceability), point of care testing does not lend itself to such certification. As of May 2005, certification has been limited to conventional laboratories.[24,25] By their nature, multiple point of care analyzers/devices may be diffusely scattered across a hospital/health system; certification of laboratories that employ multiple devices could become cumbersome and expensive. Second, the NGSP device standards do not address questions of dependency on operator skill. FDA has designated three point of care tests of HbA1c as Clinical Laboratory Improvement Amendment (CLIA)-waived. According to the CLIA statute, 42 U.S.C. Section 263a (d) (3) Examinations and Procedures, as modified by the Food and Drug Administration Modernization Act of 1997 (FDAMA)[26], testing devices can be designated as "waived" if they "are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that - 1) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or 2) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly." CLIA status for FDA-approved devices that also satisfy NGSP certification is noted in Table 1.

There is limited published data regarding the reliability of point of care HbA1c test devices in the hands of inexperienced operators versus trained laboratory personnel. Two reports suggest that operator training has little effect on reliability for Bayer DCA 2000[15] and Metrica.[25] Some concern has been raised that specific operator failures in processing (e.g., a delay that leads to specimen drying, or failure to recalibrate per manufacturer recommendations) can lead to errors. One study of the Bayer DCA 2000 in the extreme environment of the Australian outback suggests that this is not a clinically important problem. Specifically, local staff with limited on-site training achieved results with the point of care device that were highly correlated with the results from the reference laboratory ($r = 0.99$, $p<0.0001$) without evidence of bias.[28]

Notably, all HbA1c measurement devices are susceptible to a greater or lesser degree to interference by such factors as the presence of hemoglobin variants and derivatives, shortened erythrocyte survival, vitamin C and D, iron deficiency. The NGSP has reviewed this literature, tabulated by specific device. This data is reproduced in Appendices B and C (The NGSP web site lists detailed citations of all studies referenced in Appendix C).

3.2 Question 2. Is there evidence that performing hemoglobin A1c at the point of care influences patient management decisions compared to performing the test in the laboratory setting?

We identified five studies that compared management decisions based on point of care test results compared with conventional laboratory testing (delayed result availability) for HgbA1c in diabetes. One was a randomized control trial[13], two were prospective controlled trials with

allocation based on day of visit [17,18], and two were retrospective concurrent cohort comparisons.[14,15] Characteristics of these studies are described in Table 2.

The effects on management decisions were reported in different ways among these studies. Below, we report the results by study, beginning with the more straightforward, simpler analyses, and moving to more sophisticated analyses that consider more influences on provider decision making within the study.

Cagliero et al conducted a randomized control trial among diabetics all of whom were taking insulin (56% had type 1 diabetes).[13] The patients undergoing point of care testing had unchanged mean daily insulin doses at the end of the study (baseline 49.9 ± 27.5 to 50.7 ± 26.9 U/day) compared to the control group (55.3 ± 36.6 to 59.9 ± 42.6 U/day); however, the mean number of daily insulin injections increased in the point of care testing group (2.29 ± 0.97 to 2.45 ± 0.95; p= 0.001) compared to the conventional testing group. Any change in insulin regimen (dose or frequency) occurred in 83% of patients in the control group and 69% of point of care testing patients (p=0.028). Changes were initiated by the physician in most cases (74% in point of care testing group versus 66% in control group; NS), but were initiated by patients, presumably based on home blood glucose measurements between physician visits, in 34% of control patients and 26% of point of care testing patients (NS).

This study's findings of a significant change in HbA1c (see below) do not appear to be explained by differences in management decisions; however, the authors note that it is possible that insulin regimen changes in the point of care testing group may have been more clinically appropriate

than those in the conventional testing group; the appropriateness of the decisions was not examined. Furthermore, the management decisions were summed over the entire one year period. Glycemic control was better for point of care testing patients at six months and it became similar to conventional testing patients at twelve months. This study did not examine whether management decisions were merely delayed by the lack of availability of test results at the point of care.

Grieve et al report a retrospective concurrent cohort study from two hospitals, one of which routinely used point of care testing, while the other did not.[15] Patients who underwent point of care testing were more likely to have a change in management than conventional testing group (25% versus 18%; OR 1.52; 95% CI 1.02-2.26). Furthermore, patients with poor glycemic control (HbA1c > 7.5%) were more likely to have management change in the point of care testing than in the conventional testing group (32% versus 21%; OR 1.75; 95% CI 1.12-2.76). For patients with good control (HbA1c < 7.5%) the number of management changes did not differ according to the testing method employed (approximately 10% in both testing groups; OR 0.92; 95% CI 0.35-2.44).

Ferenczi et al reported a retrospective study[14] comparing two groups who received different HbA1c testing based on differences in their health care benefit: Medicare enrollees received the point of care testing while Health Maintenance Organization (HMO) patients had conventional testing. The groups were otherwise similar. Patients who received point of care testing were more likely to have therapy changes at any clinical visit (145/362 [40%] versus 19/80 [24%]; p=0.006). Considering first visit only, point of care testing was also associated with more

therapeutic changes (48/93 [52%] versus 6/22 [27%]; p=0.04). When patients were stratified by glycemic control, those with poor glycemic control (HbA1c > 8%) were more likely to have therapeutic changes associated with point of care testing (41/73 [56%]) than conventional testing (3/14 [21%]) at first visit (p=0.017). In contrast, among patients with good glycemic control (HbA1c ≤ 8%), few therapeutic changes were implemented (12 at first visit and 38 total); because of the small number of therapy changes, these data were not described according to testing group and were not analyzed.

There was no significant difference between the point of care testing group and the conventional testing group in the proportion of patients reporting at least one episode of severe hypoglycemia (30% versus 30%), the total number of episodes of severe hypoglycemia (98 versus 111), or the mean number of severe hypoglycemic episodes per year (1.14 ± 2.84 versus 1.42 ± 4.27).

In two studies[17,18] from the same institution, performed several years apart, the effect of point of care testing for HbA1c on decision making was examined in much greater detail than among the above studies. These were both prospective controlled trials with patients allocated to testing according to day of visit (odd or even). Both studies lost approximately half of the participants to followup; the loss was similar in the point of care testing and conventional testing groups. Thaler et al studied patients in a diabetic specialty clinic and found that management decisions were significantly more appropriate in the point of care testing group than convention testing group (79% versus 71%; p=0.003).[18] For this study, appropriateness was defined as intensification of treatment if and only if HbA1c was greater than 7%, thus intensification of treatment for patients with HbA1c ≤ 7% was considered inappropriate. When HbA1c was ≤ 7%, providers

inappropriately intensified more often under conventional testing than point of care testing (22% versus 10%; $p<0.0001$). This was observed to occur among patients with HbA1c $\leq$ 7% and fasting plasma glucose $\geq$ 7.8 mmol/l (140 mg/dl); among this subgroup providers intensified therapy 46% of the time with conventional testing, but only 26% of the time in point of care testing ($p=0.03$). The study included patients on insulin, oral, and diet treatments; intensification of treatment was undertaken more often among patients on insulin than oral agents (51 versus 35%) and more often than those on diet alone (14%).

The investigators used multivariable logistic regression to examine the independent contributions of point of care testing, HbA1c result (glycemic control), type of treatment, and fasting plasma glucose on the decision to intensify therapy. This analysis found that fasting plasma glucose retained an independent contribution to intensification even when controlling for HbA1c level, good or poor control.

The authors concluded that the point of care testing was most useful for preventing clinicians from inappropriately intensifying therapy among patients who were under good control when fasting plasma glucose at physician visit was elevated. Point of care testing also tended to increase intensification of therapy in patients who were poorly controlled, but this effect was not statistically significant in this study; the authors argue that in their clinic setting, the propensity to intensify therapy is already quite high. This study did not measure adverse consequences of inappropriate intensification of therapy such as hypoglycemic episodes.

Miller et al, a few years later at the same institution, but in a primary care clinic rather than a diabetic specialty unit, conducted a similarly designed study.[17] This new study stratified baseline HbA1c levels into finer ranges (< 7%; 7.0-7.9%; 8.0-8.9%; and ≥ 9%) but used the same definitions of appropriateness when evaluating intensification of therapy.

When HbA1c was greater than 7%, providers intensified more often under point of care testing than conventional testing (51% versus 32%; p=0.0003). However, this effect was markedly different for patients in the ranges 7.0-7.9%, 8.0-8.9% and ≥ 9.0%. Among patients in the 7.0-7.9% range, therapy was intensified only 12% of visits on average, and equally often in point of care testing and conventional testing; however, therapy was intensified significantly more often in point of care testing than conventional testing groups among patients in the 8.0-8.9% range (51% versus 23%; p=0.007) and in the ≥ 9.0% range (65% versus 46%; p=0.006).

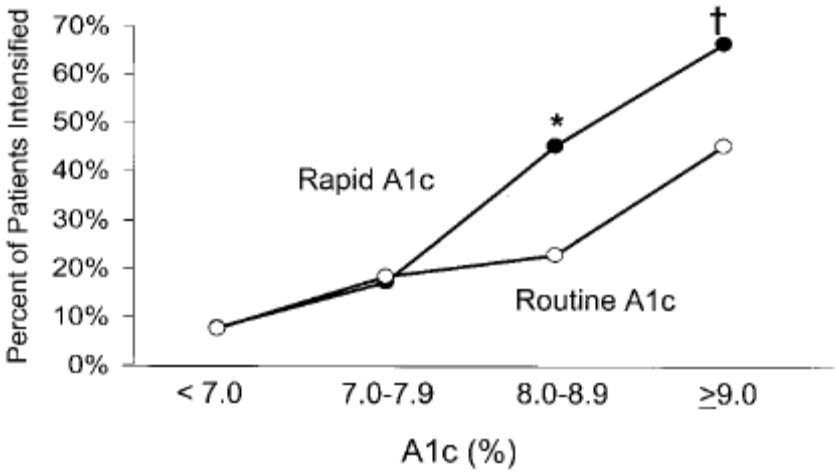

Figure 2— Intensification of therapy at baseline visit according to HbA1c level. Open circle, routine HbA1c; Closed circle, rapid HbA1c. *p = 0.032; †p = 0.002.

This study analyzed the impact of random plasma glucose, which was available at the point of care for all patients on intensification of therapy. These data show that when capillary glucose levels were > 300 mg/dl, treatment was intensified in about 60% of patient visits regardless of HbA1c test availability; however, the point of care testing group more often had therapy intensified than the conventional testing group at lower levels of capillary glucose, 201-250 mg/dl (67% versus 37%; p=0.04) and 151-200 mg/dl (54% versus 10%; p=0.001).

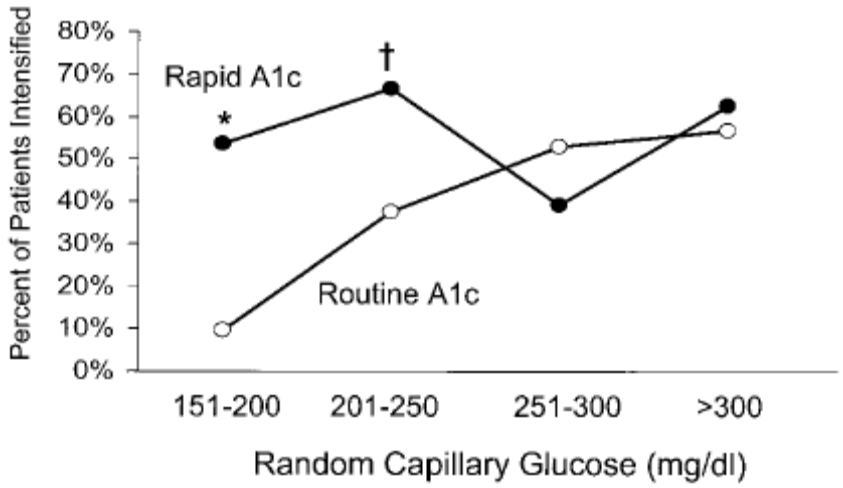

Figure 3—*Intensification of therapy at baseline visit according to random capillary blood glucose level. Open circle, routine HbA1c; Closed circle, rapid HbA1c.* *p = 0.001; †p = 0.012.

In a multivariable logistic regression analysis, controlling for age, race, sex, duration of diabetes, BMI, and glucose levels, both higher baseline HbA1c (p<0.001) and availability of point of care testing (p=0.026) increased the likelihood of intensification of therapy.

In summary, the availability of HbA1c results at the point of care seems to affect management decisions in several ways:

- providers are more likely to intensify therapy for patients with substantial elevations of HbA1c (> 8.0%);
- providers are more likely to intensify therapy in patients who have mild hyperglycemia if they also have an elevated HbA1c level; and
- providers are less likely to intensify therapy, inappropriately, in patients under good control (by HbA1c) based on an elevated random or fasting blood glucose levels at the point of care.

3.3 Question 3: Is there direct evidence (from clinical studies) or indirect evidence (e.g., from clinical studies integrated using a model) that performing hemoglobin A1c at the point of care results in better clinical outcomes for Medicare beneficiaries, such as reduced length of stay, decreased morbidity and mortality, and improved quality of life, compared to performing the test in a laboratory setting?

3.3.1 Evidence of Impact of Availability of Test Results at Point of Care on Glycemic Control

We identified five studies that compared glycemic control among diabetics undergoing point of care testing to conventional laboratory testing (delayed result availability). In addition, we found one additional study that evaluated the effect of having HbA1c results available at the time of physician visit, although results were obtained not by a point of care test device, but by home collection of blood samples mailed in advance of physician visits. We include this study, also cited in the National Academy of Clinical Biochemistry (NACB) report, because it could

plausibly influence glycemic control through the same mechanism. Classifying the studies by type of design, one study was a randomized control trial[13], two were prospective controlled trials with allocation based on day of visit[17,18], two were retrospective concurrent cohort comparisons[14,15], and one was an uncontrolled prospective trial.[16]

Study characteristics are described in Table 2. Study populations included adults with mean ages ranging from 48 to 73 years. Most included a majority of type 2 diabetes mellitus, except for Cagliero in which 56% were type 1. The duration of diabetes as reported ranged from 7.2 to 12.8 years; but was not reported in three studies. Settings varied from single specialty practices (diabetology/endocrinology) to primary care. In two studies, the allocation to type of testing was by institution[15], without regard to specialty of caregivers.

The DCA 2000 (Bayer, West Haven, CT) instrument was explicitly stated to have been used in three of the five studies using point of care testing, and implied by reference in another; one study used the Diastat instrument (Bio-Rad, Hercules, CA). Conventional lab methods were either High Performance Liquid Chromatography (HPLC) or turbidimetric immuno inhibition assay, but not specifically described in one study.[14]

The effects on HgbA1c are shown by testing group in Table 3. Mean HbA1c declined in the course of all but one study[17], regardless of testing strategy. The effect of point of care testing compared to conventional laboratory testing was estimated in different ways between studies. These methods included 1) mean change in HbA1c from baseline to follow-up (analyzing individual patients paired data)[13,17]; 2) comparing the change in mean HbA1c from baseline to

follow-up (analyzing group mean unpaired data)[14,17,18]; or 3) comparing follow-up means only, with adjustment for patient characteristics.[15] Most of the studies measured follow-up HbA1c at defined times after the initial testing at baseline, most often 6 months; however, some of the retrospective studies were unclear about when point of care testing results became available relative to the data collection period.[15]

Despite the differences in populations, study design, analysis and period of follow-up, the magnitude of the effect of point of care testing compared to conventional laboratory testing of HbA1c was relatively similar between studies. Differences in HbA1c between the two test strategies consistently favored point of care testing by a margin (differences in change of HbA1c at follow-up or if change not calculable, then difference in follow-up HbA1c) of 0.2% to 0.8%. From the better designed studies, the effect range from 0.2% to 0.46% at 6 months, while among the less applicable[17] or less rigorous studies[14,15], the effect was estimated at 0.43 to 1.0%. Note that the Holman study was uncontrolled, so its estimates are likely to be high, since most studies showed decreased in HbA1c even in the control groups.

Given the heterogeneity of study design, analysis and reporting, we did not elect to combine the estimates in a meta-analysis, despite the fact that the estimates appear to be calculable and statistically homogeneous. The various study estimates suggest that there is a statistically significant effect the magnitude of which is in the range of a decrease in HbA1c of at least 0.2% and perhaps as high as 0.8%.

Two studies provided data at more than one follow-up time period that address the issues of the durability of the effect over time. The conceptual model and the data regarding the influence on management decisions are consistent with the idea that point of care testing accelerates the therapeutic changes. Thus one would expect that over time, the benefit of point of care testing over conventional testing might decline. Cagliero reported differences in HbA1c at both six and twelve months; this study showed a greater effect at six than twelve months (-0.46% versus -0.29%); Holman et al, in uncontrolled study found an effect of -1.0% at 6 months and -0.7% at twelve months.

There is little data regarding the duration of the effect of implementing point of care testing for HbA1c; what data is available on both management decisions and HbA1c would suggest that the effect might decay over time, although there is abundant uncertainty regarding the duration and magnitude of the effect.

3.3.2 Relationship between Improved Glycemic Control and Clinical Outcomes

To address this issue, we focused on patients with type 2 diabetes, because this condition is much more prevalent than type 1 diabetes, especially in the age group of most interest to CMS. An examination of the evidence report Use of Glycated Hemoglobin and Microalbuminuria in the Monitoring of Diabetes Mellitus by the Johns Hopkins Evidence-based Practice Center[9], supplemented by a literature search of citations that were published after the cut-off date used for that evidence report, indicated that the UKPDS randomized trial was notably larger than other randomized trials, and that its results were roughly consistent with those from a heterogeneous set of cohort studies. Accordingly, we limited our analysis to reports from the UKPDS. Table 4

abstracted from Stratton[29], provides complication rates per 1,000 years of follow-up, adjusted for various patient characteristics, by HbA1c, for white males aged 50-54 and followed for an average of ten years. (Thus, most of the follow-up will be of patients in their late 50s). The complication rates are based on observed values of HbA1c, as is the risk ratio in the second column from the right. The rightmost column is based on an intent-to-treat analysis using the mean differences between the intensive intervention and usual care groups in the UKPDS.

Recognizing that the point of care versus conventional laboratory testing trials yielded mean HbA1c values in the range of 7.5-8.5%, the most appropriate comparison would likely involve the shaded columns above. Approximately speaking, a 1.0% absolute improvement in HbA1c values, maintained for an entire year would lead to the following reduction of events per 1,000 patient-years: 2 deaths, 1 myocardial infarction, 1.5 lower-limb amputations or other significant manifestation of peripheral vascular disease, 10 microvascular complications, and 2 cataract extractions.

If we assess the impact of hyperglycemia as a cumulative stressor, the same excess number of events would also be expected for a 0.5% absolute risk maintained over a period of two years. This also estimates the maximum impact of point of care testing consistent with the data at hand. An estimate of the minimum possible impact, consistent with the idea that point of care testing merely accelerates the physician's decision by six months on average, would be an 0.5% absolute impact maintained over a period of six months. In this case, the excess number of events would be one quarter of those listed above. It would be reasonable to posit that an intermediate case would have the excess number of events being one half of those listed above.

It might also be noted that the UKPDS investigators have developed a simulation model of the development of complications of type 2 diabetes, which is described in a model to estimate the lifetime health outcomes of patients[30] and also in the UKPDS Outcomes Model.[31] The public use version of this model allows the user to specify both age and HbA1c (most particularly, patients in the Medicare age range can be specified), but only the subset of complications pertaining to vascular events are reported. For the present, we assume that the pattern of data for patients in their late 50s is sufficiently representative for the purposes at hand.

Question 4: Is there evidence quantifying the impact of point of care testing for HbA1c on health care expenditures?

For this purpose, we reviewed studies that assessed health care expenditures as well as those that compared resource usage. We identified five studies that accomplished this objective; two studies that directly examined the impact of point of care testing on resource utilization and three studies that estimate the resource impact of improved glycemic control as measured by HbA1c.

Cagliero et al conducted a randomized controlled trial[13] in a diabetes center in Massachusetts. The aim of the researchers was to determine whether availability of HbA1c results at time of an office visit would lead to improved glycemic control. Two hundred and one consecutive patients were studied (about half of them had type 1 diabetes), and were randomly assigned to an immediate assay group (HbA1c results available at beginning of visit) and a control group (HbA1c results measured by diabetes laboratory). The mean age of the patients in this study

was forty nine years, and 56% of all patients had type 1 diabetes. Patients were followed for 12.8 months.

Use of health care resources was evaluated as a secondary outcome, and was determined by patient questionnaires (telephonic or mail contact with providers, requiring assistance for visit to hospital, emergency room visits or hospital admissions). Charts were reviewed to confirm this information, and for capturing the number of office visits and other relevant data. Cost of testing was not collected.

The researchers established that although glycemic control was better in the immediate assay group (and in patients with type 1 and type 2 diabetes), health care resource use was not different between the two groups (Table 5). The authors attributed this to the need for patients to contact providers in order to report other laboratory data (e.g., lipid values), but do not explain the insignificant difference between the two groups with respect to hypoglycemic episodes, emergency room visits or outpatient visits.

However, one physician demonstrated statistically significant reduction in the number of contacts in the immediate assay group (1.54 versus 2.63), suggesting that individual variation in practice could potentially influence resource use.

In a second study, Grieve et al, evaluated three forms of testing in two sites, over four months. The three forms of testing were: 1) testing using a distant laboratory with a delay of five to seven days (conventional testing); 2) testing in a local laboratory with results available prior to

consultation (near patient laboratory testing); and 3) testing by a nurse using a desktop analyzer in the clinic (point of care testing). There was no net economic difference between conventional and near patient laboratory testing.[15] However, point of care testing was more expensive than conventional testing; while number of visits were fewer for point of care testing patients (1.81 versus 2.28), the cost per visit was higher (£26.60 versus £14). This extra cost was primarily attributable to higher cost of reagents used in point of care testing (£8.82 versus £1.51). Because several point of care tests were being evaluated at the same time and the costs were not separated by type of test, it is not clear from this study which economic effects were attributable to HbA1c testing.

Three studies provide some indirect evidence regarding the economic benefit of improved glycemic control as measured by HbA1c. Menzin et al assessed the economic impact of improved glycemic control in 2,394 patients with diabetes in a clinic in New York using a retrospective cohort design.[32] Based on the mean levels of HbA1c (performed in a clinical laboratory), patients were assigned to study cohorts: good control (<8%), fair control (8-10%), and poor control (>10%). The average age of these patients was 63 years, and the study made no mention of whether these patients were type 1 or type 2 diabetes. The average duration of follow-up was forty months. A statistically significant positive relation was observed between HbA1c levels and the average number of inpatient admissions for some selected short-term complications: hypoglycemia, hyperglycemia, some infections and electrolyte imbalance even after adjustment for age, sex, presence of cancer, and presence of long-term diabetes-related complications. This statistically significant increase was found those with, and those without long-term diabetes-related complications (Table 6). The complications were identified through

International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes on inpatient bills. The relation was stronger for those patients with long-term diabetes-related complications (greater number of stays). Notably, the HbA1c levels positively correlated to average adjusted charges for inpatient treatment, and the results were more marked among patients with chronic diabetic complications.

The study has several limitations. The authors acknowledge that their estimates may be conservative, considering the inaccuracies of ICD-9-CM coding. The use of ICD-9-CM codes also precluded the researchers from distinguishing between acute hospital stays from admissions to skilled nursing facilities. The study results could be confounded by the severity and duration of diabetes, both of which could be correlated with HbA1c levels, and the reduction in costs associated with better glycemic control may have been overstated. The study utilized charges instead of true resource costs (which would be lower), and the magnitude of difference in charges would vary from one institution to another. Resource usage would also depend upon treatment patterns in any given health care setting, which may differ from place to place, limiting the generalizability of this study and any other study estimating resource usage.

Another study conducted by Wagner et al evaluated the effects of glycemic control on health care costs and utilization.[33] They followed 8,905 continuously enrolled individuals with diabetes, most of them with type 2 diabetes, in a historical cohort study. Total health care costs, percentage of patients hospitalized, and number of primary care and specialty visits were compared between the improved (defined as those whose HbA1c decreased 1% or more in one year and sustained the decline in the following year). The study concludes that a sustained reduction in HbA1c level is associated with significant cost savings within one to two years of

improvement. A study by Karter et al supports the hypothesis that improved HbA1c is associated with reductions in other resource utilization (e.g., hospitalization and ER visits) for some groups of patients.[34]

In summary, the limited available data suggest that in the short-term, point of care testing is more expensive than conventional testing (an additional £8 to £23 in one study[15]) but otherwise has no profound impact on health care resource utilization within the first year of device use. If improved glycemic control can be achieved more quickly or more readily by some means, a degree of economic benefits can be expected, and these may be more significant in patients with diabetes-related long-term complications. However, this possible economic benefit would be mitigated if efficacy of point of care testing in reducing complications diminishes over time.

4.0 Summary

The current review supports the following conclusions regarding the specific questions posed by CMS.

1. **The performance of the tests measuring hemoglobin A1c in the point of care setting and the laboratory setting**: Though there are some differences between point of care HbA1c testing devices with regard to susceptibility to interference and other performance characteristics, it seems reasonable to say that devices which satisfy criteria for accuracy and precision disseminated by the National Glycohemoglobin Standardization Program (NGSP) Certification Protocol are functionally equivalent to conventional devices. The same may not be supported for devices that do not satisfy these standards. While operator dependency is less of an issue for

devices that are CLIA-waived, the relationship between test performance and operator skill has not been well established.

2. **The influence of performing HbA1c at the point of care on patient management decisions compared to performing the test in the laboratory setting:** The evidence suggests that point of care HbA1c testing can effect management decisions, such as appropriate intensification of therapy for patients with substantial elevations of HbA1c (> 8.0%), intensification of therapy in patients who have mild hyperglycemia if they also have an elevated HbA1c level; and diminished inappropriate intensification of therapy for patients under good control by HbA1c, but who have a point of care glucose result that is discordantly high. This underlines the importance of the conscientiousness of the provider in achieving the potential benefits of HbA1c point of care testing.

3. Impact of performing HbA1c testing at the point of care on clinical outcomes for Medicare beneficiaries, compared to performing the test in a laboratory setting: No direct evidence was found that addresses this question. However, we examined this issue indirectly by assessing the evidence regarding 1) impact on HbA1c improvement, and 2) impact of HbA1c improvement on clinical outcomes. Regarding the first issue, performing HbA1c testing at the point of care appears to confer an improvement in HbA1c results the magnitude of which is in the range of a decrease in HgbA1c of at least 0.2% and perhaps as high as 0.8%. However, available data indicates that these results may not necessarily be durable or generalizable. Few data are available beyond six months, and twelve-month data from one study suggest a smaller effect on HgbA1c of point of care at twelve than at six-months. This finding is consistent with

the hypothesis that point of care testing primarily accelerates therapeutic changes, which implies that its impact will diminish over time. Moreover, the impact may be related by factors such as the current level of glycemic control by the individual patient and the degree of organization of the clinic in which testing will be done (e.g., as reflected by systematic efforts at quality improvement). Regarding the second issue, trials support a relationship between improved HbA1c and clinical outcomes. From these data, it appears that a modest benefit of point of care testing on glycemic control (an improvement on the order of 0.5%) would be expected to be associated with a reduction in the following events per 1,000 patient-years: 2 deaths, 1 myocardial infarction, 1.5 lower-limb amputations or other significant manifestation of peripheral vascular disease, 10 microvascular complications, and 2 cataract extractions.

4. Impact of point of care HbA1c testing on health care expenditures: From a modest literature it may reasonable to conclude that point of care HbA1c testing per se has no impact on health care resource use within the first year of point of care testing, even if the testing results in improved glycemic control. There is some evidence that if improved glycemic control can be achieved, irrespective of whether HbA1c is measured in the laboratory or at point-of-care, some economic benefits in terms of reduced health care resource use can be achieved, and these are more significant in patients with diabetes-related long-term complications, and over three years of glycemic control.

A variety of significant issues related to health care expenditure are not addressed by available US literature, including the magnitude of health care resources used in providing point of care testing (such as nursing time to perform testing, greater number of tests performed, capital

equipment costs) immediate cost offsets (realized and not realized, such as decreased time to follow up laboratory results that appear hours to days after the clinic visit) as well as long-term cost offsets which have major potential societal impact (such as changes in the rates of preventable events associated with poor glycemic control.)

Appendix A. Criteria for accuracy and precision disseminated by the National

Glycohemoglobin Standardization Program (NGSP) Certification Protocol[11]

C. Standardization and Certification of Methods by Manufacturers:

1. Standardization of Methods Prior to Certification of Traceability: The process by which a method is standardized to the Reference will depend on the specific method and is determined by the manufacturer, e.g., standardization may be accomplished by re-assignment of calibrator values or by conversion equation since the method may or may not include calibration by the end user. Manufacturers may request assistance from the any network laboratory to 1) help determine the best approach to standardization, 2) recommend or to evaluate different calibrator materials 3) assign preliminary values to calibrators with the understanding that an adjustment in the values may have to be made based on results of fresh sample comparisons, and/ or 4) perform analyses of fresh samples to provide the manufacturer with data on the new method's values compared to reference values in order to provide a basis for calibrator value assignments.

2. Certification of Traceability to the Reference Method: Manufacturers desiring certification of their method must contact the NETCORE. The NETCORE will then assign a SRL based on manufacturers preference, method type, and/or potential conflicts of interest. Precision testing as well as method comparison and bias estimation must be performed for certification of a method as traceable to the DCCT Reference. Before pursuing certification through the SRL, manufacturers should establish that their analytical instrument systems / methods:

- have had all required preventive maintenance procedures performed
- be in peak operating condition
- be operated with the same parameters in all runs of the comparison and precision studies (e.g. instrument, reagent lot, calibrator lot, calibrator assigned values)
- be operated in the same manner as they would by a customer

Manufacturers must perform precision testing following NCCLS EP5-A guidelines.[35] Manufacturers must also participate in a fresh blood sample comparison (n=40) for estimation of bias from the SRL. Manufacturers may perform the precision and comparison analyses at the manufacturing site or they may choose to have a laboratory (that is NOT an NGSP network laboratory) using their system perform the testing. For the sample comparison, one set of fresh samples may be split and used to evaluate several applications or methods, thus necessitating only one evaluation by the SRL. Collection of patient samples may be done either by the manufacturer (or designated laboratory) or by the SRL as long as sample stability requirements for both the SRL and the manufacturer's method can be met. All data should be sent from the manufacturer and the SRL directly to the NETCORE.

In order for a commercial method to be considered traceable to the CPRL:

total imprecision (CV) must not be statistically significantly >4%.

the 95% CI of the differences between methods (test method and SRL method) must fall within the clinically significant limits of ±1% GHB (2).

Appendix A. (continued) Criteria for accuracy and precision disseminated by the National Glycohemoglobin Standardization Program (NGSP) Certification Protocol[11]

All data analysis will be performed by the NETCORE following NCCLS EP5-A and Bland and Altman Assessment of Agreement.[36] Outliers will be analyzed for informational purposes only; an outlier is defined as > mean + 3SD of the absolute differences between pairs. All outliers will be investigated by the NETCORE to determine if the discrepancy could be due to characteristics of the specimen rather than the assay method. If results show that a discrepancy could be due to characteristics of the specimen, then the manufacturer will be asked to submit a new specimen and the data will be reanalyzed.

Manufacturers are awarded Certificates of Traceability for successfully completing precision testing and fresh sample comparisons for the specific reagent lots, calibrator lots and instrumentation used. Traceability to the DCCT applies only to results from fresh or fresh frozen blood samples. Analysis of processed (e.g., lyophilized) material may be subject to matrix effects and any comparisons to the DCCT using results from processed specimens should be made with caution. Final certification of traceability is issued by the NETCORE after review of the data by the Steering Committee. Methods should be re-certified annually. A new certification is also recommended in the event of significant changes, such as those that would require a new 510(k) form to be filed with FDA.

Appendix B. Factors that interfere with GHB (HbA1c) Test Results[11]

UPDATED 06/04

Hemoglobin Variants and Derivatives: Genetic variants (e.g. HbS trait, HbC trait) and chemically modified derivatives of hemoglobin (e.g. carbamylated Hb in patients with renal failure, acetylated Hb in patients taking large amounts of aspirin) can affect the accuracy of GHB measurements. The effects vary depending on the specific Hb variant or derivative and the specific GHB method. Appendix C contains information for most of the commonly used GHB methods for the some of the more common Hb variants and derivatives. Interferences from less common Hb variants and derivatives are discussed in Bry, et al (1) When selecting an assay method, laboratories should take into consideration characteristics of the patient population served, (i.e., high prevalence of hemoglobinopathies or renal failure).

Shortened Erythrocyte Survival: Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, hemolytic anemia) will falsely lower GHB test results regardless of the assay method used (25). GHB results from patients with HbSS, HbCC, and HbSC must be interpreted with caution given the pathological processes, including anemia, increased red cell turnover, transfusion requirements, that adversely impact GHB as a marker of long-term glycemic control. Alternative forms of testing such as glycated serum protein (fructosamine) should be considered for these patients.

Other factors: Vitamins C and E are reported to falsely lower test results, possibly by inhibiting glycation of hemoglobin (26,27); vitamin C may increase values with some assays (27). Iron-deficiency anemia is reported to increase test results (28). Hypertriglyceridemia, hyperbilirubinemia, uremia (see carbamylated Hb in Appendix C), chronic alcoholism, chronic ingestion of salicylates, and opiate addiction are reported to interfere with some assay methods, falsely increasing results (4,6,10,12-13,15,18-20, 23-24, 29-32).

Appendix C: Effects of frequently encountered Hb variants and derivatives on GHB measurement

Interference (Yes/No)

Method (listed in alphabetical order by manufacturer)	***Hb C trait***	***Hb S trait***	***Hb E trait***	***Elevated HbF***	***Carbamyl-Hb***
***Axis-Shield Nycocard** (Primus Nycocard)	No 5	No 5	-	-	-
***Bayer DCA 2000**	No 1, 6, 7	No 1, 6	No 1, 8-9	-	No 4, 10
Beckman Diatrac	Yes 1,2,11	Yes 1,2,11	-	Yes 11	Yes 1,11
***Beckman Synchron CX7**	No 5	No 5	-	-	-
***Bio-Rad D-10**	Yes 33	No 33	-	-	-
***Bio-Rad DiaSTAT**	No 33	Yes 33	-	-	-
***Bio-Rad Variant A1c**	No 1-2	Yes 1,2	No 1,8	-	Yes 1,4,12,13,15
***Bio-Rad Variant GHb**	No 5	No 5	-	-	-
***Bio-Rad Variant II A1c**	**Yes** 33/No 5	**Yes** 33/No 5	-	No (≤24% HbF)t	No 12
***Dade Dimension RxL**	No 33	No 33	-	-	-
***Drew Scientific DS5**	No 33	Yes 33	-	-	-
Helena Glyco-Tek	Yes 5,6	No 5,6	-	-	-
***Menarini HA8140**	No 5	Yes 5	Yes 1,17	No 1,17	**Yes**/No 1,4,18,19
***Menarini HA8160**	No 33	No 33	-	-	-
***Metrika A1c Now**	Yes 33	Yes 33	-	-	-
***Primus CLC 330/385**	No 1-2	No 1-2	No 1,8	-	No 1,4,10,20
***Primus PDQ**	No 33	No 33	-	-	-
***Provalis Glycosal** (Bio-Rad MicroMat)	Yes5	No5	-	-	-
***Roche Cobas Integra**	Yes 5	Yes 5	-	-	-
***Roche Tina-quant II**	No 1,2,21	No 1,2,21	No 1,21	No (≤30% HbF) 21	No 1,4,18
***Roche Unimate**	Yes 1,22	Yes 1,22	-	-	No 1,4,12
***Tosoh A1c 2.2 Plus**	No 1,2,33	No 1,2,33	Yes 1,8	-	Yes/**No** 1,4,12,15, 18,23,24
***Tosoh G7**	No 33	No 33	-	-	-

1) * indicates an NGSP certified method (as of July 2004); 2) t The manufacturer has recently lowered the level at which they claim no interference from 30% HbF to 15% HbF; 3) Yes/No indicates that there is conflicting data in the literature. The indicator in bold is the opinion of the NGSP based on review of the literature cited. **NOTE**: Many other publications have been reviewed. Only those with conclusions that are reasonably supported by data are included. For ion-exchange HPLC methods, interference from Hb variants and adducts may be dependent on the lot of reagents used (2).

Table 1. HbA1c test devices that are approved by the FDA for point of care use and satisfy the NGSP Certification Protocol .

Device	CLIA category
Axis-Shield Nycocard	Moderate complexity
Bayer DCA 2000	Waived
Bio-Rad D-10	Moderate complexity
Bio-Rad Dia-STAT	Moderate complexity
Drew Scientific DS5 (the same device as the Bio-Rad Dia-STAT except for labeling)	Moderate complexity
Metrika A1c Now (also available over the counter)	Waived
Provalis Glycosal (Bio-Rad MicroMat and Cholestech GDX)	Waived

CLIA – Clinical Laboratory Improvement Amendment;
Moderate complexity – subject to specific requirements for quality control, quality assurance, personnel qualifications and responsibilities, and proficiency testing with routine biennial inspections;
Waived – exempt from quality standards and are defined as simple tests having an insignificant risk of an erroneous result.

Table 2: Study characteristics

Study	No. of patients	Diagnoses	Patient characteristics	Testing equipment	Baseline HgbA1c	Geographic location Dates Setting
Cagliero et al	201 RCT type 1 & 2	56% type 1 DM	Age 49 yrs Sex 53% men Treatment Insulin 100% Ethnicity – NR	**POCT** - (Bayer DCA 2000) **Conventional lab** – HPLC method	8.6%	Boston, MA NR Urban academic specialty practice
Thaler et al.	1138 (574 with f/u HgbA1c) RCT	Type 2 DM Mean dur. of DM 7.2 yrs	Age 59.5 yrs Sex 68.5% women Treatment Insulin 45% Oral 37% Diet 18% Ethnicity Afro-Amer 91.0% BMI 32.9	**POCT** - Bayer DCA 2000 (implied – not explicitly stated)	7.3%	Atlanta, GA Jul 1997 – Nov 1997 Urban academic specialty practice
Miller et al.	597 (275 with f/u HgbA1c) prosp controlled trial	Type 2 DM ≥ 6 mo duration Mean dur. of DM 10.4 yrs	Age 61.7 yrs Sex 18% men Treatment Ethnicity Afro-Amer 95.4%	**POCT** – Bayer DCA 2000 – results available to provider at time of visit **Conventional lab** - results available after the pt had left the clinic	8.3 ± 0.2	Atlanta, GA Feb 1999 – Oct 1999 Urban academic primary care practice
Grieve et al.	599 visits retrospective cohort	NR, presumably type 2 Mean dur. of DM 12.8 yrs	Age 57.0 years Sex 55.7 % men Treatment Insulin 47.2 % OHA 46.4 % Diet 6.4 % Ethnicity White 70.5% Afro-Carib. 20.6% BMI 28.4	**POCT** – Bayer DCA 2000 by lab personnel or nurse in clinic Conventional testing – processing at central laboratory with delay of 5-7 days	8.6%	London, UK Oct 1995 – Mar 1996 Urban specialty practice
Ferenczi et al, 2001	115 new referrals to endocrine practice; retrospective cohort	Type 2 DM Age > 65 yrs	Age 72.6 yrs Sex 43.4% men	**POCT** – Bio-Rad Diastat **Conventional lab** results obtained within 2-3 days	8.9%	New York, NY Apr 1997 – Mar 1998 Urban private specialty practice
Holman et al.	200 patients	Type 1 DM 73%	Age 47.9 yrs	**POCT** – capillary blood sample sent in advance so HbA1c result available at MD visit	10.8%	Oxford, UK NR Specialty practice

Table 3: Clinical studies of the impact of POCT for HbA1c in diabetics on glycemic control

Study	No. pts Study design Setting	Tests	Baseline HbA1c (mean ± SD / SEM)	Glycemic control 6 mo	 12 mo
Cagliero et al	201 RCT type 1 & 2	POCT LAB Diff	8.67 ± 1.79 (SD) 8.49 ± 1.59	-0.57 ± 1.44 -0.11 ± 0.79 -0.46%	-0.40 ± 1.65 -0.19 ± 1.16 -0.29%
Thaler et al	1138 (574 with f/u HgbA1c) RCT	POCT LAB Diff	7.5 ± 0.1 (SEM) 7.2 ± 0.1	+0.4 ± NR +0.8 ± NR -0.4 (p=0.02)	Not reported
Miller et al	597 (275 with f/u HgbA1c) prosp controlled trial	POCT LAB Diff	8.4 ± 0.2 (SEM) 8.1 ± 0.2	8.1 ± 0.1 (p=0.04) [-0.3%] 8.0 ± 0.1 (p=0.31) [-0.1%] -0.2%	Not reported
Grieve et al	1000 patients retrospective cohort	POCT LAB Diff	Unadjusted Adjusted	7.79 ± 0.058 (SEM) 8.66 ± 0.056 [-0.87] 8.40 ± 0.070 8.83 ± 0.070 -0.43% p<0.001	Not reported
Ferenczi et al, 2001 #1140	115 new referrals to endocrine practice; retrospective cohort	POCT LAB Diff	9.5 ± 1.9 (SD) 8.3 ± 1.7	Not reported	-1.03 ± 0.33 (SEM) -0.33 ± 0.83 (SEM) -0.70 %
Holman et al	200 mostly type 1 on insulin	Home LAB Diff	10.8 ± 2.3 (SD)	9.8 ± 2.1 (SD) (p<0.001; paired t-test) -1.0%	10.1 ± 2.2 (p<0.05; paired t-test) -0.7%

Home – Home collected sample sent to lab for analysis prior to clinic visit.
LAB – conventional laboratory testing with results returned following clinic visit.
POCT – Point of care testing device used to obtain HbA1c results at clinic visit.
Diff – difference in HbA1c measures between two different testing strategies

Table 4. Impact of HbA1c on diabetes complication rates.

Complications per 1000 patient years \ HbA1c group	<6%	6-7%	7-8%	8-9%	9-10%	10+%	RR 0.9% HbA1c difference: cohort	RR 0.9% HbA1c difference: RCT
Mean HbA1c	5.6%	6.5%	7.5%	8.4%	9.4%	10.6%		
Any	35.9	48.7	65.5	74.5	103.2	124.9	21%	12%
Diabetes death	8.9	12.0	19.9	23.5	29.5	33.0	21%	10%
Any death	17.0	23.3	30.0	31.8	37.0	40.7	14%	6%
MI	16.0	20.8	29.2	30.0	39.6	38.6	14%	16%
Stroke	4.3	6.6	8.3	7.4	6.7	12.0	12%	-11% (0)
Amputation or PVD	1.2	1.2	2.6	4.0	10.9	12.2	43%	35%
Microvascular	6.1	9.3	14.2	22.8	40.4	57.8	37%	25%
Heart failure	2.3	3.4	5.0	4.4	5.0	11.9	16%	9%
Cataract extraction	4.1	4.5	4.9	6.9	6.6	14.4	19%	24%

Table 5: Use of health care resources (12.8 months)

	Immediate assay	Control	Significance
n	86	78	-
Age	49 ± 16	49 ± 16	NS
% patients with severe hypoglycemic episodes	30	29	NS
% patients with emergency room visits	15	14	NS
Outpatient visits (#/year)	4.72	4.98	NS
Mean # of contacts with providers	2.44	2.73	NS

Table 6: Inpatient stays and average charges for complications (3-year period)

HbA1c category	<8%	8%-10%	>10%
n	725	1,424	245
Age (mean)	65 ± 11	63 ±11	59 ± 11
Presence of long-term complications	28%	32%	33%
Average number of inpatient stays per 100 patients (all patients)	13	16	31
Average charges per patient for short term complications (all patients)	$970	$1380	$3040
Average number of inpatient stays per 100 patients (without long term complications)	4.6	4.2	9.3
Average charges per patient for short term complications (with long term complications)	$240	$270	$580
Average number of inpatient stays per 100 patients (without long term complications)	30	38	74
Average charges per patient for short term complications (with long term complications)	$2610	$3810	$8320

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List of Acronyms/Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendment
CMS	Centers for Medicare and Medicaid Services
CPRL	Central Primary Reference Laboratory
CV	Total imprecision
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
GHB	Gamma Hydroxybutyrate
HbA1c	Hemoglobin A1c
HbCC	Hemoglobin CC
HbSC	Hemoglobin SC
HbSS	Hemoglobin SS
HMO	Health Maintenance Organization
HPLC	High Performance Liquid Chromatography
ICD-9-CM	International Classification of Diseases, ninth revision, Clinical Modification
LAB	Laboratory
MeSH	Medical Subject Heading
MI	Myocardial Infarction
n	Sample Size
NACB	National Academy of Clinical Biochemistry
NCCLS EP5-A	National Committee for Clinical Laboratory Standards EP5-A Guidelines
NETCORE	Internet Service Provider
NGSP	National Glycohemoglobin Standardization Program
NR	Not reported
NS	Not significant
OHA	Oral hypoglycaemic agent
OR	Odds ratio
p	P-value
POCT	Point of care testing
PVD	Peripheral vascular disease
r	Correlation
RCT	Randomized Clinical Trial
SD	Standard deviation
SEM	Standard error of the mean
SRL	Survival Research Labs
U	Units
UKPDS	U. K. Prospective Diabetes Study